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# Copyright © 1991 by The American Society for Pharmacology and Experimental Therapeutics<br> *Protein Phosphorylation and Neuronal Function\**<br>
SVEN IVAR WALAAS<sup>5b+</sup>1 AND PAUL GREENGARD<sup>+</sup><br>
SVEN IVAR WALAAS<sup>5b+</sup>1 AND PAUL GREEN

**T L'UUCIII I HUSPIIUI YIAUIUII AIIU IVCUIUIAI F UIICUIUI**<br>SVEN IVAR WALAAS<sup>LL</sup>† AND PAUL GREENGARD<sup>2</sup><br>*Laboratory of Molecular and Cellular Neuroscience, The Rockefeller University, New York, New York, and <sup>8</sup>Neurochemica* **SVEN IVAR WALAAS<sup>\*</sup><sup>b†</sup> AND PAUL GREENGARD<sup>\*</sup><br>***Peuroscience, The Rockefeller University, New York, New York, New York, New York, Oslo, Norway* 





# *A. Functional Importance of Protein Phosphorylation*

I. Introduction<br>
Functional Importance of Protein Phosphorylation<br>
The last decades have witnessed major advances in our<br>
derstanding of the molecular mechanisms involved in 1. **Introduction**<br>2 tranding of the molecular mechanisms in our<br>2 The last decades have witnessed major advances in our<br>2 understanding of the molecular mechanisms involved in<br>2 signal transduction in neuronal tissues. Rev A. Functional Importance of Protein Phosphorylation<br>The last decades have witnessed major advances in our<br>understanding of the molecular mechanisms involved in<br>signal transduction in neuronal tissues. Reversible pro-<br>tein A. Functional Importance of Protein Phosphorylation<br>The last decades have witnessed major advances in our<br>understanding of the molecular mechanisms involved in<br>signal transduction in neuronal tissues. Reversible pro-<br>tein The last decades have witnessed major advances in our<br>understanding of the molecular mechanisms involved in<br>signal transduction in neuronal tissues. Reversible pro-<br>tein phosphorylation appears to represent one, and pos-<br>o understanding of the molecular mechanisms involved in<br>signal transduction in neuronal tissues. Reversible pro-<br>tein phosphorylation appears to represent one, and pos-<br>sibly the most important, molecular mechanism by which<br> signal transduction in neuronal tissues. Reversible potein phosphorylation appears to represent one, and posibly the most important, molecular mechanism by whitextracellular signals produce their biological responsin speci tein phosphorylation appears to represent one, and possibly the most important, molecular mechanism by which extracellular signals produce their biological responses in specific target neurons. A partial list of those neur sibly the most important, molecular mechanism by which<br>extracellular signals produce their biological responses di<br>in specific target neurons. A partial list of those neuro-<br>thransmitters that have been shown to achieve at extracellular signals produce their biological responses di<br>in specific target neurons. A partial list of those neuro-<br>transmitters that have been shown to achieve at least<br>prome of their actions in neural cells through pr 1.

some of their actions in neural cells through protein<br>phosphorylation/dephosphorylation is presented in table<br>1.<br>Early studies of carbohydrate metabolism (Walsh et<br>al., 1968) demonstrated that enzyme phosphorylation<br>could phosphorylation/dephosphorylation is presented in table<br>1. We say studies of carbohydrate metabolism (Walsh et er<br>al., 1968) demonstrated that enzyme phosphorylation re<br>could have a regulatory role (Robison et al., 1971; N van<br>
Early studies of carbohydrate metabolism (Walsh et<br>
al., 1968) demonstrated that enzyme phosphorylation<br>
ref<br>
could have a regulatory role (Robison et al., 1971; Nimmo<br>
eximed Cohen, 1977; Krebs and Beavo, 1979). Late Early studies of carbohydrate metabolism (Walsh et era<br>al., 1968) demonstrated that enzyme phosphorylation refer<br>could have a regulatory role (Robison et al., 1971; Nimmo exia<br>and Cohen, 1977; Krebs and Beavo, 1979). Later al., 1968) demonstrated that enzyme phosphorylation refer could have a regulatory role (Robison et al., 1971; Nimmo exist<br>and Cohen, 1977; Krebs and Beavo, 1979). Later work poss<br>extended this concept (Kuo and Greengard, 1 could have a regulatory role (Robison et al., 1971; Nimmo<br>and Cohen, 1977; Krebs and Beavo, 1979). Later work<br>rextended this concept (Kuo and Greengard, 1969) and<br>led to the realization that this biochemical mechanism<br>had and Cohen, 1977; Krebs and Beavo, 1979). Later work poextended this concept (Kuo and Greengard, 1969) and review led to the realization that this biochemical mechanism review had widespread importance in physiological regu extended this concept (Kuo and Greengard, 1969) and reveal to the realization that this biochemical mechanism reveal widespread importance in physiological regulation Br (for review, see Greengard, 1978). Thus, it is clear led to the realization that this biochemical mechanism<br>had widespread importance in physiological regulation Br<br>(for review, see Greengard, 1978). Thus, it is clear today gai<br>that protein phosphorylation is involved not on had widespread importance in physiological regulation (for review, see Greengard, 1978). Thus, it is clear today that protein phosphorylation is involved not only in the regulation of intermediary metabolism but also in th (for review, see Greengard, 1978). Thus, it is clear today<br>that protein phosphorylation is involved not only in the<br>regulation of intermediary metabolism but also in the<br>regulation of a wide variety of other cellular func that protein phosphorylation is involved not only in tregulation of intermediary metabolism but also in tregulation of a wide variety of other cellular function A full molecular understanding of the role of protaphosphoryl regulation of intermediary metabolism but also in the regulation of a wide variety of other cellular function A full molecular understanding of the role of protein phosphorylation in nervous tissue would require ident fica regulation of a wide variety of other cellular function.<br>A full molecular understanding of the role of protophosphorylation in nervous tissue would require idefication and characterization of the various protein phorylatio A full molecular understanding of the role of protein C<br>phosphorylation in nervous tissue would require identi-<br>fication and characterization of the various protein phos-<br>phorylation systems present in the brain. The phosp

transmitters that have been shown to achieve at least proteins involved and discuss some of the evidence that<br>some of their actions in neural cells through protein demonstrates that protein phosphorylation is directly<br>phos neuronal function include enzymes involved in neuronal function include enzymes involved in neuro-<br>transmitter biosynthesis, synaptic vesicle-associat transmitter biosynthesis, synaptic vesicle-associated<br>proteins, protein phosphatase inhibitors, neurotransmitneuronal function include enzymes involved in itransmitter biosynthesis, synaptic vesicle-asso<br>proteins, protein phosphatase inhibitors, neurotran<br>ter receptors, ion channels, and cytoskeletal protein neuronal function include enzymes involved in neuro-<br>transmitter biosynthesis, synaptic vesicle-associated<br>proteins, protein phosphatase inhibitors, neurotransmit-<br>ter receptors, ion channels, and cytoskeletal proteins (fo neuronal function include enzymes involved in neuro-<br>transmitter biosynthesis, synaptic vesicle-associated<br>proteins, protein phosphatase inhibitors, neurotransmit-<br>ter receptors, ion channels, and cytoskeletal proteins (fo transmitter biosynthesis, synaptic vesicle-associated<br>proteins, protein phosphatase inhibitors, neurotransmit-<br>ter receptors, ion channels, and cytoskeletal proteins (for<br>examples, see Nestler and Greengard, 1984; Walaas a proteins, protein phosphatase inhibitors, neurotransmitter receptors, ion channels, and cytoskeletal proteins (for examples, see Nestler and Greengard, 1984; Walaas and Greengard, 1987). In the present review, selected asp ter receptors, ion channels, and cytoskeletal proteins (for examples, see Nestler and Greengard, 1984; Walaas and Greengard, 1987). In the present review, selected aspects of phosphorylation of such proteins in the nervous examples, see Nestler and Greengard, 1984; Walaas and Greengard, 1987). In the present review, selected aspects of phosphorylation of such proteins in the nervous system and their relationship to neuronal function will be Greengard, 1987). In the present review, selected aspects of phosphorylation of such proteins in the nervous system and their relationship to neuronal function will be discussed. We will describe some general properties of of phosphorylation of such proteins in the nervous system and their relationship to neuronal function will be discussed. We will describe some general properties of the protein kinases, protein phosphatases, and substrate tem and their relationship to neuronal function will be discussed. We will describe some general properties of the protein kinases, protein phosphatases, and substrate proteins involved and discuss some of the evidence tha discussed. We will describe some general properties of<br>the protein kinases, protein phosphatases, and substrate<br>proteins involved and discuss some of the evidence that<br>demonstrates that protein phosphorylation is directly<br> the protein kinases, protein phosphatases, and substrate<br>proteins involved and discuss some of the evidence that<br>demonstrates that protein phosphorylation is directly<br>involved in nervous system functions. Evidence from a<br>v proteins involved and discuss some of the evidence that<br>demonstrates that protein phosphorylation is directly<br>involved in nervous system functions. Evidence from a<br>variety of studies will be included, but a complete cov-<br>e demonstrates that protein phosphorylation is directly involved in nervous system functions. Evidence from a variety of studies will be included, but a complete coverage of the literature is not intended, and only selected involved in nervous system functions. Evidence from a variety of studies will be included, but a complete coverage of the literature is not intended, and only selected references will be given. Indeed, the vast literature variety of studies will be included, but a complete coverage of the literature is not intended, and only selected references will be given. Indeed, the vast literature that exists concerning protein phosphorylation makes i erage of the literature is not intended, and only selected<br>references will be given. Indeed, the vast literature that<br>exists concerning protein phosphorylation makes it im-<br>possible to discuss all aspects of this topic in references will be given. Indeed, the vast literature that exists concerning protein phosphorylation makes it im-<br>possible to discuss all aspects of this topic in a single<br>review. The reader is referred to a number of othe exists concerning protein phosphorylation makes it im-<br>possible to discuss all aspects of this topic in a single<br>review. The reader is referred to a number of other<br>reviews for additional information (for examples, see<br>Bro possible to discuss all aspects of this topic in a single<br>review. The reader is referred to a number of other<br>reviews for additional information (for examples, see<br>Browning et al., 1985; Greengard, 1976, 1978, 1987; Hu-<br>ga review. The reader is referred to a number of other<br>reviews for additional information (for examples, see<br>Browning et al., 1985; Greengard, 1976, 1978, 1987; Hu-<br>ganir and Greengard, 1990; Kandel and Schwartz, 1982;<br>Kenned reviews for additional information (for examples, see<br>Browning et al., 1985; Greengard, 1976, 1978, 1987; Hu-<br>ganir and Greengard, 1990; Kandel and Schwartz, 1982;<br>Kennedy, 1983, 1989; Kaczmarek and Levitan 1987;<br>Nairn et Browning et al., 1985; Greengard, 1976, 1978, 1987; Huganir and Greengard, 1990; Kandel and Schwartz, 1982;<br>Kennedy, 1983, 1989; Kaczmarek and Levitan 1987;<br>Nairn et al., 1985b; Nestler and Greengard, 1984; Reichardt and K nir and Greengard, 1990; Kandel and Schwartz, 198<br>ennedy, 1983, 1989; Kaczmarek and Levitan 198<br>airn et al., 1985b; Nestler and Greengard, 1984; Re<br>ardt and Kelly, 1983; Walaas and Greengard, 1987).<br>Conclusive evidence for

Kennedy, 1983, 1989; Kaczmarek and Levitan 1987;<br>Nairn et al., 1985b; Nestler and Greengard, 1984; Reichardt and Kelly, 1983; Walaas and Greengard, 1987).<br>Conclusive evidence for involvement of protein phos-<br>phorylation in Nairn et al., 1985b; Nestler and Greengard, 1984;<br>chardt and Kelly, 1983; Walaas and Greengard, 198<br>Conclusive evidence for involvement of protein p<br>phorylation in neuronal function was originally diffice<br>to obtain. Early chardt and Kelly, 1983; Walaas and Greengard, 1987)<br>Conclusive evidence for involvement of protein ph<br>phorylation in neuronal function was originally diffic<br>to obtain. Early studies suggested that cyclic nucleotid<br>dependen Conclusive evidence for involvement of protein phos-<br>phorylation in neuronal function was originally difficult<br>to obtain. Early studies suggested that cyclic nucleotide-<br>dependent protein phosphorylation might be of physio



PHARMACOLOGICAL REVIEW!





\* Protein phosphorylation systems shown to be regulated by extracellular signals in intact neural cells and/or nerve terminals are included. Vasoactive intestinal peptide<br>
PKA ARPP-16 Girault et al., 1966<br>
\* Protein phosphorylation systems shown to be regulated by extracellular signals in intact neural cells and/or nerve terminals are included.<br>
Not included a AR, <sup>1</sup> Protein phosphorylation systems shown to be regulated by extracellular signals in intact neural cells and/or nerve terminity.<br>Not included are widespread, predominantly nonneuronal systems. Abbreviations: PKC, pro relations between levels of cyclic AMPs or cyclic GMP depends on the server determinantly nonneuronal systems. Abbreviations: PP-2B, protein phospatase-2B; ARPP-16, cyclic AMP-regulated phospa $\alpha$ -AR,  $\beta$ -AR,  $\alpha$ - and man signals in masse increases and constantly viations. PKC, protein kinase C; PKA, cyclic AMP-dependent protein<br>phosphoprotein, 16 kDa; mACh-R, muscarinic acetylcholine receptor;<br>opamine receptor; A<sub>3</sub>, A<sub>2</sub> type of adeno

kinase; PP-2B, protein phospatase-2B; ARPP-16, cyclic AMP-regulate  $\alpha$ -AR,  $\beta$ -AR,  $\alpha$ - and  $\beta$ -adrenergic receptors, respectively; D1, D1 type of relations between levels of cyclic AMP‡ or cyclic GMP and specific ele  $\alpha$ -AR,  $\beta$ -AR,  $\alpha$ - and  $\beta$ -adrenergic receptors, respectively; D1, D1 type of d<br>relations between levels of cyclic AMP‡ or cyclic GMP<br>and specific electrophysiological properties were ob-<br>served (for reviews, see Bl relations between levels of cyclic AMP‡ or cyclic GMP<br>and specific electrophysiological properties were ob-<br>served (for reviews, see Bloom, 1975; Bloom et al., 1975;<br>Greengard, 1976; Dunwiddie and Hoffer, 1982; Siggins,<br>19 relations between levels of cyclic AMP‡ or cyclic GMP depland specific electrophysiological properties were ob-<br>served (for reviews, see Bloom, 1975; Bloom et al., 1975; cats<br>Greengard, 1976; Dunwiddie and Hoffer, 1982; Si and specific electrophysiological properties were observed (for reviews, see Bloom, 1975; Bloom et al., 1975; Greengard, 1976; Dunwiddie and Hoffer, 1982; Siggin 1982). Subsequently, such correlations were extended tinclud served (for reviews, see Bloom, 1975; Bloom et al., 1975; c.<br>Greengard, 1976; Dunwiddie and Hoffer, 1982; Siggins, sp<br>1982). Subsequently, such correlations were extended to vinclude other second messenger-regulated protei Greengard, 1976; Dunwiddie and Hoffer, 1982; Siggins, 1982). Subsequently, such correlations were extended to include other second messenger-regulated protein phosphorylation systems. Ultimately, intracellular injection of 1982). Subsequently, such correlations were extended<br>include other second messenger-regulated protein ph<br>phorylation systems. Ultimately, intracellular injecti<br>of components of various protein phosphorylation s<br>tems into i include other second messenger-regulated protein phosphorylation systems. Ultimately, intracellular injectio of components of various protein phosphorylation systems into identified neurons has demonstrated conclusively th phorylation systems. Ultimately, intracellular injection<br>of components of various protein phosphorylation sys-<br>tems into identified neurons has demonstrated conclu-<br>sively that these systems mediate and/or regulate a num-<br> of components of various protein phosphorylation systems into identified neurons has demonstrated conclusively that these systems mediate and/or regulate a number of well-defined neurophysiological phenomena (for examples, of components of various protein phosphorylation sys-<br>the phosphoprotein phosphatases, which dephosphorylate<br>tems into identified neurons has demonstrated conclu-<br>sively that these systems mediate and/or regulate a num-<br>be 1986b; DeRiemer et al., 1985).<br>B. Protein Phosphorylation Systems examples, see Kaczmarek et al., 1980; Castellucci et al.,

1986b; DeRiemer et al., 1985).<br>
B. Protein Phosphorylation Systems<br>
All protein phosphorylation systems consist minimally<br>
of three components. These include the *phosphoproteins*<br>
themselves, which change their biological B. Protein Phosphorylation Systems<br>All protein phosphorylation systems consist minimally<br>of three components. These include the *phosphoproteins*<br>themselves, which change their biological properties dur-<br>ing phosphorylatio B. Protein Phosphorylation Systems<br>
All protein phosphorylation systems consist minimally<br>
of three components. These include the *phosphoproteins*<br>
themselves, which change their biological properties dur-<br>
ing phosphory All protein phosphorylation systems consist minima<br>of three components. These include the *phosphoprote*<br>themselves, which change their biological properties d<br>ing phosphorylation/dephosphorylation. In addition, t<br>classes emselves, which change their biological properties dur-<br>g phosphorylation/dephosphorylation. In addition, two<br>nasses of enzymes are needed for the phosphorylation/<br> $\pm$  Abbreviations: cyclic AMP and cyclic GMP, cyclic aden

rig prospinoryiation/dephosphoryiation. In addition, two<br>classes of enzymes are needed for the phosphorylation<br># Abbreviations: cyclic AMP and cyclic GMP, cyclic adenosine an<br>cyclic guanosine 3':5'-monophosphate, respectiv Classes of enzymes are needed for the phosphorylation/<br>  $\ddagger$  Abbreviations: cyclic AMP and cyclic GMP, cyclic adenosine and<br>
cyclic guanosine 3':5'-monophosphate, respectively; CNS, central nerv-<br>
ous system; C, catalytic <sup> $\dagger$ </sup> Abbreviations: cyclic AMP and cyclic GMP, cyclic adenosine ancyclic guanosine  $3'.5'.$ monophosphate, respectively; CNS, central nervous system; C, catalytic subunit; R, regulatory subunit; CaM kinase Ca<sup>3+</sup>/calmoduli **acid; 1P3, increase of the manufacture of the manufacture of the system;** C, catalytic subunit; R, regulatory subunit; CaM kinas Ca<sup>2+</sup>/calmodulin-dependent protein kinase; GABA, γ-aminobutyr acid; IP<sub>3</sub>, inositol 1,4,5cyclic guanosine 3':5'-monophosphate, respectively; CNS, central nervous system; C, catalytic subunit; R, regulatory subunit; CaM kinase; Ca<sup>2+</sup>/calmodulin-dependent protein kinase; GABA,  $\gamma$ -aminobutyric acid; IP<sub>3</sub>, ino Ca<sup>2+</sup>/calmodulin-dependent protein kinase; GABA,<br>acid; IP<sub>3</sub>, inositol 1,4,5-trisphosphate; GAP-43, growt.<br>tein, 43 kDa; MAP, microtubule-associated protein;<br>Ser, serine; protein kinase C, Ca<sup>2+</sup>/phospholipid/diacylent pr ex / cambodum dependent protein kinase; GAP-43, growth-associated periodic in, 43 kDa; MAP, microtubule-associated protein; Thr, threon<br>tein, 43 kDa; MAP, microtubule-associated protein; Thr, threon<br>Ser, serine; protein ki Let al., al., worstworf, princretublule-associated protein; Thr, threonine; the Ser, serine; protein kinase C, Ca<sup>2+</sup>/phospholipid/diacylglycerol-dependent protein kinase; LTP, long-term potentiation; MARCKS, myristoy-<br>lat **cyclic AMP-regulated** phospholipid/diacylglycerol-dependent protein kinase; LTP, long-term potentiation; MARCKS, myristoy-lated, alanine-rich C-kinase substrate; DARPP-32, dopamine- and cyclic AMP-regulated phosphoprotein ent protein kinase; LTP, long-term potentiation; MARCKS, myristoy-lated, alanine-rich C-kinase substrate; DARPP-32, dopamine- and cyclic AMP-regulated phosphoprotein,  $M_r$  32,000; NMDA, N-methyl D-aspartate; ATP, adenosine

phosphoprotein, 16 kDa; mACh-R, muscarinic acetylcholine receptor;<br>opamine receptor; A<sub>2</sub>, A<sub>2</sub> type of adenosine receptor.<br>dephosphorylation reactions. One set of these enzymes<br>includes the *protein kinases*, phosphotrans opamine receptor;  $A_2$ ,  $A_2$  type of adenosine receptor.<br>
dephosphorylation reactions. One set of these enzymes<br>
includes the *protein kinases*, phosphotransferases that<br>
catalyze transfer of phosphate from ATP to prote dephosphorylation reactions. One set of these enzymes<br>includes the *protein kinases*, phosphotransferases that<br>catalyze transfer of phosphate from ATP to proteins on<br>specific serine, threonine, or tyrosine residues (for re dephosphorylation reactions. One set of these enzymes<br>includes the *protein kinases*, phosphotransferases that<br>catalyze transfer of phosphate from ATP to proteins on<br>specific serine, threonine, or tyrosine residues (for re catalyze transfer of phosphate from ATP to proteins on specific serine, threonine, or tyrosine residues (for reviews, see Nimmo and Cohen, 1977; Krebs and Beavo, 1979; Sefton and Hunter, 1984; Hunter and Cooper, 1985, catalyze transfer of phosphate from ATP to proteins on specific serine, threonine, or tyrosine residues (for reviews, see Nimmo and Cohen, 1977; Krebs and Beavo, 1979; Sefton and Hunter, 1984; Hunter and Cooper, 1985, Edel specific serine, threonine, or tyrosine residues (for reviews, see Nimmo and Cohen, 1977; Krebs and Beavo, 1979; Sefton and Hunter, 1984; Hunter and Cooper, 1985, Edelman et al., 1987). The other set of enzymes includes th Edelman et al., 1987). The other set of enzymes includes 1979; Sefton and Hunter, 1984; Hunter and Cooper, 198<br>Edelman et al., 1987). The other set of enzymes includ<br>the *phosphoprotein phosphatases*, which dephosphoryla<br>the phosphoproteins and thereby return the particuli<br>prote Edelman et al., 1987). The other set of enzymes includes<br>the *phosphoprotein phosphatases*, which dephosphorylate<br>the phosphoproteins and thereby return the particular<br>protein phosphorylation system to its basal state (Ing the *phosphopro*<br>the phosphopro<br>protein phosph<br>britsen and Col<br>Nairn, 1991).<br>Increases in e phosphoproteins and thereby return the particution phosphorylation system to its basal state (In itsen and Cohen, 1983a,b; Cohen, 1989; Shenolikar airm, 1991).<br>Increases in the state of phosphorylation of phosphoteins ca

B. Protein Phosphorylation Systems<br>
All protein phosphorylation systems consist minimally<br>
of three components. These include the *phosphoproteins*<br>
themselves, which change their biological properties dur-<br>
themselves, wh protein phosphorylation system to its basal state (Inge-<br>britsen and Cohen, 1983a,b; Cohen, 1989; Shenolikar and<br>Nairn, 1991).<br>Increases in the state of phosphorylation of phospho-<br>proteins can be achieved either by activa britsen and Cohen, 1983a,b; Cohen, 1989; Shenolikar and<br>
Nairn, 1991).<br>
Increases in the state of phosphorylation of phospho-<br>
proteins can be achieved either by activation of protein<br>
kinases, by inhibition of protein pho Nairn, 1991).<br>Increases in the state of phosphorylation of phospho-<br>proteins can be achieved either by activation of protein<br>kinases, by inhibition of protein phosphatases, or by<br>changes in the properties of the protein it Increases in the state of phosphorylation of phosphorproteins can be achieved either by activation of protein kinases, or b changes in the properties of the protein itself as a substrate for distinct protein kinases or pho proteins can be achieved either by activation of protein kinases, by inhibition of protein phosphatases, or by changes in the properties of the protein itself as a substrate for distinct protein kinases or phosphatases. Pr kinases, by inhibition of protein phosphatases, or by changes in the properties of the protein itself as a substrate for distinct protein kinases or phosphatases. Present evidence suggests that increasing the activity of p changes in the properties of the protein itself as a substrate for distinct protein kinases or phosphatases. Present evidence suggests that increasing the activity of protein kinases represents the most common activation m strate for distinct protein kinases or phosphatases. Present evidence suggests that increasing the activity of<br>protein kinases represents the most common activation<br>mechanism in both neuronal and nonneuronal tissues.<br>Howev ent evidence suggests that increasing the activity of protein kinases represents the most common activation mechanism in both neuronal and nonneuronal tissues.<br>However, it is increasingly clear that certain protein phospha protein kinases represents the most common activation<br>mechanism in both neuronal and nonneuronal tissues.<br>However, it is increasingly clear that certain protein<br>phosphatases are subject to rapid and reversible control<br>mech mechanism in both neuronal and nonneuronal tissues.<br>However, it is increasingly clear that certain protein<br>phosphatases are subject to rapid and reversible control<br>mechanisms. Recent evidence also indicates that many<br>subst However, it is increasingly clear that certain protein<br>phosphatases are subject to rapid and reversible control<br>mechanisms. Recent evidence also indicates that many<br>substrates undergo phosphorylation by multiple protein<br>ki phosphatases are subject to rapid and reversible controlled mechanisms. Recent evidence also indicates that man<br>substrates undergo phosphorylation by multiple protein<br>kinases (table 2). Such phosphoproteins may change<br>thei mechanisms. Recent evidence also indicates that is<br>substrates undergo phosphorylation by multiple pr<br>kinases (table 2). Such phosphoproteins may ch<br>their properties as substrates for protein kinases or p<br>phatases as a resu substrates undergo phosphorylation by multiple protein<br>kinases (table 2). Such phosphoproteins may change<br>their properties as substrates for protein kinases or phos-<br>phatases as a result of phosphorylation or dephosphorylkinases (table 2). Such phosphoprotheir properties as substrates for prote<br>phatases as a result of phosphorylatio<br>ation in other regions of the molec<br>phenomena will be discussed below.<br>Mammalian brain is an unusually eir properties as substrates for protein kinases or phos-<br>atases as a result of phosphorylation or dephosphoryl-<br>ion in other regions of the molecule. These various<br>enomena will be discussed below.<br>Mammalian brain is an un

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to multisite protein phosphorylation in intact tissue. References include recent papers or reviews, where original data are described. Abbreviations: **nACh-R, nicotinic acetylcholine receptor; GABAA-R, 'y-aminobutyric acid receptor type A; Tyr K, tyrosine-specific protein kinase; other** <sup>•</sup> Table includes examples of major neuronal proteins specifically involved in signal transduction or other brain-specific functions, and sulto multisite protein phosphorylation in intact tissue. References include recent \* Table includes examples of major neuronal proteins specifically involved<br>to multisite protein phosphorylation in intact tissue. References include recent<br>nACh-R, nicotinic acetylcholine receptor; GABA<sub>A</sub>-R,  $\gamma$ -aminobu

to multisite protein phosphorylation in intact tissue. References include r mACh-R, nicotinic acetylcholine receptor;  $GABA_A-R$ ,  $\gamma$ -aminobutyric abbreviations as in legend to Table 1.<br>tein phosphorylation systems, includin modulators as in legend to Table 1.<br>debreviations as in legend to Table 1.<br>tein phosphorylation systems, including diverse protein<br>kinases, phosphoprotein substrates, phosphoprotein<br>phosphatases, and modulators thereof (Na 1985b). For example, including diverse prot<br>
1985b). For example, comparison between the endomous protein phosphorylation activities found in rat for<br>
1985b). For example, comparison between the endomous protein phosphoryl kinases, phosphoprotein substrates, phosphoprotein<br>phosphatases, and modulators thereof (Nairn et al.,<br>1985b). For example, comparison between the endoge-<br>nous protein phosphorylation activities found in rat fore-<br>brain an kinases, phosphoprotein substrates, phosphoprot<br>phosphatases, and modulators thereof (Nairn et<br>1985b). For example, comparison between the endo<br>nous protein phosphorylation activities found in rat fo<br>brain and cerebellum a phosphatases, and modulators thereof (Nairn et al<br>1985b). For example, comparison between the endoge<br>nous protein phosphorylation activities found in rat fore<br>brain and cerebellum and those found in various periph<br>eral tis 1985b). For example, comparison between the endogenous protein phosphorylation activities found in rat fore-<br>brain and cerebellum and those found in various peripheral tissues from rat has shown that the neuronal preparat nous protein phosphorylation activities found in rat fore-<br>brain and cerebellum and those found in various periph-<br>eral tissues from rat has shown that the neuronal prep-<br>arations have higher cyclic AMP-dependent and Ca<sup>2+</sup> brain and cerebellum and those found in various peripheral tissues from rat has shown that the neuronal preparations have higher cyclic AMP-dependent and  $Ca^{2+}$  calcependent protein kinase activities and a much larger su eral tissues from rat has shown that the neuronal preparations have higher cyclic AMP-dependent and  $Ca^{2+}$ -dependent protein kinase activities and a much larger number of putative endogenous substrate proteins than do pe arations have higher cyclic AMP-dependent and Ca<br>dependent protein kinase activities and a much larg<br>number of putative endogenous substrate proteins th<br>do peripheral tissues (S. I. Walaas and P. Greenga<br>unpublished eviden dependent protein k<br>number of putative e<br>do peripheral tissues<br>unpublished evidence<br>gard, 1989, p. 378). unpublished evidence presented in Nestler and Green-<br>gard, 1989, p. 378).<br>**II. Protein Kinases in Brain** 

rd, 1989, p. 378).<br>
II. Protein Kinases in Brain<br>
The number of protein kinases described has increased paratically during the last decade. Most of these pro-II. Protein Kinases in Brain<br>The number of protein kinases described has increased<br>dramatically during the last decade. Most of these pro-<br>tein kinases appear to belong to a common superfamily II. Protein Kinases in Brain<br>The number of protein kinases described has increased<br>dramatically during the last decade. Most of these pro-<br>tein kinases appear to belong to a common superfamily<br>of enzymes that share similar The number of protein kinases described has increased<br>dramatically during the last decade. Most of these pro-<br>tein kinases appear to belong to a common superfamily<br>of enzymes that share similarities in their catalytic do-<br> The number of protein kinases described has increased<br>dramatically during the last decade. Most of these pro-<br>tein kinases appear to belong to a common superfamily<br>of enzymes that share similarities in their catalytic do-<br> dramatically during the last decade. Most of these pro-<br>tein kinases appear to belong to a common superfamily<br>of enzymes that share similarities in their catalytic do-<br>mains (Hanks et al., 1988). Neuronal tissues represent tein kinases appear to belong to a common superfamily<br>of enzymes that share similarities in their catalytic do-<br>mains (Hanks et al., 1988). Neuronal tissues represent a<br>particularly abundant source for such enzymes (Nairn of enzymes that share similarities in their catalytic domains (Hanks et al., 1988). Neuronal tissues represent a particularly abundant source for such enzymes (Nairn et al., 1985b; Walaas and Greengard, 1987). The properti particularly abundant source for such enzymes (Nairn et al., 1985b; Walaas and Greengard, 1987). The properties of those protein kinases in the mammalian brain that have been examined are generally similar to the propertie particularly abundant source for such enzymes (Nairn et subunits, have primary structures similar to those sur-<br>al., 1985b; Walaas and Greengard, 1987). The properties rounding the authentic phosphorylation sites in the<br>of have been examined are generally similar to the properties of the corresponding nonneuronal enzymes. Certain differences exist, however, between brain and nonneuronal tissues, particularly with respect to the relative conc of those protein kinases in the mammalian brain that P<br>have been examined are generally similar to the proper-<br>ties of the corresponding nonneuronal enzymes. Certain<br>differences exist, however, between brain and nonneu-<br>ro have been examined are generally similar to the properties of the corresponding nonneuronal enzymes. Certain differences exist, however, between brain and nonneuronal tissues, particularly with respect to the relative conc ties of the corresponding nonneuronal enzymes. Certain<br>differences exist, however, between brain and nonneu-<br>ronal tissues, particularly with respect to the relative<br>concentrations and cellular and subcellular distribution differences exist, however, between brain and nonneu-<br>ronal tissues, particularly with respect to the relative<br>moncentrations and cellular and subcellular distributions<br>of some of the enzymes (Walter and Greengard, 1981; t ronal tissues, particularly with respect to the relative m<br>concentrations and cellular and subcellular distributions qu<br>of some of the enzymes (Walter and Greengard, 1981; th<br>Nairn et al., 1985b). In this section, we will concentrations and cellular and subcellular distributions quare of some of the enzymes (Walter and Greengard, 1981; the Nairn et al., 1985b). In this section, we will briefly describe some properties and, if known, some de of some of the enzymes (Walter and Greengard, 1981; the Nairn et al., 1985b). In this section, we will briefly<br>describe some properties and, if known, some defined tein<br>functions of some of the well-characterized brain pro Nairn et al., 1985b). In this section, we will briefly describe some properties and, if known, some defined functions of some of the well-characterized brain protein kinases, with particular emphasis being placed on the se

## *Kinases*

Most members of the protein kinase family appear to contain catalytic domains that have approximately 30 conserved in both unicellular and multicellular orga-Most members of the protein kinase family appear t<br>contain catalytic domains that have approximately 30<br>to 32-kDa molecular masses and that are relatively we<br>conserved in both unicellular and multicellular orga-<br>nisms (Han Most members of the protein kinase family appear to<br>contain catalytic domains that have approximately 30-<br>to 32-kDa molecular masses and that are relatively well<br>conserved in both unicellular and multicellular orga-<br>nisms contain catalytic domains that have approximately 30-<br>to 32-kDa molecular masses and that are relatively well<br>conserved in both unicellular and multicellular orga-<br>nisms (Hanks et al., 1988). The regulation of these<br>cataly to 32-kDa molecular masses and that are relatively well conserved in both unicellular and multicellular organisms (Hanks et al., 1988). The regulation of these catalytic activities, which display different protein substrat conserved in both unicellular and multicellular organisms (Hanks et al., 1988). The regulation of these catalytic activities, which display different protein substrate specificities, appears to be achieved in different way nisms (Hanks et al., 1988). The regulation of these catalytic activities, which display different protein substrate specificities, appears to be achieved in different ways by distinct groups of protein kinases. Recent stud catalytic activities, which display different protein substrate specificities, appears to be achieved in different ways by distinct groups of protein kinases. Recent studies have led to a general model of the mechanism und strate specificities, appears to be achieved in different<br>ways by distinct groups of protein kinases. Recent studies<br>have led to a general model of the mechanism underlying<br>such regulation, the present consensus being that ways by distinct groups of protein kinases. Recent studies<br>have led to a general model of the mechanism underlying<br>such regulation, the present consensus being that most<br>protein kinases have latent catalytic activities and have led to a general model of the mechanism underlying<br>such regulation, the present consensus being that most<br>protein kinases have latent catalytic activities and that<br>removal of inhibitory constraints can induce activati such regulation, the present consensus being that most<br>protein kinases have latent catalytic activities and that<br>removal of inhibitory constraints can induce activation<br>of the enzymes. A number of the most thoroughly studi protein kinases have latent catalytic activities and that<br>removal of inhibitory constraints can induce activation<br>of the enzymes. A number of the most thoroughly studied<br>protein kinases have been found to contain pseudosub removal of inhibitory constraints can induce activation<br>of the enzymes. A number of the most thoroughly studied<br>protein kinases have been found to contain pseudosub-<br>strate "prototopes" within their regulatory domains (for of the enzymes. A number of the most thoroughly studied<br>protein kinases have been found to contain pseudosub-<br>strate "prototopes" within their regulatory domains (for<br>reviews, see Kemp et al., 1989; Soderling, 1990). These strate "prototopes" within their regulatory domains (for reviews, see Kemp et al., 1989; Soderling, 1990). These prototopes, which may be located either on the same reviews, see Kemp et al., 1989; Soderling, 1990). These reviews, see Kemp et al., 1989; Soderling, 1990). These<br>prototopes, which may be located either on the same<br>polypeptides as the catalytic domains or on distinct R<br>subunits, have primary structures similar to those sur-<br>rou prototopes, which may be located either on the same<br>polypeptides as the catalytic domains or on distinct R<br>subunits, have primary structures similar to those sur-<br>rounding the authentic phosphorylation sites in the<br>physiol polypeptides as the catalytic domains or on distinct<br>subunits, have primary structures similar to those su<br>rounding the authentic phosphorylation sites in t<br>physiological substrates (Kemp and Pearson, 1990). T<br>prototope do subunits, have primary structures similar to those sur-<br>rounding the authentic phosphorylation sites in the<br>physiological substrates (Kemp and Pearson, 1990). The<br>prototope domains may, therefore, under basal condi-<br>tions, rounding the authentic phosphorylation sites in the<br>physiological substrates (Kemp and Pearson, 1990). The<br>prototope domains may, therefore, under basal condi-<br>tions, be tightly bound to catalytic domains within the<br>kinase physiological substrates (Kemp and Pearson, 1990). The<br>prototope domains may, therefore, under basal condi-<br>tions, be tightly bound to catalytic domains within the<br>kinase. Activation of such enzymes is achieved through<br>mec tions, be tightly bound to catalytic domains within<br>kinase. Activation of such enzymes is achieved thr<br>mechanisms that release these pseudosubstrate<br>quences and thereby allow substrate proteins acce<br>the enzymes (Kemp et al nase. Activation of such enzymes is achieved through<br>echanisms that release these pseudosubstrate se-<br>ences and thereby allow substrate proteins access to<br>e enzymes (Kemp et al., 1989; Soderling, 1990).<br>Three physiological

mechanisms that release these pseudosubstrate sequences and thereby allow substrate proteins access to the enzymes (Kemp et al., 1989; Soderling, 1990). Three physiological mechanisms that can activate protein kinases, eit quences and thereby allow substrate proteins access to<br>the enzymes (Kemp et al., 1989; Soderling, 1990).<br>Three physiological mechanisms that can activate pro-<br>tein kinases, either singly or working in concert, have<br>thus fa the enzymes (Kemp et al., 1989; Soderling, 1990).<br>Three physiological mechanisms that can activate pro-<br>tein kinases, either singly or working in concert, have<br>thus far been defined in mammalian brain: second mes-<br>senger g Three physiological mechanisms that can activate protein kinases, either singly or working in concert, have thus far been defined in mammalian brain: second messenger generation, enzyme autophosphorylation, and direct bind



PHARMACOLOGICAL REVIEW

PROTEIN PHOSPHORYLA<br>
complex. Activation through second messenger genera-<br>
tion is the best studied of these mechanisms in bra PROTEIN PHOSPHORYLATION AN<br>complex. Activation through second messenger genera-<br>tion is the best studied of these mechanisms in brain are<br>pretissue. mplex. Activation through second messenger genera-<br>
in is the best studied of these mechanisms in brain are<br>
sue.<br>
1. Activation by second messengers. Brain cells use me<br>
veral mechanisms for generating second messengers.

complex. Activation through second messenger generation is the best studied of these mechanisms in brain<br>tissue.<br>1. Activation by second messengers. Brain cells use<br>several mechanisms for generating second messengers<br>These tissue.<br>
I. Activation by second messengers. Brain cells use<br>
I. Activation by second messengers. Brain cells use<br>
several mechanisms for generating second messengers.<br>
These include neurotransmitter receptors which activa tissue.<br>
1. Activation by second messengers. Brain cells use<br>
several mechanisms for generating second messengers.<br>
These include neurotransmitter receptors which activate<br>
or inhibit adenylyl cyclase and guanylyl cyclase 1. Activation by second messengers. Brain cells use<br>several mechanisms for generating second messengers.<br>These include neurotransmitter receptors which activate<br>or inhibit adenylyl cyclase and guanylyl cyclase and alter<br>th several mechanisms for generating second messengers.<br>These include neurotransmitter receptors which activate<br>or inhibit adenylyl cyclase and guanylyl cyclase and alter<br>the synthesis of cyclic AMP and cyclic GMP, respective These include neurotransmitter receptors which activate<br>or inhibit adenylyl cyclase and guanylyl cyclase and alter<br>the synthesis of cyclic AMP and cyclic GMP, respectively<br>(for reviews, see Daly, 1977; Ferrendelli, 1978; B the synthesis of cyclic AMP and cyclic GMP, respectively<br>(for reviews, see Daly, 1977; Ferrendelli, 1978; Bockaert,<br>1981; Birnbaumer and Iyengar, 1982; Drummond, 1983)<br>(table 3). Other neurotransmitter receptors appear co the synthesis of cyclic AMP and cyclic GMP, respectively 2. Activation by autophosphorylation. Another impor-<br>(for reviews, see Daly, 1977; Ferrendelli, 1978; Bockaert, tant mechanism used for regulation of protein kinase (for reviews, see Daly, 1977; Ferrendelli, 1978; Bot 1981; Birnbaumer and Iyengar, 1982; Drummond (table 3). Other neurotransmitter receptors appeared to activation or inhibition of phospholipase C, generates IP<sub>3</sub> and di 1981; Birnbaumer and Iyengar, 1982; Drummond, 1983)<br>(table 3). Other neurotransmitter receptors appear cou-<br>pled to activation or inhibition of phospholipase C, which<br>generates  $IP_3$  and diacylglycerol from phosphatidylin (table 3). Other neurotransmitter receptors appear coupled to activation or inhibition of phospholipase C, which generates  $IP_3$  and diacylglycerol from phosphatidylino-<br>sitol-4,5-bisphosphate (Brown et al., 1984; Berridg pled to activation or inhibition of phospholipase C, which<br>generates IP<sub>3</sub> and diacylglycerol from phosphatidylino-<br>sitol-4,5-bisphosphate (Brown et al., 1984; Berridge,<br>1984, 1987; Berridge and Irvine, 1989; Downes, 1982, generates IP<sub>3</sub> and diacylglycerol from phosphatidyline sitol-4,5-bisphosphate (Brown et al., 1984; Berridge 1984, 1987; Berridge and Irvine, 1989; Downes, 198<br>1988; Fisher and Agranoff, 1987). IP<sub>3</sub> as an intracellula me sitol-4,5-bisphosphate (Brown et al., 1984; Berridge, 6<br>1984, 1987; Berridge and Irvine, 1989; Downes, 1982, 6<br>1988; Fisher and Agranoff, 1987). IP<sub>3</sub> as an intracellular consenger appears to regulate release of  $Ca^{2+}$  f 1984, 1987; Berridge and Irvine, 1989; Downes, 1982, 1988; Fisher and Agranoff, 1987). IP<sub>3</sub> as an intracellular messenger appears to regulate release of  $Ca^{2+}$  from intracellular stores (for examples, see Berridge, 1987 1988; Fisher and Agranoff, 1987). IP<sub>3</sub> as an intracellular messenger appears to regulate release of  $Ca^{2+}$  from intracellular stores (for examples, see Berridge, 1987; Berridge and Irvine, 1989). Still other neurotransm messenger appears to regulate release of  $Ca^{2+}$  from intra-<br>cellular stores (for examples, see Berridge, 1987; Berridge<br>and Irvine, 1989). Still other neurotransmitter receptors<br>are coupled to the influx of  $Ca^{2+}$ , thro and Irvine, 1989). Still other neurotransmitter receptors<br>are coupled to the influx of  $Ca^{2+}$ , through ligand-operated<br>channels (Reuter, 1983; Miller, 1987; Hess, 1990). An-<br>other signal transduction system appears to in are coupled to the influx of  $Ca^{2+}$ , through ligand-operated gawa, 1989), all of which are enriched in brain. These<br>channels (Reuter, 1983; Miller, 1987; Hess, 1990). An-<br>other signal transduction system appears to invol are coupled to the influx of  $Ca^{2+}$ , through ligand-operated<br>channels (Reuter, 1983; Miller, 1987; Hess, 1990). An-<br>other signal transduction system appears to involve re-<br>ceptors coupled to the activation of phospholipa channels (Reuter, 1983; Miller, 1987; Hess, 1990). Another signal transduction system appears to involve receptors coupled to the activation of phospholipase A<sub>2</sub>, which generates arachidonic acid and metabolites thereof f other signal transduction system appears to involve receptors coupled to the activation of phospholipase A<sub>2</sub>, which generates arachidonic acid and metabolites thereof from phospholipids (Burch, 1989; Burch et al., 1986; P ceptors coupled to the activation of phospholipase  $A_2$ , which generates arachidonic acid and metabolites thereof from phospholipids (Burch, 1989; Burch et al., 1986; Piomelli et al., 1987; Shimizu and Wolfe, 1990). Fina which generates arachidonic acid and metabolites thereof from phospholipids (Burch, 1989; Burch et al., 1986; z<br>Piomelli et al., 1987; Shimizu and Wolfe, 1990). Finally, s<br>the nerve impulse itself is involved in signal tr from phospholipids (Burch, 1989; Burch et al., 1986; zy<br>Piomelli et al., 1987; Shimizu and Wolfe, 1990). Finally, su<br>the nerve impulse itself is involved in signal transduction th<br>via  $Ca^{2+}$  influx through voltage-sensit Piomelli et al., 1987; Shimizu and Wolfe, 1990). Finally, such the nerve impulse itself is involved in signal transduction the via  $Ca^{2+}$  influx through voltage-sensitive channels (for reviews, see Augustine et al., 1987 reviews, see Augustine et al., 1987; Hess, 1990). Strong  $F$ irst messenger messenger and messenger and *first messenger and first and the effects* of





Atrial natriuretic factor († 1990)<br>
The table includes major groups of first messengers reported to<br>
<sup>4</sup> The table includes major groups of first messengers reported to<br>
change levels of second messengers in preparations c **Felder et al. (1989), Mahan et al. (1997), Drummond (1983), Fisher and Agranoff (1987), Tremblay et al. (1988), Burch (1989), Felder et al. (1989), Mahan et al. (1990). Shimizu and Wolfe (1990). Abbreviations: DAG, diacyl** lites **thereof.**

the compounds generated by these various mechanisms are achieved through direct or indirect regulation of AND NEURONAL FUNCTION 303<br>the compounds generated by these various mechanisms<br>are achieved through direct or indirect regulation of<br>protein phosphorylation systems, particularly the second AND NEURONAL FUNCTION 303<br>the compounds generated by these various mechanisms<br>are achieved through direct or indirect regulation of<br>protein phosphorylation systems, particularly the second<br>messenger-dependent protein kinas the compounds generated by these various mechanisms<br>are achieved through direct or indirect regulation of<br>protein phosphorylation systems, particularly the second<br>messenger-dependent protein kinases (table 4). These<br>enzyme the compounds generated by these various mechanisms<br>are achieved through direct or indirect regulation of<br>protein phosphorylation systems, particularly the second<br>messenger-dependent protein kinases (table 4). These<br>enzyme are achieved through direct or indirect regulation of<br>protein phosphorylation systems, particularly the second<br>messenger-dependent protein kinases (table 4). These<br>enzymes are activated by binding of the intracellular<br>mess protein phosphorylation systems, particula<br>messenger-dependent protein kinases (to<br>enzymes are activated by binding of th<br>messengers to distinct sites on the eithereby undergo conformational changes.<br>2. Activation by autop Processenger-dependent protein kinases (table 4). The zymes are activated by binding of the intracelluses<br>essengers to distinct sites on the enzymes whisereby undergo conformational changes.<br>2. Activation by autophosphoryl

enzymes are activated by binding of the intracellular<br>messengers to distinct sites on the enzymes which<br>thereby undergo conformational changes.<br>2. Activation by autophosphorylation. Another impor-<br>tant mechanism used for r messengers to distinct sites on the enzymes which<br>thereby undergo conformational changes.<br>2. Activation by autophosphorylation. Another impor-<br>tant mechanism used for regulation of protein kinase<br>activity is intramolecular thereby undergo conformational changes.<br>
2. Activation by autophosphorylation. Another important mechanism used for regulation of protein kinase<br>
activity is intramolecular autophosphorylation. The ma-<br>
jority of the prote 2. Activation by autophosphorylation. Another important mechanism used for regulation of protein kinase activity is intramolecular autophosphorylation. The majority of the protein kinases that have been studied contain aut tant mechanism used for regulation of protein kinase<br>activity is intramolecular autophosphorylation. The ma-<br>jority of the protein kinases that have been studied<br>contain autophosphorylation sites, the phosphorylation<br>of wh activity is intramolecular autophosphorylation. The majority of the protein kinases that have been studied contain autophosphorylation sites, the phosphorylation of which may profoundly change the activity of the enzyme in jority of the protein kinases that have been studies contain autophosphorylation sites, the phosphorylation of which may profoundly change the activity of the enzyme in question (for a recent review, see Blacksheet al., 19 contain autophosphorylation sites, the phosphorylation<br>of which may profoundly change the activity of the<br>enzyme in question (for a recent review, see Blackshear<br>et al., 1988). Well-known examples include cyclic AMP-<br>depen of which may profoundly change the activity of then zyme in question (for a recent review, see Blackshea<br>et al., 1988). Well-known examples include cyclic AMP<br>dependent protein kinase type II (Rubin and Roser<br>1975), CaM ki enzyme in question (for a recent review, see Blackshear<br>et al., 1988). Well-known examples include cyclic AMP-<br>dependent protein kinase type II (Rubin and Rosen,<br>1975), CaM kinase II (Lai et al., 1986; Miller and Ken-<br>nedy et al., 1988). Well-known examples include cyclic AM<br>dependent protein kinase type II (Rubin and Rose<br>1975), CaM kinase II (Lai et al., 1986; Miller and Ke<br>nedy, 1986; Lou et al., 1986; Schworer et al., 1986), a<br>the protoo dependent protein kinase type II (Rubin and Rosen, 1975), CaM kinase II (Lai et al., 1986; Miller and Kennedy, 1986; Lou et al., 1986; Schworer et al., 1986), and the protooncogene product pp60<sup>c-erc</sup> (Okada and Nakagawa, 1975), CaM kinase II (Lai et al., 1986; Miller and nedy, 1986; Lou et al., 1986; Schworer et al., 1986<br>the protooncogene product pp60<sup>c-src</sup> (Okada and I gawa, 1989), all of which are enriched in brain.<br>enzymes will be di dy, 1986; Lou et al., 1986; Schworer et al., 1986), and<br>e protooncogene product pp60<sup>c-src</sup> (Okada and Naka-<br>wa, 1989), all of which are enriched in brain. These<br>zymes will be discussed in greater detail below.<br>3. Activati

the protooncogene product  $pp60^{c-nc}$  (Okada and Naka-<br>gawa, 1989), all of which are enriched in brain. These<br>enzymes will be discussed in greater detail below.<br>3. Activation by ligand binding. A third important<br>mechanism gawa, 1989), all of which are enriched in brain. These enzymes will be discussed in greater detail below.<br>3. Activation by ligand binding. A third important mechanism for protein kinase activation is used by a group of rec enzymes will be discussed in greater detail below.<br>3. Activation by ligand binding. A third important<br>mechanism for protein kinase activation is used by a<br>group of receptor-associated protein kinases. These en-<br>zymes, most 3. Activation by ligand binding. A third important<br>mechanism for protein kinase activation is used by a<br>group of receptor-associated protein kinases. These en-<br>zymes, most of which appear to phosphorylate their<br>substrate p group of receptor-associated protein kinases. These en-<br>zymes, most of which appear to phosphorylate their<br>substrate proteins on tyrosine residues rather than on<br>the more commonly phosphorylated serine or threonine<br>residue zymes, most of which appear to phosphorylate their zymes, most of which appear to phosphorylate their<br>substrate proteins on tyrosine residues rather than on<br>the more commonly phosphorylated serine or threonine<br>residues, are often associated with receptors for various<br>growt substrate proteins on tyrosine residues rather than on<br>the more commonly phosphorylated serine or threonine<br>residues, are often associated with receptors for various<br>growth factors, hormones, and mitogens. Well-known<br>examp the more commonly phosphorylated serine or threonine<br>residues, are often associated with receptors for various<br>growth factors, hormones, and mitogens. Well-known<br>examples include the epidermal and platelet-derived<br>growth f residues, are often associated with receptors for various<br>growth factors, hormones, and mitogens. Well-known<br>examples include the epidermal and platelet-derived<br>growth factor receptors, the insulin receptor, and the<br>recept complement protein and 1986; Schworer et al., 1986; Miller and Rosen, 1975), CaM kinase II (Lai et al., 1986; Miller and Kenney, 1986; Move te al., 1986; Miller and Kenney, 1986; Move te al., 1986; Schworer et al., 1986; M examples include the epidermal and platelet-derived<br>growth factor receptors, the insulin receptor, and the<br>receptor for insulin-like growth factor-1 (somatomedin<br>C) (for reviews, see Cobb and Rosen, 1983; Yarden and<br>Ullric growth factor receptors, the insulin receptor, and t<br>receptor for insulin-like growth factor-1 (somatomed<br>C) (for reviews, see Cobb and Rosen, 1983; Yarden a<br>Ullrich, 1988; Carpenter and Cohen, 1990). In the<br>cases, binding receptor for insulin-like growth factor-1 (somatomedin C) (for reviews, see Cobb and Rosen, 1983; Yarden and Ullrich, 1988; Carpenter and Cohen, 1990). In these cases, binding of the extracellular messenger to its receptor C) (for reviews, see Cobb and Rosen, 1983; Yarden and Ullrich, 1988; Carpenter and Cohen, 1990). In these cases, binding of the extracellular messenger to its receptor appears to directly activate the protein kinase, which cases, binding of the extracellular messenger to its receptor appears to directly activate the protein kinase, which often is an integral part of the receptor itself, without any intervening second messenger generation. In cases, binding of the extracellular messenger to its receptor appears to directly activate the protein kinase, which often is an integral part of the receptor itself, without any intervening second messenger generation. In tor appears to directly activate the protein kinase, which<br>often is an integral part of the receptor itself, without<br>any intervening second messenger generation. In other<br>cases, such tyrosine-specific protein kinases may b often is an integral part of the receptor itself, without<br>any intervening second messenger generation. In other<br>cases, such tyrosine-specific protein kinases may be dis-<br>tinct from the receptors themselves, although they o any intervening second messenger generation. In othe cases, such tyrosine-specific protein kinases may be different from the receptors themselves, although they ofte are associated with membranes and functionally linke to cases, such tyrosine-specific protein kinases may be distinct from the receptors themselves, although they often are associated with membranes and functionally linked<br>to membrane receptors through unknown mechanisms.<br>Examp tinct from the receptors themselves, although they often are associated with membranes and functionally linked to membrane receptors through unknown mechanisms.<br>Examples include the tyrosine protein kinase present in *Torp* are associated with membranes and functionally linked<br>to membrane receptors through unknown mechanisms.<br>Examples include the tyrosine protein kinase present in<br>Torpedo electroplax, which is capable of phosphorylating<br>the n to membrane receptors through unknown mechanisms.<br>Examples include the tyrosine protein kinase present in<br>Torpedo electroplax, which is capable of phosphorylating<br>the nicotinic acetylcholine receptor (Huganir et al.,<br>1984 Examples include the tyrosine protein kinase present in<br>Torpedo electroplax, which is capable of phosphorylating<br>the nicotinic acetylcholine receptor (Huganir et al.,<br>1984), and the recently described protein kinase pp56<sup></sup> Torpedo electroplax, which is capable of phosphorylating<br>the nicotinic acetylcholine receptor (Huganir et al.,<br>1984), and the recently described protein kinase pp56<sup>kk</sup><br>present in lymphocytes which appears to be activated the nicotinic acetylcholine receptor (Huganir et al., 1984), and the recently described protein kinase pp56<sup>kk</sup> present in lymphocytes which appears to be activated by the CD4 or CD8 transmembrane complexes and which can 1984), and the recently described protein kinase<br>present in lymphocytes which appears to be active<br>the CD4 or CD8 transmembrane complexes and<br>can phosphorylate the antigen receptors in T-ly<br>cytes (Barber et al., 1989; Veil *B. Second Messenger-regulated Protein kinases*<br>*B. Second Messenger-regulated Protein Kinases*<br>*B. Second Messenger-regulated Protein Kinases*<br>*1. Cyclic nucleotide-dependent protein kinases. Mam-1. Cyclic nucleotide-dependent protein Kinases*<br>*1. Cyclic nucleotide-dependent protein Kinases.*<br>*1. Cyclic nucleotide-dependent protein kinases.* Mam-<br>malian brain contains two distinct subclasses of cyclic

mucleotide-dependent protein kinase activities, namely, nucleotide-dependent protein Kinases<br>1. Cyclic nucleotide-dependent protein kinases. Mam-<br>malian brain contains two distinct subclasses of cyclic<br>nucleotide-dependent protein kinase activities, namely,<br>cyclic AMP-dependent B. Second Messenger-regulated Protein Kinases<br>1. Cyclic nucleotide-dependent protein kinases. Mam-<br>malian brain contains two distinct subclasses of cyclic<br>nucleotide-dependent protein kinase activities, namely,<br>cyclic AMP-1. Cyclic nucleotide-dependent protein kinases. Mammalian brain contains two distinct subclasses of cyclic nucleotide-dependent protein kinase activities, namely, cyclic AMP-dependent and cyclic GMP-dependent protein kinas

**a**spet





ITP<br>
\* Table includes second messenger-regulated protein kinases which have<br>
processes in intact neural cells.<br>
intracellular "receptor" proteins for cyclic AMP and and<br>
cyclic GMP, respectively, in eukaryotic cells (for r \* Table includes second messenger-regulated protein kinases which<br>processes in intact neural cells.<br>intracellular "receptor" proteins for cyclic AMP and<br>cyclic GMP, respectively, in eukaryotic cells (for reviews,<br>see Nimmo processes in intact neural cells.<br>intracellular "receptor" proteins for cyclic AMP and<br>cyclic GMP, respectively, in eukaryotic cells (for reviews<br>see Nimmo and Cohen, 1977; Walter and Greengard<br>1981; Døskeland and Øgreid, intracellular "receptor" proteins for cyclic AMP and<br>cyclic GMP, respectively, in eukaryotic cells (for reviews,<br>see Nimmo and Cohen, 1977; Walter and Greengard,<br>1981; Døskeland and Øgreid, 1981; Lincoln and Corbin,<br>1983). intracellular "receptor" proteins for cyclic AMP and<br>cyclic GMP, respectively, in eukaryotic cells (for reviews,<br>see Nimmo and Cohen, 1977; Walter and Greengard,<br>1981; Døskeland and Øgreid, 1981; Lincoln and Corbin,<br>1983). cyclic GMP, respectively, in eukaryotic cells (for review<br>see Nimmo and Cohen, 1977; Walter and Greengal<br>1981; Døskeland and Øgreid, 1981; Lincoln and Corbi<br>1983). Some structural homologies between these e<br>zymes exist (Co see Nimmo and Cohen, 1977; Walter and Greengard 1981; Døskeland and Øgreid, 1981; Lincoln and Corbir 1983). Some structural homologies between these en zymes exist (Corbin and Lincoln, 1978), but the differences in substra 1983). Some structural homologies between these en-<br>zymes exist (Corbin and Lincoln, 1978), but the differ-<br>ences in substrate specificities, activation mechanisms,<br>quaternary structures, immunological cross-reactivities,<br> 1983). Some structural homologies between these en-<br>zymes exist (Corbin and Lincoln, 1978), but the differ-<br>ences in substrate specificities, activation mechanisms,<br>quaternary structures, immunological cross-reactivities,<br> zymes exist (Corbin and Lincoln, 1978), but the differ-<br>ences in substrate specificities, activation mechanisms, C s<br>quaternary structures, immunological cross-reactivities, cata<br>and tissue distributions indicate that they ences in substrate specificities, activation mechanisms,<br>quaternary structures, immunological cross-reactivities,<br>and tissue distributions indicate that they have distinct<br>physiological roles (Walter et al., 1980; Walter a

and tissue distributions indicate that they have distinct<br>physiological roles (Walter et al., 1980; Walter and<br>Greengard, 1981; Nairn et al., 1985b).<br>a. CYCLIC AMP-DEPENDENT PROTEIN KINASE. This en-<br>zyme, first described b physiological roles (Walter et al., 1980; Walter and Uh<br>Greengard, 1981; Nairn et al., 1985b). of<br>a. CYCLIC AMP-DEPENDENT PROTEIN KINASE. This en-<br>zyme, first described by Walsh et al. (1968), is present the<br>in a number of Greengard, 1981; Nairn et al., 1985b). of<br>a. CYCLIC AMP-DEPENDENT PROTEIN KINASE. This en-<br>zyme, first described by Walsh et al. (1968), is present the<br>in a number of isoforms (Cadd and McKnight, 1989) and us<br>is highly enr a. CYCLIC AMP-DEPENDENT PROTEIN KINASE. This en-<br>zyme, first described by Walsh et al. (1968), is present the<br>in a number of isoforms (Cadd and McKnight, 1989) and<br>is highly enriched in brain (Miyamoto et al., 1969; Nairn in a number of isoforms (Cadd and McKnight, 1989) and usually reproductive tissues (Cadd and McKnight, 1989).<br>
is highly enriched in brain (Miyamoto et al., 1969; Nairn Such differences may reflect adaptions of the isoenzy in a number of isoforms (Cadd and McKnight, 1989) and<br>is highly enriched in brain (Miyamoto et al., 1969; Nairn S<br>et al., 1985b). The main properties of the brain enzyme for<br>are identical with those of the enzyme prepared is highly enriched in brain (Miyamoto et al., 1969; Nairn<br>et al., 1985b). The main properties of the brain enzyme<br>are identical with those of the enzyme prepared from<br>peripheral tissues. It exists as a tetramer composed of et al., 1985b). The main properties of the brain enzyme for<br>are identical with those of the enzyme prepared from<br>peripheral tissues. It exists as a tetramer composed of for<br>two R subunits (49 to 55 kDa apparent molecular m are identical with those of the enzyme prepared from<br>peripheral tissues. It exists as a tetramer composed of f<br>two R subunits (49 to 55 kDa apparent molecular masses) a<br>joined by a disulfide bond and two C subunits (40 kD peripheral tissues. It exists as a tetramer composed of f<br>two R subunits (49 to 55 kDa apparent molecular masses)<br>joined by a disulfide bond and two C subunits (40 kDa<br>is apparent molecular mass), all of which, in the abse two R subunits (49 to 55 kDa apparent molecular masses)<br>joined by a disulfide bond and two C subunits (40 kDa<br>apparent molecular mass), all of which, in the absence<br>of cyclic AMP, bind together to produce an inactive<br>compl ned by a disulfide bond and two C subunits (40<br>parent molecular mass), all of which, in the ab-<br>cyclic AMP, bind together to produce an ina-<br>mplex (for examples, see Nimmo and Cohen, 197<br>The two main isozymic forms of cycl apparent molecular mass), all of which, in the absence<br>of cyclic AMP, bind together to produce an inactive<br>complex (for examples, see Nimmo and Cohen, 1977).<br>The two main isozymic forms of cyclic AMP-depend-<br>ent protein ki

1971), and present in most tissues, contain different protein kinase originally described (Reimann et al., inclusionally studies showing that *type I* contained RII subunits, with early studies showing that *type I* contai ent protein kinase originally described (Reimann et al., 1971), and present in most tissues, contain different R subunits, with early studies showing that *type I* contained RI subunits (49 kDa) and *type II* contained RI 1971), and present in most tissues, contain different R<br>subunits, with early studies showing that *type I* contained<br>RI subunits (49 kDa) and *type II* contained RII subunits<br>(51 to 55 kDa) (Hofmann et al., 1975; Nimmo an subunits, with early studies showing that type I contained<br>RI subunits (49 kDa) and type II contained RII subunits<br>(51 to 55 kDa) (Hofmann et al., 1975; Nimmo and Cohen,<br>1977). Further studies, in which molecular genetic a (31 to 36 kDa) (From and et al., 1975, Nimmo and Conen,<br>1977). Further studies, in which molecular genetic ap-<br>proaches were used, have shown that there are multiple<br>forms of RI, RII and C, which have distinct properties<br>a

Hu et al., 1987<br>ave been shown to mediate or modulate major classes of functional<br>and complementary DNA libraries have been found to<br>encode distinct forms of RI, designated  $RI$ - $\alpha$  and  $RI$ - $\beta$ and complementary DNA libraries have been found to encode distinct forms of RI, designated RI- $\alpha$  and RI- $\beta$ <br>(Kuno et al., 1987; Clegg et al., 1988). Moreover, two and complementary DNA libraries have been found to encode distinct forms of RI, designated RI- $\alpha$  and RI- $\beta$  (Kuno et al., 1987; Clegg et al., 1988). Moreover, two forms of RII, designated RII- $\alpha$  and RII- $\beta$ , have be and complementary DNA libraries have been found to<br>encode distinct forms of RI, designated RI- $\alpha$  and RI- $\beta$ <br>(Kuno et al., 1987; Clegg et al., 1988). Moreover, two<br>forms of RII, designated RII- $\alpha$  and RII- $\beta$ , have be encode distinct forms of  $\kappa$ 1, designated  $\kappa$ 1- $\alpha$  and  $\kappa$ 1- $\rho$ <br>(Kuno et al., 1987; Clegg et al., 1988). Moreover, two<br>forms of RII, designated RII- $\alpha$  and RII- $\beta$ , have been<br>distinguished as products of separat forms of RII, designated RII- $\alpha$  and RII- $\beta$ , have been distinguished as products of separate genes (Jahnsen et al., 1986; Scott et al., 1987). Similarly, two forms of the C subunit, designated C- $\alpha$  and C- $\beta$ , which distinguished as products of separate genes (Jahnsen et al., 1986; Scott et al., 1987). Similarly, two forms of the C subunit, designated C- $\alpha$  and C- $\beta$ , which appear to be catalytically similar but are encoded by dist al., 1986; Scott et al., 1987). Similarly, two forms of the C subunit, designated C- $\alpha$  and C- $\beta$ , which appear to be catalytically similar but are encoded by distinct genes, also exist (Uhler et al., 1986; Showers and C subunit, designated C- $\alpha$  and C- $\beta$ , which appear to be catalytically similar but are encoded by distinct genes, also exist (Uhler et al., 1986; Showers and Maurer, 1986; Uhler and McKnight, 1987; Adavani et al., 1987 catalytically similar but are encoded by district genes,<br>also exist (Uhler et al., 1986; Showers and Maurer, 1986;<br>Uhler and McKnight, 1987; Adavani et al., 1987). In each<br>of these cases, the  $\alpha$ -forms of the different s also exist (Uhler et al., 1986; Showers and Maurer, 1986; Uhler and McKnight, 1987; Adavani et al., 1987). In each of these cases, the  $\alpha$ -forms of the different subunits appear to have a widespread tissue distribution, Uhler and McKnight, 1987; Adavani et al., 1987). In each<br>of these cases, the  $\alpha$ -forms of the different subunits<br>appear to have a widespread tissue distribution, whereas<br>the  $\beta$ -forms are restricted to brain and a few o of these cases, the  $\alpha$ -forms of the different subunits appear to have a widespread tissue distribution, whereas the  $\beta$ -forms are restricted to brain and a few other, usually reproductive tissues (Cadd and McKnight, 19  $\alpha$  is a set of the set of the  $\beta$ -forms are restricted to brain and a usually reproductive tissues (Cadd and McKn Such differences may reflect adaptions of the for specific neuronal functions or localization i. Regulat e β-forms are restricted to brain and a few other,<br>ually reproductive tissues (Cadd and McKnight, 1989).<br>ch differences may reflect adaptions of the isoenzymes<br>specific neuronal functions or localizations.<br>**i. Regulation** 

usually reproductive tissues (Cadd and McKnight, 1989).<br>Such differences may reflect adaptions of the isoenzymes<br>for specific neuronal functions or localizations.<br>**i. Regulation of activity.** The general mechanism<br>for regu Such differences may reflect adaptions of the isoenzymes<br>for specific neuronal functions or localizations.<br> **i. Regulation of activity.** The general mechanism<br>
for regulation of cyclic AMP-dependent protein kinase<br>
activit for specific neuronal functions or localizations.<br> **i. Regulation of activity.** The general mechan<br>
for regulation of cyclic AMP-dependent protein kin<br>
activity in brain appears to be similar to that descr<br>
in peripheral t I. Regulation of activity. The general mechanism<br>for regulation of cyclic AMP-dependent protein kinase<br>activity in brain appears to be similar to that described<br>in peripheral tissues. Adenylyl cyclase, the membrane-<br>bound for regulation of cyclic AMP-dependent protein kinase<br>activity in brain appears to be similar to that described<br>in peripheral tissues. Adenylyl cyclase, the membrane-<br>bound enzyme that catalyzes the formation of cyclic<br>AMP in peripheral tissues. Adenylyl cyclase, the membrane-<br>bound enzyme that catalyzes the formation of cyclic<br>AMP, is controlled by receptor-regulated stimulation or<br>inhibition through GTP-binding proteins (for examples,<br>see bound enzyme that catalyzes the formation of cyclic AMP, is controlled by receptor-regulated stimulation or inhibition through GTP-binding proteins (for examples, see Rodbell, 1980; Gilman, 1987) and, in some tissues, inc minotion through OT1-binding proteins (to examples, see Rodbell, 1980; Gilman, 1987) and, in some tissues, including the brain, also by  $Ca^{2+}/calmodulin$  (Brostrom et al., 1977; Coussen et al., 1985; Rosenberg and Storm, 1987; et al., 1977; Coussen et al., 1985; Rosenberg and Storm, 1987; Eliot et al., 1989). Each R subunit of the cyclic AMP -dependent protein kinase has two binding sites for cyclic AMP and exhibits cooperative binding of the nu 1987; Eliot et al., 1989). Each R subunit of the cyclic AMP-dependent protein kinase has two binding sites for cyclic AMP and exhibits cooperative binding of the nucleotide (for examples, see  $\mathcal{O}$ greid et al., 1983; Robison-Steiner and Corbin, 1983; Døskeland and  $\mathcal{O}$ g AMP and exhibits cooperative binding sites for<br>cyclic AMP and exhibits cooperative binding of the nu-<br>cleotide (for examples, see Øgreid et al., 1983; Robison-<br>Steiner and Corbin, 1983; Døskeland and Øgreid, 1984).<br>The new Cyclic AMF and exhibits cooperative binding of the independent of the enzymes, see Øgreid et al., 1983; Robison-Steiner and Corbin, 1983; Døskeland and Øgreid, 1984).<br>The newly formed intracellular cyclic AMP binds to the

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PROTEIN PHOSPHORYLATION AN<br>units to dissociate from the holoenzyme and making the ac<br>enzyme catalytically active. The hydrolysis of cyclic Co enzyme catalytically active. The hydrolectric state of the seeing the seeing the seeing the seeing the seeing the property active. The hydrolysis of cyclic Company and MMP by cyclic nucleotide phosphodiesterase (Appleman p **PROTEIN PHOSPHORYLATION**<br>
units to dissociate from the holoenzyme and making the<br>
enzyme catalytically active. The hydrolysis of cyclic<br>
AMP by cyclic nucleotide phosphodiesterase (Appleman<br>
et al., 1982; Strada et al., 1 units to dissociate from the holoenzyme and making the achienzyme catalytically active. The hydrolysis of cyclic Cor<br>AMP by cyclic nucleotide phosphodiesterase (Appleman protet al., 1982; Strada et al., 1984; Beavo, 1988) units to dissociate from the holoenzyme and making tenzyme catalytically active. The hydrolysis of cyc<br>AMP by cyclic nucleotide phosphodiesterase (Applem<br>et al., 1982; Strada et al., 1984; Beavo, 1988) leads<br>reassociation enzyme catalytically active. The hydrolysis of cyclic (AMP by cyclic nucleotide phosphodiesterase (Appleman et al., 1982; Strada et al., 1984; Beavo, 1988) leads to reassociation and regeneration of the inactive holoen-zym AMP by cyclic nucleotide phosphodiesterase (Appleman<br>et al., 1982; Strada et al., 1984; Beavo, 1988) leads to<br>reassociation and regeneration of the inactive holoen-<br>zyme. Autophosphorylation of RII, which is stimulated 2<br>b et al., 1982; Strada et al., 1984; Beavo, 1988) leads to se<br>reassociation and regeneration of the inactive holoen-<br>zyme. Autophosphorylation of RII, which is stimulated 2,<br>by cyclic AMP, retards reassociation of the type I reassociation and regeneration of the inactive holoen-<br>zyme. Autophosphorylation of RII, which is stimulated<br>by cyclic AMP, retards reassociation of the type II hol-<br>oenzyme and thereby enhances its response to cyclic<br>AMP 1976). cyclic AMP, retards reassociation of the type II holphom and thereby enhances its response to cyclic function to the R subunits, many tissues contain a subseted.<br>In addition to the R subunits, many tissues contain a subset

oenzyme and thereby enhances its response to cy<br>AMP (Rubin and Rosen, 1975; Rangel-Aldao and Ros<br>1976).<br>In addition to the R subunits, many tissues contain<br>small, heat-stable protein inhibitor of cyclic AMP-<br>pendent protei AMP (Rubin and Rosen, 1975; Rangel-Aldao and Rosen, 1976).<br>1976).<br>In addition to the R subunits, many tissues contain a<br>small, heat-stable protein inhibitor of cyclic AMP-de-<br>pendent protein kinase that can bind to and ina 1976).<br>
In addition to the R subunits, many tissues contain a<br>
small, heat-stable protein inhibitor of cyclic AMP-de-<br>
pendent protein kinase that can bind to and inactivate<br>
the free C subunit (Walsh et al., 1971; Ashby a In addition to the R subunits, many tissues contain a<br>small, heat-stable protein inhibitor of cyclic AMP-de-<br>pendent protein kinase that can bind to and inactivate b<br>the free C subunit (Walsh et al., 1971; Ashby and Walsh, small, heat-stable protein inhibitor of cyclic AMP-de-<br>pendent protein kinase that can bind to and inactivate<br>the free C subunit (Walsh et al., 1971; Ashby and Walsh,<br>1972). It is possible that changes in the levels of thi pendent protein kinase that can bind to and inactivate the free C subunit (Walsh et al., 1971; Ashby and Walsh, 1972). It is possible that changes in the levels of this pinhibitor may play a role in more protracted regulat the free C subunit (Walsh et a<br>1972). It is possible that ch<br>inhibitor may play a role in<br>of cyclic AMP-dependent p<br>examples, see Costa, 1977).<br>ii. Distribution in brain 72). It is possible that changes in the levels of this possible that changes in the levels of this verticle in the cyclic AMP-dependent protein kinase activity (for amples, see Costa, 1977).<br> **ii. Distribution in brain.**

inhibitor may play a role in more protracted regulation<br>of cyclic AMP-dependent protein kinase activity (for<br>examples, see Costa, 1977).<br>ii. Distribution in brain. Both type I and type II<br>cyclic AMP-dependent protein kinas of cyclic AMP-dependent protein kinase activity (for<br>examples, see Costa, 1977).<br>ii. Distribution in brain. Both type I and type II mii<br>cyclic AMP-dependent protein kinases are widely dis-<br>tributed throughout the brain (Wa examples, see Costa, 1977).<br>
ii. Distribution in brain. Both type I and type II<br>
cyclic AMP-dependent protein kinases are widely dis-<br>
tributed throughout the brain (Walter et al., 1978; De<br>
Camilli et al., 1986; Cadd and ii. Distribution in brain. Both type I and type II<br>cyclic AMP-dependent protein kinases are widely dis-<br>tributed throughout the brain (Walter et al., 1978; De<br>Camilli et al., 1986; Cadd and McKnight, 1989). Total<br>cyclic AM cyclic AMP-dependent protein kinases are widely dis-<br>tributed throughout the brain (Walter et al., 1978; De<br>examilli et al., 1986; Cadd and McKnight, 1989). Total<br>specie AMP-dependent protein kinase activity is highest (f<br> tributed throughout the brain (Walter et al., 1978; De<br>Camilli et al., 1986; Cadd and McKnight, 1989). Total<br>cyclic AMP-dependent protein kinase activity is highest<br>in basal ganglia and cortical regions, with lowest activi Camilli et al., 1986; Cadd and McKnight, 1989). Total<br>cyclic AMP-dependent protein kinase activity is highest<br>in basal ganglia and cortical regions, with lowest activity<br>found in brain stem and spinal cord (Walaas et al., cyclic AMP-dependent protein kinase activity is highest (in basal ganglia and cortical regions, with lowest activity afound in brain stem and spinal cord (Walaas et al., 1983b,c). Analysis of kinase levels (Walter et al., in basal ganglia and cortical regions, with lowest activity al., found in brain stem and spinal cord (Walaas et al., mill 1983b,c). Analysis of kinase levels (Walter et al., 1979) nelagrees with results obtained in studies found in brain stem and spinal cord (Walaas et al., m<br>1983b,c). Analysis of kinase levels (Walter et al., 1979) n<br>agrees with results obtained in studies of gene expression m<br>in mouse brain, which indicates that transcript 1983b,c). Analysis of kinase levels (Walter et al., 1979) nagrees with results obtained in studies of gene expression in mouse brain, which indicates that transcripts for both ptypes I and II of cyclic AMP-dependent prote agrees with results obtained in studies of gene expression<br>in mouse brain, which indicates that transcripts for both<br>types I and II of cyclic AMP-dependent protein kinase<br>are present in neuronal cells, and type I in additi aL, 1987). pes I and II of cyclic AMP-dependent protein kinase<br>e present in neuronal cells, and type I in addition<br>pears to be enriched in myelin and glial cells (Stein et<br>, 1987).<br>Analysis of messenger RNAs for the different isoform

are present in neuronal cells, and type I in addition<br>appears to be enriched in myelin and glial cells (Stein<br>al., 1987).<br>Analysis of messenger RNAs for the different isoform<br>of the enzyme subunits also reveals interesting appears to be enriched in myelin and glial cells (Stein et for al., 1987).<br>
analysis of messenger RNAs for the different isoforms K<br>
of the enzyme subunits also reveals interesting differ-<br>
ences in regional distribution. al., 1987). min<br>Analysis of messenger RNAs for the different isoforms Ker<br>of the enzyme subunits also reveals interesting differ-<br>ences in regional distribution. Two general patterns of tion<br>expression have been observed. Analysis of messenger RNAs for the different isoforms Ken<br>of the enzyme subunits also reveals interesting differ-<br>ences in regional distribution. Two general patterns of tion<br>expression have been observed. One of these, s of the enzyme subunits also reveals interesting differences in regional distribution. Two general patterns of expression have been observed. One of these, shown by  $C-\alpha$ ,  $\mathrm{RI}-\alpha$ , and  $\mathrm{RI}-\beta$ , showed preferential enri expression have been observed. One of these, shown by intracellular injection of the C subunit of this enzyme  $C-\alpha$ , RI- $\alpha$ , and RI- $\beta$ , showed preferential enrichment in into distinct nerve cells was found to regulate by a lower expression in the thalamus and in the CA1-3 C- $\alpha$ , RI- $\alpha$ , and RI- $\beta$ , showed preferential enrichment in intersectner, caudatoputamen, hypothalamus, thalamus, of and hippocampus. Another pattern, which was shared by of C- $\beta$  and RII- $\beta$ , was distinguished from meocortex, caudatoputamen, hypothalamus, thalamus, of and hippocampus. Another pattern, which was shared by of C- $\beta$  and RII- $\beta$ , was distinguished from the C- $\alpha$  pattern Ap by a lower expression in the thalamus and in and hippocampus. Another pattern, which was shared by<br>  $C-\beta$  and RII- $\beta$ , was distinguished from the  $C-\alpha$  pattern<br>
by a lower expression in the thalamus and in the CA1-3<br>
regions of the hippocampus. RII- $\alpha$  was unique  $C-\beta$  and RII- $\beta$ , was distinguished from the  $C-\alpha$  pattern Aply<br>by a lower expression in the thalamus and in the CA1-3 tials<br>regions of the hippocampus. RII- $\alpha$  was unique in being nels<br>highly expressed only in the med by a lower expression in the thalamus and in the CA1-3 regions of the hippocampus. RII- $\alpha$  was unique in being highly expressed only in the medial habenular nucleus of the epithalamus. Although these transcript levels do highly expressed only in the medial habenular nucleus<br>of the epithalamus. Although these transcript levels do<br>not necessarily reflect protein levels, they suggest that<br>isoform-specific holoenzymes of cyclic AMP-dependent<br>p highly expressed only in the medial habenular nucleus reg of the epithalamus. Although these transcript levels do Aponot necessarily reflect protein levels, they suggest that latiisoform-specific holoenzymes of cyclic AMPof the epithalamus.<br>not necessarily refl<br>isoform-specific hol<br>protein kinase exist<br>McKnight, 1989).<br>In contrast to mo. t necessarily reflect protein levels, they suggest the oform-specific holoenzymes of cyclic AMP-depende otein kinase exist in distinct brain regions (Cadd an eKnight, 1989).<br>In contrast to most other tissues, in which cycl isoform-specific holoenzymes of cyclic AMP-dependent al.,<br>protein kinase exist in distinct brain regions (Cadd and have<br>McKnight, 1989). R15<br>In contrast to most other tissues, in which cyclic AMP- neu<br>dependent protein ki

protein kinase exist in distinct brain regions (Cadd and hand McKnight, 1989).<br>
In contrast to most other tissues, in which cyclic AMP-<br>
dependent protein kinase is found almost exclusively in<br>
the soluble fraction, mammal McKnight, 1989).<br>In contrast to most other tissues, in which cyclic AMP-<br>dependent protein kinase is found almost exclusively in<br>the soluble fraction, mammalian brain has a high activity<br>of the enzyme in both particulate a In contrast to most other tissues, in which cyclic AMP-<br>dependent protein kinase is found almost exclusively in<br>the soluble fraction, mammalian brain has a high activity<br>of the enzyme in both particulate and soluble fracti dependent protein kinase is found almost exclusively in<br>the soluble fraction, mammalian brain has a high activity<br>of the enzyme in both particulate and soluble fractions,<br>with highest specific activities in the synaptic me the soluble fraction, mammalian brain has a high activ of the enzyme in both particulate and soluble fraction with highest specific activities in the synaptic membra and cytosol fractions (for examples, see Maeno et a 1971 of the enzyme in both particulate and soluble fractions, kinase in neurons in *Helix*, in cardiac myocytes, and in with highest specific activities in the synaptic membrane prolactin-secreting pituitary cells (for reviews,

Corbin et al., 1977). Type II cyclic AMP-dependent AND NEURONAL FUNCTION<br>achieved through the R subunits (Rubin et al., 197<br>Corbin et al., 1977). Type II cyclic AMP-depende<br>protein kinase is also bound through the RII subunits protein kinase is also bound through the RIl subunits to achieved through the R subunits (Rubin et al., 19<br>Corbin et al., 1977). Type II cyclic AMP-depend<br>protein kinase is also bound through the RII subunits<br>several cytoplasmic brain proteins, including the calmo<br>ulin-binding p achieved through the R subunits (Rubin et al., 197<br>Corbin et al., 1977). Type II cyclic AMP-depende<br>protein kinase is also bound through the RII subunits<br>several cytoplasmic brain proteins, including the calmo<br>ulin-bindin Corbin et al., 1977). Type II cyclic AMP-dependent<br>protein kinase is also bound through the RII subunits to<br>several cytoplasmic brain proteins, including the calmod-<br>ulin-binding protein p75, the cytoskeletal protein MAPprotein kinase is also bound through the RII subunits to<br>several cytoplasmic brain proteins, including the calmod-<br>ulin-binding protein p75, the cytoskeletal protein MAP-<br>2, calcineurin, a Ca<sup>2+</sup>- and calmodulin-dependent several cytoplasmic brain proteins, including the calmod-<br>ulin-binding protein p75, the cytoskeletal protein MAP-<br>2, calcineurin, a  $Ca^{2+}$ - and calmodulin-dependent protein<br>phosphatase, and a number of proteins of unknow ulin-binding protein p75, the cytoskeletal protein MAP-2, calcineurin, a Ca<sup>2+</sup>- and calmodulin-dependent protein<br>phosphatase, and a number of proteins of unknown<br>function (Hathaway et al., 1981; Lohmann and Walter,<br>1984). phosphatase, and a number of proteins of unknown<br>function (Hathaway et al., 1981; Lohmann and Walter,<br>1984). Such interactions may be important in localizing<br>and concentrating the enzyme close to its physiological function (Hathaway et al., 1981; Lohmann and Walter, 1984). Such interactions may be important in localizing and concentrating the enzyme close to its physiological substrates. For example, approximately one-third of cy-to function (Hathaway et al., 1981; Lohmann and Walter, 1984). Such interactions may be important in localizing and concentrating the enzyme close to its physiological substrates. For example, approximately one-third of cytos 1984). Such interactions may be important in localizing<br>and concentrating the enzyme close to its physiological<br>substrates. For example, approximately one-third of cy-<br>tosolic cyclic AMP-dependent protein kinase appears to and concentrating the enzyme close to its physiological<br>substrates. For example, approximately one-third of cy-<br>tosolic cyclic AMP-dependent protein kinase appears to<br>be bound to MAP-2 (Theurkauf and Vallee, 1983; De<br>Camil tosolic cyclic AMP-dependent protein kinase appears to be bound to MAP-2 (Theurkauf and Vallee, 1983; De Camilli et al., 1986), and this protein is also efficiently phosphorylated by this kinase (Sloboda et al., 1975; Vallee, 1980; Walaas and Nairn, 1989). bound to MAP-2 (Theurkauf and Vallee, 1983; De<br>milli et al., 1986), and this protein is also efficiently<br>osphorylated by this kinase (Sloboda et al., 1975;<br>illee, 1980; Walaas and Nairn, 1989).<br>**iii. Functional importance** 

Camilli et al., 1986), and this protein is also efficient<br>phosphorylated by this kinase (Sloboda et al., 197<br>Vallee, 1980; Walaas and Nairn, 1989).<br>iii. Functional importance in nerve cells. The<br>response of any cell to inc phosphorylated by this kinase (Sloboda et al., 1975;<br>
Vallee, 1980; Walaas and Nairn, 1989).<br>
iii. Functional importance in nerve cells. The<br>
response of any cell to increases in cyclic AMP is deter-<br>
mined by the identity Vallee, 1980; Walaas and Nairn, 1989).<br>
iii. Functional importance in nerve cells.<br>
response of any cell to increases in cyclic AMP is a<br>
mined by the identity and localization of the prote<br>
the cell that are phosphorylate iii. Functional importance in nerve cells. The<br>response of any cell to increases in cyclic AMP is deter-<br>mined by the identity and localization of the proteins in<br>the cell that are phosphorylated by cyclic AMP-depend-<br>ent response of any cell to increases in cyclic AMP is deter-<br>mined by the identity and localization of the proteins in<br>the cell that are phosphorylated by cyclic AMP-depend-<br>ent protein kinase. The enzyme has a broad substrat mined by the identity and localization of the proteins in<br>the cell that are phosphorylated by cyclic AMP-depend-<br>ent protein kinase. The enzyme has a broad substrate<br>specificity and phosphorylates many neuronal proteins<br>(f ent protein kinase. The enzyme has a broad substrate specificity and phosphorylates many neuronal proteins (for reviews, see Nestler and Greengard, 1984; Nairn et al., 1985b), including proteins involved in neurotrans-<br>mit ent protein kinase. The enzyme has a broad substraspecificity and phosphorylates many neuronal protein (for reviews, see Nestler and Greengard, 1984; Nairn al., 1985b), including proteins involved in neurotran mitter relea specificity and phosphorylates many neuronal proteins (for reviews, see Nestler and Greengard, 1984; Nairn et al., 1985b), including proteins involved in neurotransmitter release, as well as transmitter receptors, ion chan (for reviews, see Nestler and Greengard, 1984; Nairn et al., 1985b), including proteins involved in neurotransmitter release, as well as transmitter receptors, ion channels, cytoskeletal proteins, phosphatase inhibitors, a al., 1985b), including proteins involved in neurotransmitter release, as well as transmitter receptors, ion channels, cytoskeletal proteins, phosphatase inhibitors, and many enzymes. Most of these substrate proteins are ph mitter release, as well as transmitter receptors, ion channels, cytoskeletal proteins, phosphatase inhibitors, and many enzymes. Most of these substrate proteins are phosphorylated on serine residues, and the consensus seq nels, cytoskeletal proteins, phosphatase inhibitors, and<br>many enzymes. Most of these substrate proteins are<br>phosphorylated on serine residues, and the consensus<br>sequence around the phosphorylation site(s) consists of<br>two o many enzymes. Most of these substrate proteins<br>phosphorylated on serine residues, and the consen<br>sequence around the phosphorylation site(s) consist<br>two or more basic amino acids (arginine and/or lysii<br>followed by another phosphorylated on serine residues, and the consensus<br>sequence around the phosphorylation site(s) consists of<br>two or more basic amino acids (arginine and/or lysine),<br>followed by another amino acid immediately NH<sub>2</sub>-ter-<br>min sequence around the phospheuvo or more basic amino acifollowed by another amino<br>followed by another amino<br>minal to the phosphorylated<br>Kemp and Pearson, 1990).<br>A major step forward in % or more basic amino acids (arginine and/or lysine)<br>llowed by another amino acid immediately  $NH<sub>2</sub>$ -ten<br>inal to the phosphorylated residue (Kemp et al., 1978)<br>emp and Pearson, 1990).<br>A major step forward in the eluci pubsplorylated op this knasse (soloom is the state of any composition of the proteines in the response of any cell to increases in cyclic AMP is deter-<br>response of any cell to increases in cyclic AMP is deter-<br>response to

followed by another amino acid immediately  $NH_2$ -terminal to the phosphorylated residue (Kemp et al., 1975;<br>Kemp and Pearson, 1990).<br>A major step forward in the elucidation of the func-<br>tions regulated by protein phosphor minal to the phosphorylated residue (Kemp et al., 1975;<br>Kemp and Pearson, 1990).<br>A major step forward in the elucidation of the func-<br>tions regulated by protein phosphorylation came when<br>intracellular injection of the C su Kemp and Pearson, 1990).<br>
A major step forward in the elucidation of the func-<br>
tions regulated by protein phosphorylation came when<br>
intracellular injection of the C subunit of this enzyme<br>
into distinct nerve cells was f A major step forward in the elucidation of the functions regulated by protein phosphorylation came when intracellular injection of the C subunit of this enzyme into distinct nerve cells was found to regulate a variety of n tions regulated by protein phosphorylation came when<br>intracellular injection of the C subunit of this enzyme<br>into distinct nerve cells was found to regulate a variety<br>of neurophysiological phenomena. For example, injection intracellular injection of the C subunit of this enzym<br>into distinct nerve cells was found to regulate a varie<br>of neurophysiological phenomena. For example, injection<br>of this enzyme into bag cell neurons from the mollu<br>*Ap* into distinct nerve cells was found to regulate a variet of neurophysiological phenomena. For example, injectic of this enzyme into bag cell neurons from the mollus *Aplysia* regulated the frequency of firing of action po of neurophysiological phenomena. For example, injection<br>of this enzyme into bag cell neurons from the mollusk<br>Aplysia regulated the frequency of firing of action poten-<br>tials, an effect mediated through regulation of K<sup>+</sup> tials, an effect mediated through regulation of  $K^+$  channels (Kaczmarek et al., 1980). Similarly, this enzyme regulated transmitter release from a sensory neuron in *Aplysia*, an effect that appeared to be produced by r nels (Kaczmarek et al., 1980). Similarly, this enzyme regulated transmitter release from a sensory neuron in *Aplysia*, an effect that appeared to be produced by regulation of a different type of  $K^+$  channel (Castellucc nels (Kaczmarek et al., 1980). Similarly, this enzyme<br>regulated transmitter release from a sensory neuron in<br>Aplysia, an effect that appeared to be produced by regu-<br>lation of a different type of K<sup>+</sup> channel (Castellucci regulated transmitter release from a sensory neuron in Aplysia, an effect that appeared to be produced by regulation of a different type of  $K^+$  channel (Castellucci et al., 1980, 1982; Siegelbaum et al., 1982).  $K^+$  ch R15 neurons in *Aplysia* (Adams and Levitan, 1982), in lation of a different type of K<sup>+</sup> channel (Castellucci<br>al., 1980, 1982; Siegelbaum et al., 1982). K<sup>+</sup> chann<br>have also been found to be regulated by this kinase<br>R15 neurons in *Aphysia* (Adams and Levitan, 1982),<br>neurons al., 1980, 1982; Siegelbaum et al., 1982). K<sup>+</sup> channels<br>have also been found to be regulated by this kinase in<br>R15 neurons in *Aplysia* (Adams and Levitan, 1982), in<br>neurons in *Helix* (De Peyer et al., 1982), and in phot have also been found to be regulated by this kinase in R15 neurons in Aplysia (Adams and Levitan, 1982), in neurons in *Helix* (De Peyer et al., 1982), and in photo-receptor cells in *Hermissenda* (Alkon et al., 1983), and R15 neurons in *Aplysia* (Adams and Levitan, 1982), in<br>neurons in *Helix* (De Peyer et al., 1982), and in photo-<br>receptor cells in *Hermissenda* (Alkon et al., 1983), and<br>Ca<sup>2+</sup> channels have been found to be regulated by neurons in *Helix* (De Peyer et al., 1982), and in photo-<br>receptor cells in *Hermissenda* (Alkon et al., 1983), and<br>Ca<sup>2+</sup> channels have been found to be regulated by this<br>kinase in neurons in *Helix*, in cardiac myocytes, receptor cells in *Hermissenda* (Alkon et al., 1983), and Ca<sup>2+</sup> channels have been found to be regulated by this kinase in neurons in *Helix*, in cardiac myocytes, and in prolactin-secreting pituitary cells (for reviews,  $Ca^{2+}$  channels have been found to be regulated by this kinase in neurons in *Helix*, in cardiac myocytes, and in prolactin-secreting pituitary cells (for reviews, see Eckert et al., 1986; Armstrong, 1989; Hess, 1990). R kinase in neurons in  $He$ <br>prolactin-secreting pitui<br>et al., 1986; Armstrong,<br>ion channels by protein<br>cussed in section V.B.

PHARMACOLOGICAL REVIEWS

WALAAS AND GREENGARD<br>b. CYCLIC GMP-DEPENDENT PROTEIN KINASE. Cyclic iii. Functional importance in nerve cells. Little is<br>GMP-dependent protein kinase, which was initially known about physiological substrates for cyclic GMP WALAAS AND GF<br>b. CYCLIC GMP-DEPENDENT PROTEIN KINASE. Cyclic<br>GMP-dependent protein kinase, which was initially ki<br>found in invertebrates (Kuo and Greengard, 1970), is de wall as a wall wall as a wall as a wall as a wall as a wall as b. cyclic GMP-dependent protein kinase, which was initially known found in invertebrates (Kuo and Greengard, 1970), is depresent in several mammalian tissues, b. CYCLIC GMP-DEPENDENT PROTEIN KINASE. Cyclic<br>GMP-dependent protein kinase, which was initially kn<br>found in invertebrates (Kuo and Greengard, 1970), is depresent in several mammalian tissues, including brain the<br>(Greengar b. CYCLIC GMP-DEPENDENT PROTEIN KINASE. Cyclic i<br>GMP-dependent protein kinase, which was initially know<br>found in invertebrates (Kuo and Greengard, 1970), is dep<br>present in several mammalian tissues, including brain tha<br>(Gr GMP-dependent protein kinase, which was initially k<br>found in invertebrates (Kuo and Greengard, 1970), is depresent in several mammalian tissues, including brain the<br>(Greengard and Kuo, 1970; Walter, 1981; Walter and sp<br>Gre found in invertebrates (Kuo and Greengard, 1970), is<br>present in several mammalian tissues, including brain<br>(Greengard and Kuo, 1970; Walter, 1981; Walter and<br>Greengard, 1981). The brain enzyme, partially purified<br>from the present in several mammalian tissues, including brain the Greengard and Kuo, 1970; Walter, 1981; Walter and Screengard, 1981). The brain enzyme, partially purified (from the cerebellum (Takai et al., 1975), has properties (Greengard and Kuo, 1970; Walter, 1981; Walter and speengard, 1981). The brain enzyme, partially purified (I from the cerebellum (Takai et al., 1975), has properties Numilar to the lung and heart enzymes. Other isozymic su Greengard, 1981). The brain enzyme, partially purified (I<br>from the cerebellum (Takai et al., 1975), has properties N<br>similar to the lung and heart enzymes. Other isozymic su<br>forms found in intestine (de Jonge, 1981) and sm from the cerebellum (Takai et al., 1975), has properties Namilar to the lung and heart enzymes. Other isozymic suforms found in intestine (de Jonge, 1981) and smooth kinasele (Wolfe et al., 1989) have also been studied. T similar to the lung and heart enzymes. Other isozy<br>forms found in intestine (de Jonge, 1981) and smo<br>muscle (Wolfe et al., 1989) have also been studied. 7<br>cyclic GMP-dependent protein kinase enzymes exist<br>homodimers, each forms found in intestine (de Jonge, 1981) and smooth kimuscle (Wolfe et al., 1989) have also been studied. The becyclic GMP-dependent protein kinase enzymes exist as Ahomodimers, each subunit (molecular mass approxi-planat muscle (Wolfe et al., 1989) have also been studied. The cyclic GMP-dependent protein kinase enzymes exist as *h* homodimers, each subunit (molecular mass approximately 74 kDa) of which has two binding sites for cyclic p GM cyclic GMP-dependent protein kinase enzymes exist as Ait homodimers, each subunit (molecular mass approximately 74 kDa) of which has two binding sites for cyclic phonomately 74 kDa) of which has two binding sites for cycli homodimers, each subunit (molecular ma<br>mately 74 kDa) of which has two binding sit<br>GMP (Corbin et al., 1986) and one catalytic<br>reviews, see Walter and Greengard, 1981; I<br>Corbin, 1983; Nairn and Greengard, 1983).<br>**i. Regula** ately 74 kDa) of which has two binding sites for cyclic pMP (Corbin et al., 1986) and one catalytic domain (for F<br>views, see Walter and Greengard, 1981; Lincoln and reportion, 1983; Nairn and Greengard, 1983).<br>**i. Regulati** 

reviews, see Walter and Greengard, 1981; Lincoln and Corbin, 1983; Nairn and Greengard, 1983).<br> **i. Regulation of activity.** When cyclic GMP bind<br>
to the enzyme, a conformational change in the protein is<br>
induced, inhibito Corbin, 1983; Nairn and Greengard, 1983).<br> **i. Regulation of activity.** When cyclic GMP binds<br>
to the enzyme, a conformational change in the protein is<br>
induced, inhibitory domains are removed, and the cata-<br>
lytic domain i. Regulation of activity. When cyclic GMP bit to the enzyme, a conformational change in the proteinduced, inhibitory domains are removed, and the clytic domain can proceed to phosphorylate substration (Lincoln et al., 197 to the enzyme, a conformational change in the protein is reinduced, inhibitory domains are removed, and the catalytic domain can proceed to phosphorylate substrates self-<br>incoln et al., 1978). A variety of neurotransmitte induced, inhibitory domains are removed, and the cata-<br>lytic domain can proceed to phosphorylate substrates sere<br>(Lincoln et al., 1978). A variety of neurotransmitters, din<br>drugs, hormones, or increases in neuronal activi lytic domain can proceed to phosphorylate substrates (Lincoln et al., 1978). A variety of neurotransmitters, drugs, hormones, or increases in neuronal activity cause Ca<sup>2+</sup>-dependent increases in the formation of cyclic GM (Lincoln et al., 1978). A variety of neurotransmitters, c<br>drugs, hormones, or increases in neuronal activity cause<br> $Ca^{2+}$ -dependent increases in the formation of cyclic GMP (<br>in nerve cells (for examples, see Ferrendelli drugs, hormones, or increases in neuronal activity caus<br>Ca<sup>2+</sup>-dependent increases in the formation of cyclic GM<br>in nerve cells (for examples, see Ferrendelli, 1978; Mitta<br>and Murad, 1982; Tremblay et al., 1988). Recent ev in nerve cells (for examples, see Ferrendelli, 1978; Mittal and Murad, 1982; Tremblay et al., 1988). Recent evidence has indicated that glutamate receptor-stimulated increases in levels of nitric oxide, generated during co in nerve cells (for examples, see Ferrendelli, 1978; Mittal the effects of acetylcholine and cyclic GMP on these cells<br>and Murad, 1982; Tremblay et al., 1988). Recent evidence (Stone et al., 1975; Woody et al., 1978; Swar and Murad, 1982; Tremblay et al., 1988). Recent evidence<br>has indicated that glutamate receptor-stimulated in-<br>creases in levels of nitric oxide, generated during conver-<br>sion of arginine to citrulline, can increase the lev has indicated that glutamate receptor-stimulated in-<br>creases in levels of nitric oxide, generated during conver-<br>sion of arginine to citrulline, can increase the levels of<br>cyclic GMP in brain (Böhme et al., 1984; Garthwait creases in levels of nitric oxide, generated during conversion of arginine to citrulline, can increase the levels of for cyclic GMP in brain (Böhme et al., 1984; Garthwaite et tis al., 1988; Bredt and Snyder, 1989; Wood et sion of arginine to citrulline, can increase the levels cyclic GMP in brain (Böhme et al., 1984; Garthwait al., 1988; Bredt and Snyder, 1989; Wood et al., 19<br>Inactivation of cyclic GMP-dependent protein kinas caused by cyc al., 1988; Bredt and Snyder, 1989; Wood et al., 1990).<br>Inactivation of cyclic GMP-dependent protein kinase is<br>caused by cyclic nucleotide phosphodiesterase-catalyzed<br>hydrolysis of the cyclic nucleotide (Appleman et al., 19 al., 1988; Bredt and Snyder, 1989<br>Inactivation of cyclic GMP-depene<br>caused by cyclic nucleotide phosph<br>hydrolysis of the cyclic nucleotide (<br>Strada et al., 1984; Beavo, 1988).<br>**ii. Distribution in brain.** Cy activation of cyclic GMP-dependent protein kinase<br>used by cyclic nucleotide phosphodiesterase-catalyz<br>drolysis of the cyclic nucleotide (Appleman et al., 198<br>rada et al., 1984; Beavo, 1988).<br>ii. **Distribution in brain**. Cy

caused by cyclic nucleotide phosphodiesterase-catalyzed we<br>hydrolysis of the cyclic nucleotide (Appleman et al., 1982; que<br>Strada et al., 1984; Beavo, 1988). Show ii. Distribution in brain. Cyclic GMP-dependent yla<br>protein hydrolysis of the cyclic nucleotide (Appleman et al., 1982; quarried at al., 1984; Beavo, 1988).<br> **Strada et al., 1984; Beavo, 1988**). Showing significant activity is protein kinase has a very uneven tissue distribution, w Strada et al., 1984; Beavo, 1988). Shewash ii. Distribution in brain. Cyclic GMP-dependent ylaprotein kinase has a very uneven tissue distribution, with an only a few peripheral tissues showing significant activity ion (Li ii. Distribution in brain. Cyclic GMP-dependent y<br>protein kinase has a very uneven tissue distribution, with<br>only a few peripheral tissues showing significant activity is<br>(Lincoln and Corbin, 1983; Nairn et al., 1985b). In protein kinase has a very uneven tissue distribution, with and<br>only a few peripheral tissues showing significant activity ions<br>(Lincoln and Corbin, 1983; Nairn et al., 1985b). In the pho<br>brain, only the cerebellum contains only a few peripheral tissues showing significant activity (Lincoln and Corbin, 1983; Nairn et al., 1985b). In the brain, only the cerebellum contains high activity. This activity is due to the enzyme being highly enriched (Lincoln and Corbin, 1983; Nairn et al., 1985b). In the photonin, only the cerebellum contains high activity. This man activity is due to the enzyme being highly enriched in late Purkinje cells (Schlichter et al., 1980; Lo brain, only the cerebellum contains high activity. This matrivity is due to the enzyme being highly enriched in late Purkinje cells (Schlichter et al., 1980; Lohmann et al., by 1981; De Camilli et al., 1984a; Levitt et al. activity is due to the enzyme being highly enriched in late<br>
Purkinje cells (Schlichter et al., 1980; Lohmann et al., by<br>
1981; De Camilli et al., 1984a; Levitt et al., 1984). In (S<br>
these inhibitory, GABAergic cells, whic Purkinje cells (Schlichter et al., 1980; Lohmann et al., by<br>1981; De Camilli et al., 1984a; Levitt et al., 1984). In (S<br>these inhibitory, GABAergic cells, which represent the jis<br>final common pathway through which informat 1981; De Camilli et al., 1984a; Levitt et al., 1984). In these inhibitory, GABAergic cells, which represent the final common pathway through which information is funneled out of the cerebellum, immunoreactivity is found th these inhibitory, GABAergic cells, which represent the final common pathway through which information is funneled out of the cerebellum, immunoreactivity is found throughout the cytosol in cell bodies, dendrites, axons, an funneled out of the cerebellum, immunoreactivity is be particularly important in brain (Schulman, 1988; Kenfound throughout the cytosol in cell bodies, dendrites, nedy, 1989), with high levels of CaM kinase activity and a funneled out of the cerebellum, immunoreactivity is b<br>found throughout the cytosol in cell bodies, dendrites, n<br>axons, and axon terminals (De Camilli et al., 1984a). a<br>This is in agreement with the cytosolic distribution o found throughout the cytosol in cell bodies, dendrites, axons, and axon terminals (De Camilli et al., 1984a).<br>This is in agreement with the cytosolic distribution of this enzyme observed in most peripheral tissues (Lincoln axons, and axon terminals (De Camilli et al., 1984a). a la<br>This is in agreement with the cytosolic distribution of beir<br>this enzyme observed in most peripheral tissues (Lincoln a.<br>and Corbin, 1983). Cyclic GMP-dependent pr This is in agreement with the cytosolic distribution of be<br>this enzyme observed in most peripheral tissues (Lincoln<br>and Corbin, 1983). Cyclic GMP-dependent protein ki-<br>nase also appears to be present, albeit at lower level this enzyme observed in most peripheral tissues (Lincoln<br>and Corbin, 1983). Cyclic GMP-dependent protein ki-<br>nase also appears to be present, albeit at lower levels, in<br>cother neurons in the mammalian CNS, such as the<br>medi and Corbin, 1983). Cyclic GMP-dependent protein lase also appears to be present, albeit at lower levels, other neurons in the mammalian CNS, such as t medium-sized spiny neurons of the neostriatum. In the latter cells, low nase also appears to be present, albeit at lower levels, in cother neurons in the mammalian CNS, such as the ted medium-sized spiny neurons of the neostriatum. In the datter cells, low levels of both cyclic GMP-dependent i other neurons in the mammalian CNS, such as the medium-sized spiny neurons of the neostriatum. In the latter cells, low levels of both cyclic GMP-dependent protein kinase immunoreactivity and enzyme activity have been desc

**iii. Functional importance in nerve cells. Little is** FREENGARD<br>
iii. Functional importance in nerve cells. Little<br>
known about physiological substrates for cyclic GM<br>
dependent protein kinase in brain, although it appea GREENGARD<br>iii. Functional importance in nerve cells. Little is<br>known about physiological substrates for cyclic GMP-<br>dependent protein kinase in brain, although it appears<br>that the enzyme has a much more narrow substrate that the enzyme has a much more narrow substrate specificity than does the cyclic AMP-dependent enzyme iii. Functional importance in nerve cells. Little is<br>known about physiological substrates for cyclic GMP-<br>dependent protein kinase in brain, although it appears<br>that the enzyme has a much more narrow substrate<br>specificity known about physiological substrates for cyclic GMP-<br>dependent protein kinase in brain, although it appears<br>that the enzyme has a much more narrow substrate<br>specificity than does the cyclic AMP-dependent enzyme<br>(Lincoln an dependent protein kinase in brain, although it appears<br>that the enzyme has a much more narrow substrate<br>specificity than does the cyclic AMP-dependent enzyme<br>(Lincoln and Corbin, 1983; Nairn and Greengard, 1983;<br>Nairn et a that the enzyme has a much more narrow substrate<br>specificity than does the cyclic AMP-dependent enzyme<br>(Lincoln and Corbin, 1983; Nairn and Greengard, 1983<br>Nairn et al., 1985b). "G-substrate," a neuron-specific<br>substrate p specificity than does the cyclic AMP-dependent enzyme<br>(Lincoln and Corbin, 1983; Nairn and Greengard, 1983;<br>Nairn et al., 1985b). "G-substrate," a neuron-specific<br>substrate protein that has been found in cerebellar Pur-<br>ki (Lincoln and Corbin, 1983; Nairn and Greengard, 1983; Nairn et al., 1985b). "G-substrate," a neuron-specific substrate protein that has been found in cerebellar Purkinje cells (Schlichter et al., 1978; Detre et al., 1984), Nairn et al., 1985b). "G-substrate," a neuron-specific<br>substrate protein that has been found in cerebellar Pur-<br>kinje cells (Schlichter et al., 1978; Detre et al., 1984), has<br>been well characterized (Aswad and Greengard, 1 substrate protein that has been found in cerebellar Pur-<br>kinje cells (Schlichter et al., 1978; Detre et al., 1984), has<br>been well characterized (Aswad and Greengard, 1981a,b;<br>Aitken et al., 1981). Under certain conditions, kinje cells (Schlichter et al., 1978; Detre et al., 1984), has<br>been well characterized (Aswad and Greengard, 1981a,b;<br>Aitken et al., 1981). Under certain conditions, this phos-<br>phoprotein has been found to be active as a p been well characterized (Aswad and Greengard, 1981a,b;<br>Aitken et al., 1981). Under certain conditions, this phos-<br>phoprotein has been found to be active as a protein<br>phosphatase inhibitor (Nairn et al., 1985b; A. C. Nairn, Aitken et al., 1981). Under certs<br>phoprotein has been found to<br>phosphatase inhibitor (Nairn et<br>P. Simonelli, H. C. Li and P.<br>results; see also section III.A).<br>Intracellular injection of ac Interpretering has been found to be active as a pro-<br>Interpretation (Nairn et al., 1985b; A. C. Na<br>Simonelli, H. C. Li and P. Greengard, unpublis<br>sults; see also section III.A).<br>Intracellular injection of activated cyclic

reviews, see Walter and Greengard, 1981; Lincoln and results; see also section III.A).<br>Corbin, 1983; Nairn and Greengard, 1983). Intracellular injection of activated cyclic GMP-de-<br>i. Regulation of activity. When cyclic GM phosphatase inhibitor (Nairn et al., 1985b; A. C. Nairn, P. Simonelli, H. C. Li and P. Greengard, unpublished results; see also section III.A).<br>Intracellular injection of activated cyclic GMP-dependent protein kinase has b enzyme potentiated and probably mediated the effects of results; see also section III.A).<br>
Intracellular injection of activated cyclic GMP-de-<br>
pendent protein kinase has been found to induce distinct<br>
responses in certain nerve cells. In neurons in *Helix*, the<br>
enzyme potent Intracellular injection of activated cyclic GMP-<br>pendent protein kinase has been found to induce disti<br>responses in certain nerve cells. In neurons in *Helix*,<br>enzyme potentiated and probably mediated the effect<br>serotonin pendent protein kinase has been found to induce distinct<br>responses in certain nerve cells. In neurons in *Helix*, the<br>enzyme potentiated and probably mediated the effects of<br>serotonin on voltage-dependent  $Ca^{2+}$ -channels responses in certain nerve cells. In neurons in *Helix*, the enzyme potentiated and probably mediated the effects of serotonin on voltage-dependent  $Ca^{2+}$ -channels (Paupardin-Tritsch et al., 1986a,b). In neurons in cat c enzyme potentiated and probably mediated the effects of<br>serotonin on voltage-dependent Ca<sup>2+</sup>-channels (Paupar-<br>din-Tritsch et al., 1986a,b). In neurons in cat cerebral<br>cortex, the enzyme induced increases in input resista serotonin on voltage-dependent  $Ca^{2+}$ -channels (Paupardin-Tritsch et al., 1986a,b). In neurons in cat cerebral cortex, the enzyme induced increases in input resistance (Woody et al., 1986), an effect that mimicked some o din-Tritsch et al., 1986a,b). In neurons in cat cerebral<br>cortex, the enzyme induced increases in input resistance<br>(Woody et al., 1986), an effect that mimicked some of<br>the effects of acetylcholine and cyclic GMP on these c cortex, the enzy<br>(Woody et al., 1<br>the effects of ace<br>(Stone et al., 1<br>Woody, 1979).<br>2.  $Ca^{2+}/cal$ *2. Voody et al., 1986), an effect that mimicked some of* e effects of acetylcholine and cyclic GMP on these cells tone et al., 1975; Woody et al., 1978; Swartz and oody, 1979).<br>
2.  $Ca^{2+}/cal$  calmodulin-dependent protein ki

the effects of acetylcholine and cyclic GMP on these cells<br>
(Stone et al., 1975; Woody et al., 1978; Swartz and<br>
Woody, 1979).<br>
2.  $Ca^{2+}/calmodulin-dependent protein kinases$ . A role<br>
for  $Ca^{2+}$ -dependent protein phosphorylation in neuronal<br>
tissues (Stone et al., 1975; Woody et al., 1978; Swartz and Woody, 1979).<br>
2.  $Ca^{2+}/calodmodulin-dependent protein kinases$ . A role<br>
for  $Ca^{2+}$ -dependent protein phosphorylation in neuronal<br>
tissues was first suggested by studies of isolated nerve<br>
terminals Woody, 1979).<br>
2.  $Ca^{2+}/calmodulin-dependent protein, kinases.$  A role<br>
for  $Ca^{2+}$ -dependent protein phosphorylation in neuronal<br>
tissues was first suggested by studies of isolated nerve<br>
terminals (synaptosomes) from rat cerebral cortex<br>
(Krueger 2.  $Ca^{2+}/calmodulin-dependent protein kinases$ . A role for  $Ca^{2+}$ -dependent protein phosphorylation in neuronal tissues was first suggested by studies of isolated nerve terminals (synaptosomes) from rat cerebral cortex (Krueger et al., 1976, 1977). for  $Ca^{2+}$ -dependent protein phosphorylation in neuror<br>tissues was first suggested by studies of isolated ner<br>terminals (synaptosomes) from rat cerebral cort<br>(Krueger et al., 1976, 1977). When such preparatio<br>were prelab tissues was first suggested by studies of isolated nerve<br>terminals (synaptosomes) from rat cerebral cortex<br>(Krueger et al., 1976, 1977). When such preparations<br>were prelabeled with  $[^{32}P]$ orthophosphate, and subse-<br>quen (Krueger et al., 1976, 1977). When such preparations<br>were prelabeled with [<sup>32</sup>P]orthophosphate, and subse-<br>quently subjected to K<sup>+</sup> depolarization, several proteins<br>showed  $Ca^{2+}$ -dependent increases in levels of phosph (Krueger et al., 1976, 1977). When such preparations<br>were prelabeled with  $[^{32}P]$ orthophosphate, and subse-<br>quently subjected to K<sup>+</sup> depolarization, several proteins<br>showed  $Ca^{2+}$ -dependent increases in levels of phos were prelabeled with  $[^{32}P]$ orthophosphate, and subsequently subjected to K<sup>+</sup> depolarization, several proteins showed  $Ca^{2+}$ -dependent increases in levels of phosphor-<br>ylation. Studies of broken cell preparations conf showed Ca<sup>2+</sup>-dependent increases in levels of phosphor-<br>ylation. Studies of broken cell preparations confirmed<br>and extended these findings, because addition of Ca<sup>2+</sup><br>ions to synaptosomal membranes increased the phos-<br>ph showed  $Ca^{2+}$ -dependent increases in levels of phosphericulary plation. Studies of broken cell preparations confirm and extended these findings, because addition of  $Ca$ ions to synaptosomal membranes increased the phorpho ions to synaptosomal membranes increased the phos-<br>phorylation of several proteins (DeLorenzo, 1976; Schul-<br>man and Greengard, 1978a,b). Much of this  $Ca^{2+}$ -regu-<br>lated protein phosphorylation was found to be mediated and extended these findings, because addition of  $Ca^{2+}$ <br>ions to synaptosomal membranes increased the phos-<br>phorylation of several proteins (DeLorenzo, 1976; Schul-<br>man and Greengard, 1978a,b). Much of this  $Ca^{2+}$ -regu-<br> ions to synaptosomal membranes increased the phos-<br>phorylation of several proteins (DeLorenzo, 1976; Schul-<br>man and Greengard, 1978a,b). Much of this  $Ca^{2+}$ -regu-<br>lated protein phosphorylation was found to be mediated<br>by phorylation of several proteins (DeLorenzo, 1976; Schulman and Greengard, 1978a,b). Much of this Ca<sup>2+</sup>-regulated protein phosphorylation was found to be mediated by the ubiquitous Ca<sup>2+</sup>-binding protein calmodulin (Schulm man and Greengard, 1978a,b). Much of this  $Ca^{2+}$ -regulated protein phosphorylation was found to be mediated by the ubiquitous  $Ca^{2+}$ -binding protein calmodulin (Schulman and Greengard, 1978a,b; Yamauchi and Fujisawa, 19 lated protein phosphorylation was found to be mediated<br>by the ubiquitous  $Ca^{2+}$ -binding protein calmodulin<br>(Schulman and Greengard, 1978a,b; Yamauchi and Fu-<br>jisawa, 1979; O'Callaghan et al., 1980).  $Ca^{2+}$ - and cal-<br>mod (Schulman and Greengard, 1978a,b; Yamauchi and Fu-<br>jisawa, 1979; O'Callaghan et al., 1980).  $Ca^{2+}$ - and cal-(Schulman and Greengard, 1978a,b; Yamauchi and Fu-<br>jisawa, 1979; O'Callaghan et al., 1980). Ca<sup>2+</sup>- and cal-<br>modulin-dependent protein phosphorylation appears to<br>be particularly important in brain (Schulman, 1988; Ken-<br>ne jisawa, 1979; O'Callaghan et al., 1980). Ca<sup>2+</sup>- and cal-<br>modulin-dependent protein phosphorylation appears to<br>be particularly important in brain (Schulman, 1988; Ken-<br>nedy, 1989), with high levels of CaM kinase activity a

a.  $CA^{2+}/CALMODULIN-DEPENDENT$  PROTEIN KINASE II. nedy, 1989), with high levels of CaM kinase activity and<br>a large number of brain-specific endogenous substrates<br>being present (Walaas et al., 1983b,c).<br>a.  $CA^{2+}/CALMODULIN-DEFENDENT PROTEIN KINASE II.$ <br>Following the observation that synaptoso a large number of brain-specific endogenous substrates<br>being present (Walaas et al., 1983b,c).<br>a.  $CA^{2+}/CALMODULIN-DEFENDENT PROTEIN KINASE II$ .<br>Following the observation that synaptosomal membranes<br>contain  $Ca^{2+}$ -dependent protein phosphoryla being present (Walaas et al., 1983b,c).<br>
a.  $CA^{2+}/CALMODULIN-DEPENDENT PROTEIN KIN$ <br>
Following the observation that synaptosomal mem<br>
contain  $Ca^{2+}$ -dependent protein phosphorylatio<br>
tems, one of the major substrates for  $Ca^{2+}/cal$ <br>
dependen a.  $CA^{2+}/CALMODULIN-DEPENDENT$  PROTEIN KINASE II.<br>Following the observation that synaptosomal membranes<br>contain  $Ca^{2+}$ -dependent protein phosphorylation sys-<br>tems, one of the major substrates for  $Ca^{2+}/cal$ calmodulin-<br>dependent protei Following the observation that synaptosomal membranes<br>contain  $Ca^{2+}$ -dependent protein phosphorylation sys-<br>tems, one of the major substrates for  $Ca^{2+}/calmathrm{calmod}$ <br>independent protein phosphorylation in synaptosomes was<br>iden contain  $Ca^{2+}$ -dependent protein phosphorylation systems, one of the major substrates for  $Ca^{2+}/c$ almodulin-dependent protein phosphorylation in synaptosomes was identified as synapsin I (Sieghart et al., 1979), a protei tems, one of the major substrates for  $Ca^{2+}/calmodulin$ -dependent protein phosphorylation in synaptosomes was identified as synapsin I (Sieghart et al., 1979), a protein that was previously known to be one of the major substrat

PROTEIN PHOSPHORYLA<br>nervous system (Johnson et al., 1971; Ueda and Green<br>gard, 1977). Synapsin I can be phosphorylated by t PROTEIN PHOSPHORYLATION AND<br>nervous system (Johnson et al., 1971; Ueda and Green-hor<br>gard, 1977). Synapsin I can be phosphorylated by two net<br>distinct CaM kinases, CaM kinase I, which phosphoryl-are PROTEIN PHOSPHORYI<br>nervous system (Johnson et al., 1971; Ueda and Grand, 1977). Synapsin I can be phosphorylated by<br>distinct CaM kinases, CaM kinase I, which phosphates the same serine residue (site 1) as does cyclic A nervous system (Johnson et al., 1971; Ueda and Gree<br>gard, 1977). Synapsin I can be phosphorylated by tv<br>distinct CaM kinases, CaM kinase I, which phosphory<br>ates the same serine residue (site 1) as does cyclic AM<br>dependent nervous system (Johnson et al., 1971; Ueda and Green-<br>gard, 1977). Synapsin I can be phosphorylated by two numeration can be phosphoryled by two numerates the same serine residue (site 1) as does cyclic AMP-<br>dependent pro gard, 1977). Synapsin I can be phosphorylated by tweedistinct CaM kinases, CaM kinase I, which phosphory ates the same serine residue (site 1) as does cyclic AMI dependent protein kinase in the  $NH_2$ -terminal "head region ates the same serine residue (site 1) as does cyclic AMP-<br>dependent protein kinase in the  $NH_2$ -terminal "head"<br>region of the protein, and CaM kinase II, which phos-<br>phorylates two serine residues (sites 2 and 3) in the<br>C dependent protein kinase in the  $NH_2$ -terminal "head" (To<br>region of the protein, and CaM kinase II, which phos-<br>subphorylates two serine residues (sites 2 and 3) in the<br>COOH-terminal "tail" region of the protein (Huttner region of the protein, and CaM kinase II, which phos-<br>phorylates two serine residues (sites 2 and 3) in the t<br>COOH-terminal "tail" region of the protein (Huttner a<br>and Greengard, 1979; Huttner et al., 1981; Kennedy and r<br>G phorylates two serine residues (sites 2 and 3) in the COOH-terminal "tail" region of the protein (Huttnand Greengard, 1979; Huttner et al., 1981; Kennedy are Greengard, 1981; Czernik et al., 1987). The latter enzym appears COOH-terminal "tail" region of the protein (Huttner<br>and Greengard, 1979; Huttner et al., 1981; Kennedy and<br>Greengard, 1981; Czernik et al., 1987). The latter enzyme<br>appears to represent the major CaM kinase in the mam-<br>mal Greengard, 1981; Czernik et al., 1987). The latter enzyme appears to represent the major CaM kinase in the mammalian CNS (McGuinness et al., 1985b; Nairn et al., 1985b; Walaas and Nairn, 1985; Schulman, 1988; Cohen, 1988). pears to represent the major CaM kinase in the mam-chialian CNS (McGuinness et al., 1985b; Nairn et al., alo<br>85b; Walaas and Nairn, 1985; Schulman, 1988; Cohen, aut<br>88). CaM kinase II has been purified from rat brain and z

malian CNS (McGuinness et al., 1985b; Nairn et al., 1985b; Walaas and Nairn, 1985; Schulman, 1988; Cohen, 1988).<br>
1988).<br>
CaM kinase II has been purified from rat brain and acharacterized by a number of investigators (Fuku 1985b; Walaas and Nairn, 1985; Schulman, 1988; Cohen, 1988).<br>
CaM kinase II has been purified from rat brain and<br>
characterized by a number of investigators (Fukunaga et<br>
al., 1982; Bennett et al., 1983; Goldenring et al., 1988).<br>CaM kinase II has been purified from rat brain and<br>characterized by a number of investigators (Fukunaga et<br>al., 1982; Bennett et al., 1983; Goldenring et al., 1983;<br>Yamauchi and Fujisawa, 1983a; Schulman, 1984; Mc-<br> CaM kinase II has been purified from rat brain and<br>characterized by a number of investigators (Fukunaga et<br>al., 1982; Bennett et al., 1983; Goldenring et al., 1983;<br>Yamauchi and Fujisawa, 1983a; Schulman, 1984; Mc-<br>Guinnes characterized by a number of investigators (Fukunaga et act al., 1982; Bennett et al., 1983; Goldenring et al., 1983; to the Yamauchi and Fujisawa, 1983a; Schulman, 1984; Mc-<br>Guinness et al., 1985a). Purified CaM kinase II al., 1982; Bennett et al., 1983; Goldenring et al., 1983; Yamauchi and Fujisawa, 1983a; Schulman, 1984; Mc-<br>Guinness et al., 1985a). Purified CaM kinase II exhibits<br>a broad substrate specificity, with synapsin I (sites 2 a Yamauchi and Fujisawa, 1983a; Schulman, 1984; Mc-<br>Guinness et al., 1985a). Purified CaM kinase II exhibits the<br>a broad substrate specificity, with synapsin I (sites 2 and (I<br>3) being the most efficient substrate tested. In a broad substrate specificity, with synapsin I (sites 2 and<br>3) being the most efficient substrate tested. In addition,<br>the MAPs, MAP-2 and tau factor, together with glycogen<br>synthase, smooth muscle myosin light chain, tyro 3) being the most efficient substrate tested. In addition<br>the MAPs, MAP-2 and tau factor, together with glycog<br>synthase, smooth muscle myosin light chain, tyrosi<br>hydroxylase, calcineurin, myelin basic protein, riboson<br>pro the MAPs, MAP-2 and tau factor, together with glycogen<br>synthase, smooth muscle myosin light chain, tyrosine<br>hydroxylase, calcineurin, myelin basic protein, ribosomal<br>protein S6, and Ca<sup>2+</sup>/calmodulin-sensitive cyclic nucle synthase, smooth muscle myosin light chain, tyrosine e<br>hydroxylase, calcineurin, myelin basic protein, ribosomal n<br>protein S6, and Ca<sup>2+</sup>/calmodulin-sensitive cyclic nucleo-<br>tide phosphodiesterase are among the proteins t hydroxylase, calcineurin, myelin basic protein, ribosomal<br>protein S6, and Ca<sup>2+</sup>/calmodulin-sensitive cyclic nucleo-<br>tide phosphodiesterase are among the proteins that ap-<br>pear to be relatively good substrates for this enz protein S6, and Ca<sup>2+</sup>/calmodulin-sensitive cyclic nucleotide phosphodiesterase are among the proteins that appear to be relatively good substrates for this enzyme (Endo and Hidaka, 1980; Yamauchi and Fujisawa, 1982; McGui tide phosphodiesterase are among the proteins that appear to be relatively good substrates for this enzyme (Endo and Hidaka, 1980; Yamauchi and Fujisawa, 1982; McGuinness et al., 1983; Iwasa et al., 1984; Pearson et al., 1 pear to be relatively good substrates for this enzym<br>(Endo and Hidaka, 1980; Yamauchi and Fujisawa, 198<br>McGuinness et al., 1983; Iwasa et al., 1984; Pearson<br>al., 1985; Sharma and Wang, 1986; Hashimoto et a<br>1988; for review McGuinness et al., 1983; Iwasa et al., 1984; Pearson et al., 1985; Sharma and Wang, 1986; Hashimoto et al., 1988; for reviews, see McGuinness et al., 1985b; Schulman, 1988).<br>The purified, native enzyme from brain has a mol al., 1985; Sharma and Wang, 1986; Hashimoto et al..

The purified, native enzyme from brain has a molec-<br>ull of which cross-react with monoclonal antibodies pre-<br>ular mass of 500 to 700 kDa (Bennett et al., 1983; pared against CaM kinase II from rat forebrain (Mc-<br>McGuinnes man, 1988). We vanish the suburband mass of 500 to 700 kDa (Bennett et al., 1983; particular mass of 500 to 700 kDa (Bennett et al., 1983; particular mass et al., 1985a). The complementary DNAs Grading for the subunits of The purified, native enzyme from brain has a molecular mass of 500 to 700 kDa (Bennett et al., 1983; McGuinness et al., 1985a). The complementary DNAs coding for the subunits of rat brain CaM kinase II have recently been i ular mass of 500 to 700 kDa (Bennett et al., 1983<br>McGuinness et al., 1985a). The complementary DNA<br>coding for the subunits of rat brain CaM kinase II hav<br>recently been isolated and characterized and their de<br>duced amino ac McGuinness et al., 1985a). The complementary DNA<br>coding for the subunits of rat brain CaM kinase II have<br>recently been isolated and characterized and their d<br>duced amino acid sequences described (Bennett and Ker<br>nedy, 1987 coding for the subunits of rat brain CaM kinase II have depending to recently been isolated and characterized and their de-<br>duced amino acid sequences described (Bennett and Kennedy, 1987; Lin et al., 1987; Bulleit et al. recently been isolated and characterized and their de-<br>duced amino acid sequences described (Bennett and Ken-<br>nedy, 1987; Lin et al., 1987; Bulleit et al., 1988; Tobi-<br>matsu et al., 1988; Tobimatsu and Fujisawa, 1989). Th duced amino acid sequences described (Bennett and Kennedy, 1987; Lin et al., 1987; Bulleit et al., 1988; Tobi-<br>matsu et al., 1988; Tobimatsu and Fujisawa, 1989). These is<br>studies showed that the enzyme is composed of majo nedy, 1987; Lin et al., 1987; Bulleit et al., 1988; Tobi-<br>matsu et al., 1988; Tobimatsu and Fujisawa, 1989). These is b<br>studies showed that the enzyme is composed of major  $\alpha$ - caln<br>subunits of 54 kDa, together with  $\beta$ matsu et al., 1988; Tobimatsu and Fujisawa, 1989). These is<br>studies showed that the enzyme is composed of major  $\alpha$ -<br>subunits of 54 kDa, together with  $\beta$ - and  $\beta'$ -subunits of the<br>60 and 58 kDa, respectively, and  $\gamma$ studies showed that the enzyme is composed of major  $\alpha$ -<br>subunits of 54 kDa, together with  $\beta$ - and  $\beta'$ -subunits of<br>60 and 58 kDa, respectively, and  $\gamma$ - and  $\delta$ -subunits of 59<br>and 60 kDa, respectively. Moreover, th subunits of 54 kDa, together with  $\beta$ - and  $\beta'$ -subunits of 59<br>60 and 58 kDa, respectively, and  $\gamma$ - and  $\delta$ -subunits of 59<br>and 60 kDa, respectively. Moreover, these subunits are<br>the products of highly homologous tran 60 and 58 kDa, respectively, and  $\gamma$ - and  $\delta$ -subunits of 5 and 60 kDa, respectively. Moreover, these subunits at the products of highly homologous transcription unit<br>with the presence or absence of amino acid insertion and 60 kDa, respectively. Moreover, these subunits are<br>the products of highly homologous transcription units,<br>with the presence or absence of amino acid insertions at<br>the COOH-terminal side of the calmodulin-binding do-<br>ma the products of highly homologous transcription units,<br>with the presence or absence of amino acid insertions at<br>the COOH-terminal side of the calmodulin-binding do-<br>main accounting for the different sizes of the subunits<br>( with the presence or absence of amino acid insertions at<br>the COOH-terminal side of the calmodulin-binding do-<br>main accounting for the different sizes of the subunits<br>(Schulman, 1988; Tobimatsu and Fujisawa, 1989). All<br>subu the COOH-terminal side of the calmodulin-bindi<br>main accounting for the different sizes of the su<br>(Schulman, 1988; Tobimatsu and Fujisawa, 198<br>subunits contain three domains, designated the ca<br>protein kinase domain, the reg main accounting for the different sizes of the subunits (Schulman, 1988; Tobimatsu and Fujisawa, 1989). Alsubunits contain three domains, designated the catalytic protein kinase domain, the regulatory, calmodulin-binding (Schulman, 1988; Tobimatsu and Fujisawa, 1989). All subunits contain three domains, designated the catalytic protein kinase domain, the regulatory, calmodulin-bind-<br>ing domain, and the association domain (Schulman, 1988). subunits contain three domains, designated the catalytic function is protein kinase domain, the regulatory, calmodulin-bind-<br>ing domain, and the association domain (Schulman, 1988). All subunits can be autophosphorylated protein kinase domain, the regulatory, calmodulin-bind-<br>ing domain, and the association domain (Schulman,<br>1988). All subunits can be autophosphorylated in a  $Ca^{2+}/$ <br>calmodulin-dependent manner and can bind calmodulin<br>and g domain, and the association domain (Schulman, C<br>88). All subunits can be autophosphorylated in a  $Ca^{2+}/$  almodulin-dependent manner and can bind calmodulin 1<br>id ATP (for examples, see McGuinness et al., 1985a). et<br>The e

distinct CaM kinases, CaM kinase I, which phosphoryl-<br>are primarily found in brain, whereas transcripts for the<br>ates the same serine residue (site 1) as does cyclic AMP-<br> $\gamma$ - and  $\delta$ -subunits are present in a number of **PROTEIN PHOSPHORYLATION AND NEURONAL FUNCTION** 307<br>al., 1971; Ueda and Green-homomeric complexes containing 10 to 12 subunits (Ben-<br>be phosphorylated by two nett et al., 1983). Transcripts for the  $\alpha$ - and  $\beta$ -subunits AND NEURONAL FUNCTION 307<br>homomeric complexes containing 10 to 12 subunits (Ben-<br>nett et al., 1983). Transcripts for the  $\alpha$ - and  $\beta$ -subunits<br>are primarily found in brain, whereas transcripts for the AND NEURONAL FUNCTION 307<br>homomeric complexes containing 10 to 12 subunits (Ben-<br>nett et al., 1983). Transcripts for the  $\alpha$ - and  $\beta$ -subunits<br>are primarily found in brain, whereas transcripts for the<br> $\gamma$ - and  $\delta$ -sub homomeric complexes containing 10 to 12 subunits (Bennett et al., 1983). Transcripts for the  $\alpha$ - and  $\beta$ -subunits are primarily found in brain, whereas transcripts for the  $\gamma$ - and  $\delta$ -subunits are present in a numbe homomeric complexes containing 10 to 12 subunits (Bennett et al., 1983). Transcripts for the  $\alpha$ - and  $\beta$ -subunits are primarily found in brain, whereas transcripts for the  $\gamma$ - and  $\delta$ -subunits are present in a numbe nett et al., 1983). Transcripts for the  $\alpha$ - and  $\beta$ -subunits<br>are primarily found in brain, whereas transcripts for the<br> $\gamma$ - and  $\delta$ -subunits are present in a number of tissues<br>(Tobimatsu and Fujisawa, 1989). Both the  $\gamma$ - and  $\delta$ -subunits are present in a number of tissues<br>(Tobimatsu and Fujisawa, 1989). Both the  $\alpha$ - and  $\beta$ -<br>subunits have been expressed in nonneuronal cells, and<br>these studies have shown that the  $\alpha$ -subunit, ex subunits have been expressed in nonneuronal cells, and<br>these studies have shown that the  $\alpha$ -subunit, expressed<br>alone, behaves identically with the holoenzyme with<br>respect to aggregation, autophosphorylation, and ensuing subunits have been expressed in nonneuronal cells, at<br>hese studies have shown that the  $\alpha$ -subunit, express<br>alone, behaves identically with the holoenzyme w<br>respect to aggregation, autophosphorylation, and ensu<br>calmoduli these studies have shown that the  $\alpha$ -subunit, expressed<br>alone, behaves identically with the holoenzyme with<br>respect to aggregation, autophosphorylation, and ensuing<br>calmodulin independence (Hanson et al., 1989; Yamau-<br>c respect to aggregation, autophosphorylation, and ensuing calmodulin independence (Hanson et al., 1989; Yamau-<br>chi et al., 1989). In contrast, expression of the  $\beta$ -subunit<br>alone led to an enzyme that did not aggregate, a respect to aggregation, autophosphorylation, and ensuing<br>calmodulin independence (Hanson et al., 1989; Yamau-<br>chi et al., 1989). In contrast, expression of the  $\beta$ -subunit<br>alone led to an enzyme that did not aggregate, a calmodulin independence (Hanson et al., 1989; Yamau-<br>chi et al., 1989). In contrast, expression of the  $\beta$ -subunit<br>alone led to an enzyme that did not aggregate, although<br>autophosphorylation and the ensuing  $Ca^{2+}/calcalend}$ ca chi et al., 1989). In contrast, expression of the  $\beta$ -subunit<br>alone led to an enzyme that did not aggregate, although<br>autophosphorylation and the ensuing  $Ca^{2+}/calmodulin$ <br>independence (see below) was also seen with this iso-<br> alone led to an enzyme that did not aggregate, although autophosphorylation and the ensuing  $Ca^{2+}/cal{c}$ dmodulin independence (see below) was also seen with this isozymic form (Yamauchi et al., 1989). Thus, both enzyme act autophosphorylation and<br>independence (see below<br>zymic form (Yamauchi e<br>activity and modulatory µ<br>to the different subunits.<br>A number of CaM kina dependence (see below) was also seen with this isomic form (Yamauchi et al., 1989). Thus, both enzyme<br>tivity and modulatory properties appear to be inherent<br>the different subunits.<br>A number of CaM kinases prepared from tis

Guinness et al., 1985a). Purified CaM kinase II exhibits than brain, including Torpedo californica electric organ a broad substrate specificity, with synapsin I (sites 2 and (Palfrey et al., 1983b), turkey erythrocytes (P al., 1985; Sharma and Wang, 1986; Hashimoto et al., of tryptic peptides with the brain enzyme (Shenolikar et 1988; for reviews, see McGuinness et al., 1985b; Schul-<br>man, 1988).<br>with apparent molecular masses of 59, 58, an zymic form (Yamauchi et al., 1989). Thus, both enzyme<br>activity and modulatory properties appear to be inherent<br>to the different subunits.<br>A number of CaM kinases prepared from tissues other<br>than brain, including *Torpedo c* activity and modulatory properties appear to be inherent<br>to the different subunits.<br>A number of CaM kinases prepared from tissues other<br>than brain, including *Torpedo californica* electric organ<br>(Palfrey et al., 1983b), tu to the different subunits.<br>
A number of CaM kinases prepared from tissues other<br>
than brain, including *Torpedo californica* electric organ<br>
(Palfrey et al., 1983b), turkey erythrocytes (Palfrey et<br>
al., 1983a), mammalian A number of CaM kinases prepared from tissues other<br>than brain, including *Torpedo californica* electric organ<br>(Palfrey et al., 1983b), turkey erythrocytes (Palfrey et<br>al., 1983a), mammalian heart (Jett et al., 1987), live than brain, including *Torpedo californica* electric organ (Palfrey et al., 1983b), turkey erythrocytes (Palfrey et al., 1983a), mammalian heart (Jett et al., 1987), liver (Ahmad et al., 1982; Payne et al., 1983), lung (Sc al., 1983a), mammalian heart (Jett et al., 1987), liver al., 1983a), mammalian heart (Jett et al., 1987), liver<br>(Ahmad et al., 1982; Payne et al., 1983), lung (Schulman<br>et al., 1985), pancreas (Gorelick et al., 1983), and skeletal<br>muscle (Woodgett et al., 1982), have properties (Ahmad et al., 1982; Payne et al., 1983), lung (Schulman<br>
et al., 1985), pancreas (Gorelick et al., 1983), and skeletal<br>
muscle (Woodgett et al., 1982), have properties similar<br>
to those of CaM kinase II from brain. For e et al., 1985), pancreas (Gorelick et al., 1983), and skeletal muscle (Woodgett et al., 1982), have properties similar to those of CaM kinase II from brain. For example, Ca<sup>2+</sup>/calmodulin-dependent glycogen synthase kinase muscle (Woodgett et al., 1982), have properties similar<br>to those of CaM kinase II from brain. For example, Ca<sup>2+</sup>/<br>calmodulin-dependent glycogen synthase kinase from<br>skeletal muscle displays a substrate specificity identic to those of CaM kinase II from brain. For example, Ca<sup>2+</sup>/<br>calmodulin-dependent glycogen synthase kinase from<br>skeletal muscle displays a substrate specificity identical<br>with that of CaM kinase II (McGuinness et al., 1983), calmodulin-dependent glycogen synthase kinase from<br>skeletal muscle displays a substrate specificity identical<br>with that of CaM kinase II (McGuinness et al., 1983),<br>has a native molecular mass of 800 kDa, shares a number<br>of skeletal muscle displays a substrate specificity identical<br>with that of CaM kinase II (McGuinness et al., 1983),<br>has a native molecular mass of 800 kDa, shares a number<br>of tryptic peptides with the brain enzyme (Shenolikar with that of CaM kinase II (McGuinness et al., 1983), has a native molecular mass of 800 kDa, shares a number of tryptic peptides with the brain enzyme (Shenolikar et al., 1986), and contains autophosphorylatable subunits has a native molecular mass of 800 kDa, shares a number<br>of tryptic peptides with the brain enzyme (Shenolikar et<br>al., 1986), and contains autophosphorylatable subunits<br>with apparent molecular masses of 59, 58, and 54 kDa,<br> of tryptic peptides with the brain enzyme (Shenolikar e al., 1986), and contains autophosphorylatable subunit with apparent molecular masses of 59, 58, and 54 kDs all of which cross-react with monoclonal antibodies prepar al., 1986), and contains autophosphorylatable su<br>with apparent molecular masses of 59, 58, and 5<br>all of which cross-react with monoclonal antibodi<br>pared against CaM kinase II from rat forebrain<br>Guinness et al., 1983). The all of which cross-react with monoclonal antibodies preall of which cross-react with mon<br>pared against CaM kinase II fre<br>Guinness et al., 1983). These vai<br>dependent enzymes, therefore, a<br>zymic forms of CaM kinase II.<br>i. Regulation of activity. T red against CaM kinase II from rat forebrain (Mc-<br>inness et al., 1983). These various  $Ca^{2+}/calcdmoduli$ <br>pendent enzymes, therefore, appear to represent iso-<br>mic forms of CaM kinase II.<br>**i. Regulation of activity.** The mechanism

vation of CaM kinase II in brain by  $Ca^{2+}$  and calmodulin<br>is believed to be similar to that of most other  $Ca^{2+}/$ dependent enzymes, therefore, appear to represent iso-<br>zymic forms of CaM kinase II.<br>i. Regulation of activity. The mechanism of activation of CaM kinase II in brain by  $Ca^{2+}$  and calmodulin<br>is believed to be similar to zymic forms of CaM kinase II.<br>
i. Regulation of activity. The mechanism of activity<br>
vation of CaM kinase II in brain by Ca<sup>2+</sup> and calmodulin<br>
is believed to be similar to that of most other Ca<sup>2+</sup>/<br>
calmodulin-dependent i. Regulation of activity. The mechanism of activation of CaM kinase II in brain by  $Ca^{2+}$  and calmodulin is believed to be similar to that of most other  $Ca^{2+}/$  calmodulin-dependent enzymes, i.e., calmodulin will, in th vation of CaM kinase II in brain by Ca<sup>2+</sup> and calmod<br>is believed to be similar to that of most other C<br>calmodulin-dependent enzymes, i.e., calmodulin will<br>the presence of micromolar concentrations of C<br>undergo conformatio is believed to be similar to that of most other  $Ca^{2+}/$ <br>calmodulin-dependent enzymes, i.e., calmodulin will, in<br>the presence of micromolar concentrations of  $Ca^{2+}$ ,<br>undergo conformational changes that expose hydropho-<br>bi the presence of micromolar concentrations of  $Ca^{2+}$ , undergo conformational changes that expose hydrophobic domains in the molecule. These domains then bind to calmodulin-binding domains on the target enzyme (for review, undergo conformational changes that expose hydrophoundergo conformational changes that expose hydropho-<br>bic domains in the molecule. These domains then bind<br>to calmodulin-binding domains on the target enzyme (for<br>review, see Manalan and Klee, 1984). Recent studies<br>have sho bic domains in the molecule. These domains then bind<br>to calmodulin-binding domains on the target enzyme (for<br>review, see Manalan and Klee, 1984). Recent studies<br>have shown that autophosphorylation further modulates<br>CaM kin to calmodulin-binding domains on the target enzyme (for<br>review, see Manalan and Klee, 1984). Recent studie<br>have shown that autophosphorylation further modulate<br>CaM kinase II. Ca<sup>2+</sup>/calmodulin-induced activation lead<br>to a review, see Manalan and Klee, 1984). Recent studies<br>have shown that autophosphorylation further modulates<br>CaM kinase II. Ca<sup>2+</sup>/calmodulin-induced activation leads<br>to a rapid phosphorylation of threonine residues (Thr-<br>28 have shown that autophosphorylation further modulates<br>CaM kinase II. Ca<sup>2+</sup>/calmodulin-induced activation leads<br>to a rapid phosphorylation of threonine residues (Thr-<br>286 in the  $\alpha$ -subunit, Thr-287 in the  $\beta$ -subunit), CaM kinase II. Ca<sup>2+</sup>/calmodulin-induced activation leads<br>to a rapid phosphorylation of threonine residues (Thr-<br>286 in the  $\alpha$ -subunit, Thr-287 in the  $\beta$ -subunit), and this<br>leads to the enzyme becoming largely indepen to a rapid phosphorylation of threonine residues (Thr-286 in the  $\alpha$ -subunit, Thr-287 in the  $\beta$ -subunit), and this leads to the enzyme becoming largely independent of  $Ca^{2+}$  and calmodulin (Saitoh and Schwartz, 1985; 286 in the  $\alpha$ -subunit, Thr-287 in the  $\beta$ -subunit), and this<br>leads to the enzyme becoming largely independent of<br>Ca<sup>2+</sup> and calmodulin (Saitoh and Schwartz, 1985; Miller<br>and Kennedy, 1986; Lou et al., 1986; Lai et al., leads to the enzyme becoming largely independent of Ca<sup>2+</sup> and calmodulin (Saitoh and Schwartz, 1985; Miller and Kennedy, 1986; Lou et al., 1986; Lai et al., 1986, 1987; Thiel et al., 1988; Schworer et al., 1986; Hashimoto Ca<sup>2+</sup> and calmodulin (Saitoh and Schwartz, 1985; Miller<br>and Kennedy, 1986; Lou et al., 1986; Lai et al., 1986,<br>1987; Thiel et al., 1988; Schworer et al., 1986; Hashimoto<br>et al., 1987; Fukunaga et al., 1989; Waxham et al.,

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the enzyme and, thus, prolong the duration of the cellular<br>the enzyme and, thus, prolong the duration of the cellular<br>response to a transient elevation of  $Ca^{2+}$ . However, the 308 waLaas and thus, prolong the duration of the cellular response to a transient elevation of  $Ca^{2+}$ . However, the wigeneration of the  $Ca^{2+}/cal$ calmodulin-independent form of its 308 waLAAS AND GF<br>the enzyme and, thus, prolong the duration of the cellular<br>response to a transient elevation of  $Ca^{2+}$ . However, the<br>generation of the  $Ca^{2+}/cal$ calmodulin-independent form of it<br>the enzyme is reversed by the enzyme and, thus, prolong the duration of the cell<br>response to a transient elevation of  $Ca^{2+}$ . However,<br>generation of the  $Ca^{2+}/calmathrm{calmod}$ ulin-independent form<br>the enzyme is reversed by the action of protein phosp<br>tase the enzyme and, thus, prolong the duration of the cellular in response to a transient elevation of  $Ca^{2+}$ . However, the widd generation of the  $Ca^{2+}/cal$  calmodulin-independent form of its he enzyme is reversed by the acti response to a transient elevation of  $Ca^{2+}$ . However, the generation of the  $Ca^{2+}/cal$ calmodulin-independent form of it the enzyme is reversed by the action of protein phosphantases (Saitoh et al., 1987; Shields et al., 19 generation of the Ca<sup>2+</sup>/calmodulin-independent form of<br>the enzyme is reversed by the action of protein phospha-<br>tases (Saitoh et al., 1987; Shields et al., 1985), and in<br>intact nerve terminals both the autophosphorylatio the enzyme is reversed by the action of protein phosphatases (Saitoh et al., 1987; Shields et al., 1985), and in essintact nerve terminals both the autophosphorylation of prof. Thr-286 in the  $\alpha$ -subunit and the generati tases (Saitoh et al., 1987; Shields et al., 1985), and<br>intact nerve terminals both the autophosphorylation<br>Thr-286 in the  $\alpha$ -subunit and the generation of the Ca<br>calmodulin-independent form of the enzyme were fou<br>to be Thr-286 in the  $\alpha$ -subunit and the generation of the Ca<sup>2+</sup>/ C<sub>2</sub> calmodulin-independent form of the enzyme were found giato be transient, making the extent to which this mechanism operates in generation of prolonged res to be transient, making the extent to which this mechanism operates in generation of prolonged responses in intact nervous tissue somewhat unclear (Gorelick et al., 1988). Finally, recent studies have indicated that arachi intact nervous tissue somewhat unclear (Gorelick et al., intact nervous tissue somewhat unclear (Gorelick et al., 1988). Finally, recent studies have indicated that arachidonic acid and lipoxygenase derivatives can inhibit CaM kinase II both in vitro and in preparations containi 1988). Finally, recent studies have indicated that are donic acid and lipoxygenase derivatives can inhibit kinase II both in vitro and in preparations conta isolated nerve terminals, suggesting a role for these ond messeng donic acid and lipoxygenase derivatives can inhibit CaM<br>kinase II both in vitro and in preparations containing<br>isolated nerve terminals, suggesting a role for these sec-<br>ond messengers in regulating this protein phosphoryl ond messengers in regulating this protein phosphorylation system in intact nerve cells (Piomelli et al., 1989).<br> **ii. Distribution in brain.** CaM kinase II is present<br>
in very high concentrations in the brain, comprising a isolated nerve terminals, suggesting a role for these sectional measurements in regulating this protein phosphorylation system in intact nerve cells (Piomelli et al., 1989). en in **Distribution in brain**. CaM kinase II is

ond messengers in regulating this protein phosphorylation system in intact nerve cells (Piomelli et al., 1989).<br> **ii. Distribution in brain.** CaM kinase II is present in very high concentrations in the brain, comprising as tion system in intact nerve cells (Piomelli et al., 1989). en<br>ii. Distribution in brain. CaM kinase II is present main<br>in very high concentrations in the brain, comprising as<br>tion<br>much as 2% of total protein in certain bra ii. Distribution in brain. CaM kinase II is present may<br>in very high concentrations in the brain, comprising as tion<br>much as 2% of total protein in certain brain regions synt<br>(Erondu and Kennedy, 1985). The enzyme is found in very high concentrations in the brain, comprising as much as 2% of total protein in certain brain regions (Erondu and Kennedy, 1985). The enzyme is found throughout nerve cells, being particularly enriched in dendrites much as 2% of total protein in certain brain regions (Erondu and Kennedy, 1985). The enzyme is found throughout nerve cells, being particularly enriched in dendrites (Ouimet et al., 1984a; Erondu and Kennedy, 1985), but al (Erondu and Kennedy, 1985). The enzyme is found<br>throughout nerve cells, being particularly enriched in<br>dendrites (Ouimet et al., 1984a; Erondu and Kennedy,<br>1985), but also being concentrated in certain populations<br>of nerve throughout nerve cells, being particularly enriched in be<br>dendrites (Ouimet et al., 1984a; Erondu and Kennedy, sp<br>1985), but also being concentrated in certain populations In<br>of nerve terminals (Walaas et al., 1989c). In a dendrites (Ouimet et al., 1984a; Erondu and Kenned 1985), but also being concentrated in certain populatio of nerve terminals (Walaas et al., 1989c). In a region survey of CaM kinase II activity in rat brain, high activity 1985), but also being concentrated in certain populations In<br>of nerve terminals (Walaas et al., 1989c). In a regional tei<br>survey of CaM kinase II activity in rat brain, high activity an<br>was found in cortical regions, parti of nerve terminals (Walaas et al., 1989c). In a regional survey of CaM kinase II activity in rat brain, high activity was found in cortical regions, particularly in the hippocampus, and relatively low activity was found i survey of CaM kinase II activity in rat brain, high activity a<br>was found in cortical regions, particularly in the hippo-<br>campus, and relatively low activity was found in the<br>cerebellum, brain stem, and spinal cord (Walaas was found in cortical regions, particularly in the hippo<br>campus, and relatively low activity was found in the<br>cerebellum, brain stem, and spinal cord (Walaas et al.<br>1983b,c). Moreover, the  $\alpha$ - and  $\beta$ -subunits of the e campus, and relatively low activity was found in the cerebellum, brain stem, and spinal cord (Walaas et al., 1983b,c). Moreover, the  $\alpha$ - and  $\beta$ -subunits of the enzyme differ in their regional and cellular localization cerebellum, bra<br>1983b,c). More<br>differ in their<br>Guinness et al.,<br>et al., 1988b).<br>The subunit 1983b,c). Moreover, the  $\alpha$ - and  $\beta$ -subunits of the enzyme enzyme is presently unknown.<br>differ in their regional and cellular localizations (Mc-<br>Guinness et al., 1985a; Miller and Kennedy, 1985; Walaas This enzyme has

differ in their regional and cellular localizations (Mc-<br>Guinness et al., 1985a; Miller and Kennedy, 1985; Walaas<br>et al., 1988b).<br>The subunits of the enzyme have been found to be<br>present in postsynaptic density fractions, Guinness et al., 1985a; Miller and Kennedy, 1985; Walaas This<br>et al., 1988b). from<br>The subunits of the enzyme have been found to be (Na<br>present in postsynaptic density fractions, which are sub-<br>membranous postsynaptic fibr et al., 1988b).<br>The subunits of the enzyme have been found to be<br>present in postsynaptic density fractions, which are sub-<br>membranous postsynaptic fibrous structures enriched in<br>asymmetrical excitatory synapses in mammali The subunits of the enzyme have been found to be (N<br>present in postsynaptic density fractions, which are sub-<br>membranous postsynaptic fibrous structures enriched in syn<br>asymmetrical excitatory synapses in mammalian brain. present in postsynaptic density fractions, which are sub-<br>membranous postsynaptic fibrous structures enriched in<br>asymmetrical excitatory synapses in mammalian brain.<br>Indeed, the  $\alpha$ -subunit of the kinase is identical wit membranous postsynaptic fibrous structures enriched in<br>asymmetrical excitatory synapses in mammalian brain.<br>Indeed, the  $\alpha$ -subunit of the kinase is identical with the<br>"major postsynaptic density protein" (Kelly and Cotm asymmetrical excitatory synapses in mammalian brain.<br>Indeed, the  $\alpha$ -subunit of the kinase is identical with the<br>"major postsynaptic density protein" (Kelly and Cotman,<br>1978) and represents 20 to 50% of total postsynapti Indeed, the  $\alpha$ -subunit of the kinase is identical with the<br>"major postsynaptic density protein" (Kelly and Cotman,<br>1978) and represents 20 to 50% of total postsynaptic<br>density protein (Kennedy et al., 1983; Kelly et al. 1978) and represents 20 to 50% of total postsynaptic density protein (Kennedy et al., 1983; Kelly et al., 1984; Goldenring et al., 1984). The nature of the association between the usually soluble CaM kinase II (McGuinness 1978) and represents 20 to 50% of total postsynaptic ((density protein (Kennedy et al., 1983; Kelly et al., 1984; for Goldenring et al., 1984). The nature of the association appletive postsynaptic density et al., 1985b) an density protein (Kennedy et al., 1983; Kelly et al., 1984; foldenring et al., 1984). The nature of the association appetween the usually soluble CaM kinase II (McGuinness het al., 1985b) and the insoluble postsynaptic dens Goldenring et al., 1984). The nature of the association<br>between the usually soluble CaM kinase II (McGuinness<br>et al., 1985b) and the insoluble postsynaptic density<br>structure appears intriguing. Although the regulation of<br>t between the usually soluble CaM kinase II (McGuinness<br>et al., 1985b) and the insoluble postsynaptic density<br>structure appears intriguing. Although the regulation of<br>the postsynaptic density-associated enzyme appears sim-<br>i et al., 1985b) and the insoluble postsynaptic density examined, suggesting that additional physiological sub-<br>structure appears intriguing. Although the regulation of strates for the enzyme exist (Nairn and Greengard, 198 structure appears intriguing. Although the regulation of<br>the postsynaptic density-associated enzyme appears sim-<br>ilar to that found in the soluble enzyme, the former<br>enzyme appears to have an unusually low specific activit the postsynaptic density-associated enzyme appears similar to that found in the soluble enzyme, the former enzyme appears to have an unusually low specific activity (Rostas et al., 1986; Rich et al., 1989). Whether intrins ilar to that found in the soluble enzyme, the former<br>enzyme appears to have an unusually low specific activity<br>(Rostas et al., 1986; Rich et al., 1989). Whether intrinsic<br>postsynaptic density proteins are physiological sub enzyme appears to have an unusually low specific activity specifica (Rostas et al., 1986; Rich et al., 1989). Whether intrinsic as maming postsynaptic density proteins are physiological sub-<br>postsynaptic density proteins a (Rostas et al., 1986; Rich et al., 1989). Whether intrins postsynaptic density proteins are physiological sultates for CaM kinase II (Gurd, 1985) remains unclear Therefore, the high levels and tight association of Cal kina postsynaptic density proteins are physiological sub-<br>strates for CaM kinase II (Gurd, 1985) remains unclear. al<br>Therefore, the high levels and tight association of CaM el<br>kinase II with the postsynaptic density remain unex strates for CaM kinase II (Gurd, 1985) remains unclear. al.<br>Therefore, the high levels and tight association of CaM elconsise II with the postsynaptic density remain unex-<br>plained, and possible structurel, nonenzymatic rol Therefore, the high levels and tight asso<br>kinase II with the postsynaptic density<br>plained, and possible structural, nonenz<br>the protein in this structure have been s<br>and Cotman, 1978; Rostas et al., 1986).

nism operates in generation of prolonged responses in abilized synaptosomes from rat cerebral cortex (Nichols intact nervous tissue somewhat unclear (Gorelick et al., et al., 1990) indicate that depolarization-induced neur WALAAS AND GREENGARD<br>ithe cellular **iii. Functional importance in nerve cells.** The<br>owever, the widespread distribution of CaM kinase II in brain and its broad substrate specificity suggest that this enzyme GREENGARD<br>iii. **Functional importance in nerve cells.** The<br>widespread distribution of CaM kinase II in brain and<br>its broad substrate specificity suggest that this enzyme<br>mediates or modulates a variety of  $Ca^{2+}$ -regulate iii. Functional importance in nerve cells. The widespread distribution of CaM kinase II in brain an its broad substrate specificity suggest that this enzym mediates or modulates a variety of  $Ca^{2+}$ -regulated processes in iii. Functional importance in nerve cells. The widespread distribution of CaM kinase II in brain and its broad substrate specificity suggest that this enzyme mediates or modulates a variety of  $Ca^{2+}$ -regulated processes widespread distribution of CaM kinase II in brain and<br>its broad substrate specificity suggest that this enzyme<br>mediates or modulates a variety of  $Ca^{2+}$ -regulated proc-<br>esses in the nervous system. Evidence for an import its broad substrate specificity suggest that this enzyme<br>mediates or modulates a variety of Ca<sup>2+</sup>-regulated proc-<br>esses in the nervous system. Evidence for an important<br>presynaptic role has been obtained. Direct injection esses in the nervous system. Evidence for an important presynaptic role has been obtained. Direct injection of CaM kinase II into the presynaptic digit of the squid giant axon (Llinás et al., 1985, in press; Lin et al., 19 presynaptic role has been obtained. Direct injection of abilized synaptosomes from rat cerebral cortex (Nichols and introduction of the enzyme into transiently permegiant axon (Llinás et al., 1985, in press; Lin et al., 1990), and introduction of the enzyme into transiently perme-<br>abilized synaptosomes from rat cerebral cortex (Nichols et al., 1990) indicate that depolarization-induce and introduction of the enzyme into transiently perme-<br>abilized synaptosomes from rat cerebral cortex (Nichols<br>et al., 1990) indicate that depolarization-induced neuro-<br>transmitter release from nerve terminals is potentiat abilized synaptosomes from rat cerebral cortex (Nichols et al., 1990) indicate that depolarization-induced neuro-<br>transmitter release from nerve terminals is potentiated<br>by this enzyme, possibly through phosphorylation of<br> et al., 1990) indicate that depolarization-induced neuro-<br>transmitter release from nerve terminals is potentiated<br>by this enzyme, possibly through phosphorylation of<br>synapsin I. In the case of the squid giant axon studies, transmitter release from nerve terminals is potentiated<br>by this enzyme, possibly through phosphorylation of<br>synapsin I. In the case of the squid giant axon studies,<br>this effect was seen without any apparent effect on ion<br>c by this enzyme, possibly through phosphorylation of synapsin I. In the case of the squid giant axon studies, this effect was seen without any apparent effect on ion channel properties (Llinás et al., 1985, in press;). The synapsin I. In the case of the squid giant axon studies this effect was seen without any apparent effect on channel properties (Llinás et al., 1985, in press;). enrichment of the enzyme in dendrites indicates this may als this effect was seen without any apparent effect on io:<br>channel properties (Llinás et al., 1985, in press;). Th<br>enrichment of the enzyme in dendrites indicates that i<br>may also be involved in responses following depolariza<br> channel properties (Llinás et al., 1985, in press;). The enrichment of the enzyme in dendrites indicates that it may also be involved in responses following depolarization-induced or receptor-induced  $Ca^{2+}$  influx into p enrichment of the enzyme in dendrites indicates that it may also be involved in responses following depolarization-induced or receptor-induced  $Ca^{2+}$  influx into post-synaptic compartments. Injection of peptide inhibitor may also be involved in responses following depolariza-<br>tion-induced or receptor-induced  $Ca^{2+}$  influx into post-<br>synaptic compartments. Injection of peptide inhibitors<br>of CaM kinase II into hippocampal pyramidal cells h synaptic compartments. Injection of peptide inhibitors<br>of CaM kinase II into hippocampal pyramidal cells has<br>been reputed to prevent certain neurophysiological re-<br>sponses (Malenka et al., 1989a,b; Malinow et al., 1989).<br>I synaptic compartments. Injection of peptide inhibitors<br>of CaM kinase II into hippocampal pyramidal cells has<br>been reputed to prevent certain neurophysiological re-<br>sponses (Malenka et al., 1989a,b; Malinow et al., 1989).<br>I of CaM kinase II into hippocampal pyramidal cells has<br>been reputed to prevent certain neurophysiological re-<br>sponses (Malenka et al., 1989a,b; Malinow et al., 1989).<br>In addition, a number of postsynaptically localized probeen reputed to prevent certain neurophysiological responses (Malenka et al., 1989a,b; Malinow et al., 1989).<br>In addition, a number of postsynaptically localized proteins, including membrane glycoproteins (Gurd, 1985)<br>and sponses (Malenka et al., 1989a,b; Malinow et al., 1989).<br>In addition, a number of postsynaptically localized proteins, including membrane glycoproteins (Gurd, 1985)<br>and cytoskeletal proteins (Yamauchi and Fujisawa, 1982;<br>G In addition, a number of postsynaptically localized proteins, including membrane glycoproteins (Gurd, 1985) and cytoskeletal proteins (Yamauchi and Fujisawa, 1982; Goldenring et al., 1983; Vallano et al., 1985), are possib teins, including membrane glycoproteins (Gurd, 1985)<br>and cytoskeletal proteins (Yamauchi and Fujisawa, 1982;<br>Goldenring et al., 1983; Vallano et al., 1985), are possible<br>substrates for CaM kinase II. Nevertheless, the exac and cytoskeletal proteins (Yan<br>Goldenring et al., 1983; Vallan<br>substrates for CaM kinase II<br>nature of the postsynaptic re<br>enzyme is presently unknown.<br>b. CA<sup>2+</sup>/CALMODULIN-DEPEP

substrates for CaM kinase II. Nevertheless, the exact<br>nature of the postsynaptic responses mediated by this<br>enzyme is presently unknown.<br>b. CA<sup>2+</sup>/CALMODULIN-DEPENDENT PROTEIN KINASE I.<br>This enzyme has been purified to app nature of the postsynaptic responses mediated by this<br>enzyme is presently unknown.<br>b.  $CA^{2+}/CALMODULIN-DEPENDENT$  PROTEIN KINASE I.<br>This enzyme has been purified to apparent homogeneity<br>from bovine brain, using synapsin I (site 1) as enzyme is presently unknown.<br>
b. CA<sup>2+</sup>/CALMODULIN-DEPENDENT PROTEIN KINASE I.<br>
This enzyme has been purified to apparent homogeneity<br>
from bovine brain, using synapsin I (site 1) as substrate<br>
(Nairn and Greengard, 1987). This enzyme has been purified to apparent homogeneity<br>from bovine brain, using synapsin I (site 1) as substrate<br>(Nairn and Greengard, 1987). At present, CaM kinase I<br>has been found to efficiently phosphorylate only the<br>syn from bovine brain, using synapsin I (site 1) as substrate<br>(Nairn and Greengard, 1987). At present, CaM kinase I<br>has been found to efficiently phosphorylate only the<br>synaptic vesicle-associated proteins synapsins I and II<br>( (Nairn and Greengard, 1987). At present, CaM kinase I<br>has been found to efficiently phosphorylate only the<br>synaptic vesicle-associated proteins synapsins I and II<br>(see section IV.A.2), and these phosphorylations take<br>place has been found to efficiently phosphorylate only the synaptic vesicle-associated proteins synapsins I and II (see section IV.A.2), and these phosphorylations take place on serine residues located in domains in the two prot synaptic vesicle-associated proteins synapsins I and II (see section IV.A.2), and these phosphorylations take place on serine residues located in domains in the two proteins that show extensive homologies to each other (Cz (see section IV.A.2), and these phosphorylations take<br>place on serine residues located in domains in the two<br>proteins that show extensive homologies to each other<br>(Czernik et al., 1987; Südhof et al., 1989). The enzyme is<br> place on serine residues located in domains in the two<br>proteins that show extensive homologies to each other<br>(Czernik et al., 1987; Südhof et al., 1989). The enzyme is<br>found in highest concentrations in the brain, where it (Czernik et al., 1987; Südhof et al., 1989). The enzyme is found in highest concentrations in the brain, where it appears to be present in all parts of nerve cells. It has, however, also been found in cytosol from all rat strates for the enzyme exist (Nairn and Greengard, 1987). found in highest concentrations in the brain, where it appears to be present in all parts of nerve cells. It has, however, also been found in cytosol from all rat tissues examined, suggesting that additional physiological however, also been found in cytosol from all rat tissues<br>examined, suggesting that additional physiological sub-<br>strates for the enzyme exist (Nairn and Greengard, 1987).<br>c. CA<sup>2+</sup>/CALMODULIN-DEPENDENT PROTEIN KINASE III.<br>

examined, suggesting that additional physiological substrates for the enzyme exist (Nairn and Greengard, 1987).<br>
c.  $CA^{2+}/CALMODULIN-DEFENDENT PROTEIN KINASE III.$ <br>
This enzyme, which is highly enriched in pancreas and<br>
specifically phosphoryla strates for the enzyme exist (Nairn and Greengard, 1987).<br>c. CA<sup>2+</sup>/CALMODULIN-DEPENDENT PROTEIN KINASE III.<br>This enzyme, which is highly enriched in pancreas and<br>specifically phosphorylates a 100-kDa protein identified<br>as This enzyme, which is highly enriched in pancreas and<br>specifically phosphorylates a 100-kDa protein identified<br>as mammalian elongation factor-2 (Nairn and Palfrey,<br>1987; Ryazanov, 1987), is also present in brain (Nairn et<br> specifically phosphorylates a 100-kDa protein identified<br>as mammalian elongation factor-2 (Nairn and Palfrey,<br>1987; Ryazanov, 1987), is also present in brain (Nairn et<br>al., 1985a). CaM kinase III-catalyzed phosphorylation as mammalian elongation factor-2 (Nairn and Palfrey, 1987; Ryazanov, 1987), is also present in brain (Nairn et al., 1985a). CaM kinase III-catalyzed phosphorylation of elongation factor-2 has been found to inhibit ribosoma 1987; Ryazanov, 1987), is also present in brain (Nairn et al., 1985a). CaM kinase III-catalyzed phosphorylation of elongation factor-2 has been found to inhibit ribosomal protein synthesis in vitro (Nairn and Palfrey, 1987 al., 1985a). CaM kinase III-catalyzed phosphorylation of elongation factor-2 has been found to inhibit ribosomal protein synthesis in vitro (Nairn and Palfrey, 1987). Because CaM kinase III appears to be rapidly regulated elongation factor-2 has been found to inhibit ribosomal<br>protein synthesis in vitro (Nairn and Palfrey, 1987).<br>Because CaM kinase III appears to be rapidly regulated<br>in a variety of cells and tissues (Haycock et al., 1988a;

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**PROTEIN PHOSPHORYLATION A**<br>mitters, neuropeptides, and hormones that can regulate<br>the levels of intracellular Ca<sup>2+</sup>, protein synthesis in these **EXECUTE PROTEIN PHOSPHORYLATION AT THE SET OF SET INTEREST ASSET IN EXECUTE 15 AT A SET ALLOW THE SET ASSET AND THE SET AND THE SET AND COLLS THE SET AND NOTE CA2+, protein synthesis in these** protein synthesis in these **EXEMPLE PHOSPHORYLATION**<br>mitters, neuropeptides, and hormones that can regulate<br>the levels of intracellular  $Ca^{2+}$ , protein synthesis in these<br>cells may be regulated by such extracellular stimuli.<br>Moreover, nerve growth mitters, neuropeptides, and hormones that can regulate che levels of intracellular  $Ca^{2+}$ , protein synthesis in these poells may be regulated by such extracellular stimuli. In Moreover, nerve growth factor has been found mitters, neuropeptides, and hormones that can regulate of the levels of intracellular  $Ca^{2+}$ , protein synthesis in these procells may be regulated by such extracellular stimuli. Humoreover, nerve growth factor has been f cells may be regulated by such extracellular stimuli.<br>Moreover, nerve growth factor has been found to regulate<br>not the activity but the levels of the enzyme in PC12<br>cells, a pheochromocytoma cell line with neuron-like<br>prop cells may be regulated by such extracellular stimuli.<br>Moreover, nerve growth factor has been found to regulate<br>not the activity but the levels of the enzyme in PC12<br>cells, a pheochromocytoma cell line with neuron-like<br>prop Moreover, nerve growth factor has been found to regulate not the activity but the levels of the enzyme in PC1 cells, a pheochromocytoma cell line with neuron-lip properties, indicating that this enzyme may also be in volve not the activity but the<br>cells, a pheochromocyto<br>properties, indicating the<br>volved in long-term regul<br>ity (Nairn et al., 1987).<br>d. MYOSIN LIGHT CH. lls, a pheochromocytoma cell line with neuron-like kipperties, indicating that this enzyme may also be in-<br>lyed in long-term regulation of protein synthetic activ-<br>represent (Nairn et al., 1987).<br>d. MYOSIN LIGHT CHAIN KINA

properties, indicating that this enzyme may also be in-<br>volved in long-term regulation of protein synthetic activ-<br>ity (Nairn et al., 1987).<br>d. MYOSIN LIGHT CHAIN KINASE. This enzyme has (for<br>been purified from forebrain a properties in long-term regulation of protein synthetic activity (Nairn et al., 1987).<br>
d. MYOSIN LIGHT CHAIN KINASE. This enzyme has<br>
been purified from forebrain and has been found to have<br>
properties similar to those of ity (Nairn et al., 1987).<br>
d. MYOSIN LIGHT CHAIN KINASE. This enzyme has (if<br>
been purified from forebrain and has been found to have<br>
11<br>
properties similar to those of the smooth muscle enzyme, and<br>
including the specifi d. MYOSIN LIGHT CHAIN KINASE. This enzyme has<br>been purified from forebrain and has been found to have<br>properties similar to those of the smooth muscle enzyme,<br>including the specific phosphorylation of smooth muscle<br>myosin been purified from forebrain and has been found to have<br>properties similar to those of the smooth muscle enzyme,<br>including the specific phosphorylation of smooth muscle<br>myosin light chain (Dabrowska and Hartshorne, 1978;<br>D properties similar to those of the smooth muscle enzyme,<br>including the specific phosphorylation of smooth muscle<br>myosin light chain (Dabrowska and Hartshorne, 1978;<br>Dabrowska et al., 1978; Hathaway et al., 1981; Bartelt et myosin light chain (Dabrowska and Hartshorne, 1978;<br>Dabrowska et al., 1978; Hathaway et al., 1981; Bartelt et<br>al., 1987). Such phosphorylation is believed to be a pre-<br>requisite for interaction between myosin and actin (Se Dabrowska et al., 1978; Hathaway et al., 1981; Bartelt et al., 1987). Such phosphorylation is believed to be a pre-<br>requisite for interaction between myosin and actin (Sell-<br>ers and Adelstein, 1987), and the brain enzyme i Dabrowska et al., 1978; Hathaway et al., 1981; Bartelt et va<br>al., 1987). Such phosphorylation is believed to be a pre-<br>requisite for interaction between myosin and actin (Sell-<br>bers and Adelstein, 1987), and the brain enzy al., 1987). Such phosphorylation is believed to be a pre-<br>requisite for interaction between myosin and actin (Sell-<br>ers and Adelstein, 1987), and the brain enzyme is prob-<br>ably involved in the same function in nerve cells. requisite for interaction between myosin and actin (Sell-<br>ers and Adelstein, 1987), and the brain enzyme is prob-<br>foly involved in the same function in nerve cells. As<br>interaction as interved as interact myosin<br>isolated my ers and Adelstein, 1987), and the brain enzyme is prob-<br>form (Hably involved in the same function in nerve cells. As 1989); or<br>mentioned above, CaM kinase II can also phosphorylate site and<br>isolated myosin light chains as ably involved in the same function in nerve cells. As 19<br>mentioned above, CaM kinase II can also phosphorylate sit<br>isolated myosin light chains as well as intact myosin do<br>(Tanaka et al., 1986). Given the enrichment of CaM mentioned above, CaM kinase II can also phosphory<br>isolated myosin light chains as well as intact my<br>(Tanaka et al., 1986). Given the enrichment of C<br>kinase II in brain as compared to myosin light ch<br>kinase, it is possible isolated myosin light chains as well as intact myos<br>(Tanaka et al., 1986). Given the enrichment of Ca<br>kinase II in brain as compared to myosin light cha<br>kinase, it is possible that myosin light chain phosphor<br>ylation in si ylation in situ may be catalyzed by both enzymes (Edel-

immunological differences from the muscle enzyme and apparently not yet been characterized in nervous tissue,<br>may be a distinct isoenzyme (Taira et al., 1982), can be despite their messenger RNAs being abundant in brain may be a distinct isoenzyme (Taira et al., 1982), can be despite their messenger RNAs being abundant in brain activated both by  $Ca^{2+}$  and by cyclic AMP-dependent (Ono et al., 1989; Ohno et al., 1988), and little is know e. PHOSPHORYLASE KINASE. This enzyme has been nasidentified in brain (Ozawa, 1973). The brain form of phosphorylase kinase, which appears to express certain ger immunological differences from the muscle enzyme and app may identified in brain (Ozawa, 1973). The brain form<br>phosphorylase kinase, which appears to express certs<br>immunological differences from the muscle enzyme a<br>may be a distinct isoenzyme (Taira et al., 1982), can<br>activated bot phosphorylase kinase, which appears to express certain<br>immunological differences from the muscle enzyme and<br>may be a distinct isoenzyme (Taira et al., 1982), can be<br>activated both by  $Ca^{2+}$  and by cyclic AMP-dependent<br>ph immunological differences from the muscle enzyme and and may be a distinct isoenzyme (Taira et al., 1982), can be distinct activated both by  $Ca^{2+}$  and by cyclic AMP-dependent (the phosphorylation (Taira et al., 1982). I may be a distinct isoenzyme (Taira et al., 1982), can be activated both by  $Ca^{2+}$  and by cyclic AMP-dependent phosphorylation (Taira et al., 1982). It is likely that  $Ca^{2+}$ -induced activation of brain phosphorylase kina phosphorylation (Taira et al., 1982). It is likely that about their role in nervous system function.<br>Ca<sup>2+</sup>-induced activation of brain phosphorylase kinase a. REGULATION OF ACTIVITY. The group A isoforms of regulates gly regulates glycogen breakdown in neurons, a process that<br>has been shown to be enhanced by electrical stimulation<br>(King et al., 1967).<br> $3. Ca^{2+}/phospholipid-dependent protein kinases$ . Another type of  $Ca^{2+}$ -dependent protein phosphorylation  $3^{2+}$ -induced activation of brain phosphorylase kinas<br>gulates glycogen breakdown in neurons, a process that<br>is been shown to be enhanced by electrical stimulatio<br>ing et al., 1967).<br>*3.*  $Ca^{2+}/phospholipid-dependent protein, kinases.$  An<br>her type of

regulates glycogen breakdown in neurons, a process that<br>has been shown to be enhanced by electrical stimulation<br>(King et al., 1967).<br>3.  $Ca^{2+}/phospholipid-dependent$  protein kinases. An-<br>other type of  $Ca^{2+}$ -dependent protein phosphoryl has been shown to be enhanced by electrical stimulation add<br>
(King et al., 1967). Ser<br>
3.  $Ca^{2+}/phospholipid-dependent protein kinases$ . Andia<br>
other type of  $Ca^{2+}$ -dependent protein phosphorylation fousystem, catalyzed by protein kinase C, has also (King et al., 1967).<br>
3.  $Ca^{2+}/phospholipid-dependent protein, kinases$ . And<br>
other type of  $Ca^{2+}$ -dependent protein phosphorylation for<br>
system, catalyzed by protein kinase C, has also been C<br>
found to be active in neuronal tissue, e.g., in intact 3.  $Ca^{2+}/phospholipid-dependent protein kinases$ . Another type of  $Ca^{2+}$ -dependent protein phosphorylation faystem, catalyzed by protein kinase C, has also been (found to be active in neuronal tissue, e.g., in intact nerve (terminals and brain slice other type of Ca<sup>2+</sup>-dependent protein phosphorylation fast stem, catalyzed by protein kinase C, has also been C found to be active in neuronal tissue, e.g., in intact nerve (terminals and brain slices (Wu et al., 1982; Du system, catalyzed by protein kinase C, has also been (found to be active in neuronal tissue, e.g., in intact nerve (terminals and brain slices (Wu et al., 1982; Dunkley et al., 1986; Wang et al., 1988; Yip and Kelly, 1989 found to be active in neuronal tissue, e.g., in intact<br>terminals and brain slices (Wu et al., 1982; Dunk<br>al., 1986; Wang et al., 1988; Yip and Kelly, 1989)<br>protein phosphorylation system, which mediates of<br>those Ca<sup>2+</sup>-mob terminals and brain slices (Wu et al., 1982; Dunkle al., 1986; Wang et al., 1988; Yip and Kelly, 1989). T<br>protein phosphorylation system, which mediates eff<br>of those Ca<sup>2+</sup>-mobilizing hormones and neurotransiters that act al., 1986; Wang et al., 1988; Yip and Kelly, 1989). This protein phosphorylation system, which mediates effects of those Ca<sup>2+</sup>-mobilizing hormones and neurotransmitters that act through increased phosphatidylinosito turno protein phosphorylation system, which mediates effects glyc<br>of those Ca<sup>2+</sup>-mobilizing hormones and neurotransmit-<br>liters that act through increased phosphatidylinositol acyl<br>turnover (for examples, see Michell, 1975; Nish ters that act through increased phosphatidylinositol acylglycerol, generated from the receptor-induced break-<br>turnover (for examples, see Michell, 1975; Nishizuka, down either of polyphosphoinositides (Downes, 1982;<br>1984; ters that act through increased phosphatidylinositol acy<br>turnover (for examples, see Michell, 1975; Nishizuka, dov<br>1984; Berridge and Irvine, 1989), is present in brain in Ber<br>very high concentrations (Kuo et al., 1980; Wr turnover (for examples, see Michael 1984; Berridge and Irvine, 1989), very high concentrations (Kuo et a 1980; Minakuchi et al., 1981; Walahis important in neuronal function.<br>Protein kinase C was first purific 84; Berridge and Irvine, 1989), is present in brain in Bery high concentrations (Kuo et al., 1980; Wrenn et al., ticker, 1981; Walaas et al., 1983b,c) and comportant in neuronal function. See protein kinase C was first pur

very high concentrations (Kuo et al., 1980; Wrenn et al., 1980; Minakuchi et al., 1981; Walaas et al., 1983b,c) and is important in neuronal function.<br>Protein kinase C was first purified from cerebellum as a cyclic nucleo 1980; Minakuchi et al., 1981; Walaas et al., 1983b,c) as important in neuronal function.<br>
Protein kinase C was first purified from cerebellum<br>
a cyclic nucleotide-independent protein kinase activi<br>
which could be proteoly is important in neuronal function.<br>
Protein kinase C was first purified from cerebellum as<br>
a cyclic nucleotide-independent protein kinase activity,<br>
which could be proteolytically activated by a  $Ca^{2+}$ -de-<br>
pendent prot Protein kinase C was first purified from cerebellum as<br>a cyclic nucleotide-independent protein kinase activity,<br>which could be proteolytically activated by a  $Ca^{2+}$ -de-<br>pendent protease (Inoue et al., 1977; Takai et al.,

kinase II in brain as compared to myosin light chain distinct immunological characteristics (Huang and<br>kinase, it is possible that myosin light chain phosphor-<br>ylation in situ may be catalyzed by both enzymes (Edel-<br>simil properties (Coussens et al., 1986; Knopf et al., 1986; AND NEURONAL FUNCTION 309<br>of distinct isoenzymes, which exhibit slightly different<br>properties (Coussens et al., 1986; Knopf et al., 1986;<br>Huang et al., 1986; Jaken and Kiley, 1987; Woodgett and 309<br>
of distinct isoenzymes, which exhibit slightly different<br>
properties (Coussens et al., 1986; Knopf et al., 1986;<br>
Huang et al., 1986; Jaken and Kiley, 1987; Woodgett and<br>
Hunter, 1987; Kikkawa et al., 1987; Akita et a of distinct isoenzymes, which exhibit slightly different<br>properties (Coussens et al., 1986; Knopf et al., 1986;<br>Huang et al., 1986; Jaken and Kiley, 1987; Woodgett and<br>Hunter, 1987; Kikkawa et al., 1987; Akita et al., 1990 of distinct isoenzymes, which exhibit slightly different<br>properties (Coussens et al., 1986; Knopf et al., 1986;<br>Huang et al., 1986; Jaken and Kiley, 1987; Woodgett and<br>Hunter, 1987; Kikkawa et al., 1987; Akita et al., 1990 properties (Coussens et al., 1986; Knopf et al., 1986;<br>Huang et al., 1986; Jaken and Kiley, 1987; Woodgett and<br>Hunter, 1987; Kikkawa et al., 1987; Akita et al., 1990;<br>for review, see Nishizuka, 1988).One group of protein<br> Huang et al., 1986; Jaken and Kiley, 1987; Woodgett and<br>Hunter, 1987; Kikkawa et al., 1987; Akita et al., 1990;<br>for review, see Nishizuka, 1988).One group of protein<br>kinase C isoenzymes, termed group A and including types Hunter, 1987; Kikkawa et al., 1987; Akita et al., 1990;<br>for review, see Nishizuka, 1988).One group of protein<br>kinase C isoenzymes, termed group A and including types<br>I, II, and III, is derived from genes termed  $\gamma$ ,  $\beta$ for review, see Nishizuka, 1988).One group of protein<br>kinase C isoenzymes, termed group A and including types<br>I, II, and III, is derived from genes termed  $\gamma$ ,  $\beta$ , and  $\alpha$ ,<br>respectively (Nishizuka, 1988; Huang, 1989). kinase C isoenzymes, termed group A and including types<br>I, II, and III, is derived from genes termed  $\gamma$ ,  $\beta$ , and  $\alpha$ ,<br>respectively (Nishizuka, 1988; Huang, 1989). These en-<br>zymes have been purified from brain and oth I, II, and III, is derived from genes termed  $\gamma$ ,  $\beta$ , and  $\alpha$ , respectively (Nishizuka, 1988; Huang, 1989). These en-<br>zymes have been purified from brain and other tissues<br>(for examples, see Kikkawa et al., 1982; Wise respectively (Nishizuka, 1988; Huang, 1989). These e<br>zymes have been purified from brain and other tissu<br>(for examples, see Kikkawa et al., 1982; Wise et a<br>1982a,b; Schatzman et al., 1983; Huang et al., 1986; Jak<br>and Kiley zymes have been purified from brain and other tissues<br>(for examples, see Kikkawa et al., 1982; Wise et al.,<br>1982a,b; Schatzman et al., 1983; Huang et al., 1986; Jaken<br>and Kiley, 1987; Woodgett and Hunter, 1987) and exten-<br> (for examples, see Kikkawa et al., 1982; Wise et al., 1982a,b; Schatzman et al., 1983; Huang et al., 1986; Jaken and Kiley, 1987; Woodgett and Hunter, 1987) and extensively characterized. The enzymes are all monomers of 77 1982a,b; Schatzman et al., 1983; Huang et al., 1986; Jaken<br>and Kiley, 1987; Woodgett and Hunter, 1987) and exten-<br>sively characterized. The enzymes are all monomers of<br>77 to 83 kDa, which contain four conserved and five<br>va sively characterized. The enzymes are all monomers of 77 to 83 kDa, which contain four conserved and five variable regions (Nishizuka, 1988). One of the conserved regions contains a pseudosubstrate sequence which may sively characterized. The enzymes are all monomers of<br>77 to 83 kDa, which contain four conserved and five<br>variable regions (Nishizuka, 1988). One of the conserved<br>regions contains a pseudosubstrate sequence which may<br>be re 77 to 83 kDa, which contain four conserved and five variable regions (Nishizuka, 1988). One of the conserved regions contains a pseudosubstrate sequence which may be responsible for maintaining the enzyme in its inactive f variable regions (Nishizuka, 1988). One of the conserved<br>regions contains a pseudosubstrate sequence which may<br>be responsible for maintaining the enzyme in its inactive<br>form (House and Kemp, 1987; Kemp et al., 1989; Huang, regions contains a pseudosubstrate sequence which may<br>be responsible for maintaining the enzyme in its inactive<br>form (House and Kemp, 1987; Kemp et al., 1989; Huang<br>1989); other parts of the enzyme contain the catalytic<br>si form (House and Kemp, 1987; Kemp et al., 1989; Huang, 1989); other parts of the enzyme contain the catalytic site and the diacylglycerol- and phospholipid-binding domains (Nishizuka, 1988). The various group A enform (House and Kemp, 1987; Kemp et al., 1989; Huang, 1989); other parts of the enzyme contain the catalytic site and the diacylglycerol- and phospholipid-binding domains (Nishizuka, 1988). The various group A enzymes disp site and the diacylglycerol- and phospholipid-binding<br>domains (Nishizuka, 1988). The various group A en-<br>zymes display distinct autophosphorylation sites and<br>distinct immunological characteristics (Huang and<br>Huang, 1986; H site and the diacylglycerol- and phospholipid-binding<br>domains (Nishizuka, 1988). The various group A en-<br>zymes display distinct autophosphorylation sites and<br>distinct immunological characteristics (Huang and<br>Huang, 1986; H domains (Nishizuka, 1988). The various group A en-<br>zymes display distinct autophosphorylation sites and<br>distinct immunological characteristics (Huang and<br>Huang, 1986; Huang et al., 1986) but appear to have<br>similar substrat xymes display distinct autophosphorylation sites and<br>distinct immunological characteristics (Huang and<br>Huang, 1986; Huang et al., 1986) but appear to have<br>similar substrate specificities, which are different from<br>those of those of both cyclic nucleotide-dependent and CaM ki-

those of both cyclic nucleotide-dependent and CaM kinases.<br>
Another group of isoenzymes (group B), derived from<br>
genes designated  $\delta$ ,  $\epsilon$ , and  $\zeta$  (Ono et al., 1987), has<br>
apparently not yet been characterized in ner nases.<br>
Another group of isoenzymes (group B), derived from<br>
genes designated  $\delta$ ,  $\epsilon$ , and  $\zeta$  (Ono et al., 1987), has<br>
apparently not yet been characterized in nervous tissue,<br>
despite their messenger RNAs being abu Another group of isoenzymes (group B), derived from<br>genes designated  $\delta$ ,  $\epsilon$ , and  $\zeta$  (Ono et al., 1987), has<br>apparently not yet been characterized in nervous tissue,<br>despite their messenger RNAs being abundant in br apparently not yet been characterized in nervous tissue,<br>despite their messenger RNAs being abundant in brain<br>(Ono et al., 1989; Ohno et al., 1988), and little is known<br>about their role in nervous system function.<br>a. REGUL

despite their messenger RNAs being abundant in brain<br>(Ono et al., 1989; Ohno et al., 1988), and little is known<br>about their role in nervous system function.<br>a. REGULATION OF ACTIVITY. The group A isoforms of<br>protein kinase (Ono et al., 1989; Ohno et al., 1988), and little is k<br>about their role in nervous system function.<br>a. REGULATION OF ACTIVITY. The group A isofor-<br>protein kinase C were found to be activated by<br>addition of membrane phosph about their role in nervous system function.<br>
a. REGULATION OF ACTIVITY. The group A isoforms of<br>
protein kinase C were found to be activated by the<br>
addition of membrane phospholipids (e.g., phosphatidyl-<br>
serine),  $Ca^{2+$ a. REGULATION OF ACTIVITY. The group A isoforms of<br>protein kinase C were found to be activated by the<br>addition of membrane phospholipids (e.g., phosphatidyl-<br>serine),  $Ca^{2+}$ , and low concentrations of unsaturated 1,2-<br>di protein kinase C were found to be activated by the addition of membrane phospholipids (e.g., phosphatidylencies).  $Ca^{2+}$ , and low concentrations of unsaturated 1,2-diacylglycerols, which (under optimal conditions) were f serine),  $Ca^{2+}$ , and low concentrations of unsaturated 1,2-<br>diacylglycerols, which (under optimal conditions) were<br>found to decrease the apparent activation constant for<br> $Ca^{2+}$  from the high micromolar to the nanomolar serine),  $Ca^{2+}$ , and low concentrations of unsaturated 1,2-<br>diacylglycerols, which (under optimal conditions) were<br>found to decrease the apparent activation constant for<br> $Ca^{2+}$  from the high micromolar to the nanomolar diacylglycerols, which (under optimal conditions) were<br>found to decrease the apparent activation constant for<br>Ca<sup>2+</sup> from the high micromolar to the nanomolar range<br>(Takai et al., 1979a,b). This activation follows the genfound to decrease the apparent activation constant  $1$  Ca<sup>2+</sup> from the high micromolar to the nanomolar ran (Takai et al., 1979a,b). This activation follows the generation of a membrane-associated complex consisting the e Ca<sup>2+</sup> from the high micromolar to the nanomolar range (Takai et al., 1979a,b). This activation follows the generation of a membrane-associated complex consisting of the enzyme,  $Ca^{2+}$ , membrane phospholipids, and diacyl (Takai et al., 1979a,b). This activation follows the generation of a membrane-associated complex consisting of the enzyme,  $Ca^{2+}$ , membrane phospholipids, and diacylglycerol (for review, see Bell, 1986; Woodgett et al., eration of a membrane-associated complex consisting<br>the enzyme, Ca<sup>2+</sup>, membrane phospholipids, and diac;<br>glycerol (for review, see Bell, 1986; Woodgett et al., 198<br>Nishizuka, 1986, 1988; Huang, 1989). In this way, excylgl the enzyme, Ca<sup>2+</sup>, membrane phospholipids, and diacyl-<br>glycerol (for review, see Bell, 1986; Woodgett et al., 1987;<br>Nishizuka, 1986, 1988; Huang, 1989). In this way, di-<br>acylglycerol, generated from the receptor-induced b glycerol (for review, see Bell, 1986; Woodgett et al., 1987; Nishizuka, 1986, 1988; Huang, 1989). In this way, di-Nishizuka, 1986, 1988; Huang, 1989). In this way, acylglycerol, generated from the receptor-induced bre<br>down either of polyphosphoinositides (Downes, 19<br>Berridge, 1987; Fisher and Agranoff, 1987), of phosp<br>tidylcholine (Bi acylglycerol, generated from the receptor-induced break-<br>down either of polyphosphoinositides (Downes, 1982;<br>Berridge, 1987; Fisher and Agranoff, 1987), of phospha-<br>tidylcholine (Billah and Anthes, 1990), or of inositol-<br>c down either of polyphosphoinositides (Downes, 1982;<br>Berridge, 1987; Fisher and Agranoff, 1987), of phospha-<br>tidylcholine (Billah and Anthes, 1990), or of inositol-<br>containing glycolipids (Saltiel et al., 1986), can act as Berridge, 1987; Fisher and Agranoff, 1987), of phospha-<br>tidylcholine (Billah and Anthes, 1990), or of inositol-<br>containing glycolipids (Saltiel et al., 1986), can act as a<br>second messenger together with Ca<sup>2+</sup> in activatin tidylcholine (Billah and Anthes, 1990), or of inositol-<br>containing glycolipids (Saltiel et al., 1986), can act as a<br>second messenger together with  $Ca^{2+}$  in activating these<br>protein kinases. This group of enzymes can app second messenger together with  $Ca^{2+}$  in activating these<br>protein kinases. This group of enzymes can apparently<br>also be activated by certain lipid oxidation products<br>(O'Brian et al., 1988), fatty acids and arachidonate d second messenger together with  $Ca^{2+}$  in activating these<br>protein kinases. This group of enzymes can apparently<br>also be activated by certain lipid oxidation products<br> $(O'Brian et al., 1988)$ , fatty acids and arachidonate de-<br>rivat protein kinases. This group of enzymes can apparently also be activated by certain lipid oxidation products (O'Brian et al., 1988), fatty acids and arachidonate de-<br>rivatives (Sekiguchi et al., 1987; for review, see Huang,

310 **WALAAS AND GREENGARD**<br>zymes has been found to represent the major receptor associated p<br>for the tumor-promoting phorbol esters, which appar- and Zwiers, waLAAS .<br>zymes has been found to represent the major recept<br>for the tumor-promoting phorbol esters, which appar-<br>ently can substitute for diacylglycerol and induce a pi waLAAS AN<br>zymes has been found to represent the major receptor<br>for the tumor-promoting phorbol esters, which appar-<br>ently can substitute for diacylglycerol and induce a pro-<br>longed activation of the enzyme (Castagna et al. zymes has been found to represent the major receptor<br>for the tumor-promoting phorbol esters, which appar-<br>ently can substitute for diacylglycerol and induce a pro-<br>longed activation of the enzyme (Castagna et al., 1982;<br>Ki zymes has been found to represent the major receptor<br>for the tumor-promoting phorbol esters, which appar-<br>ently can substitute for diacylglycerol and induce a pro-<br>longed activation of the enzyme (Castagna et al., 1982;<br>Ki r the tumor-promoting phorbol esters, which ap<br>tly can substitute for diacylglycerol and induce a<br>nged activation of the enzyme (Castagna et al., 1<br>likkawa et al., 1983; Parker et al., 1986; Baraban, 19<br>The group B enzymes

ently can substitute for diacylglycerol and induce a pro-<br>longed activation of the enzyme (Castagna et al., 1982;<br>Kikkawa et al., 1983; Parker et al., 1986; Baraban, 1987).<br>The group B enzymes, which are less well characte Kikkawa et al., 1983; Parker et al., 1986; Baraban, 1987).<br>The group B enzymes, which are less well character-<br>ized, also appear to be regulated by phospholipids and,<br>in some cases, diacylglycerol [depending on the type of The group B enzymes, which are less well character-<br>ized, also appear to be regulated by phospholipids and,<br>in some cases, diacylglycerol [depending on the type of<br>substrate used to assay the enzyme (Ono et al., 1989)]<br>bu ized, also appear to be regulated by phospholipids and, histon<br>in some cases, diacylglycerol [depending on the type of good s<br>substrate used to assay the enzyme (Ono et al., 1989)] kawa<br>but to be independent of Ca<sup>2+</sup> (Ni substrate used to assay the enzyme (Ono et al., 1989)] kave but to be independent of Ca<sup>2+</sup> (Nishizuka, 1988; Huang, eviluately 1989). For example, the translational products of the  $\epsilon$ -<br>and  $\delta$ -genes, when expressed in but to be independent of Ca<sup>2+</sup> (Nishizuka, 1988; Hua<br>1989). For example, the translational products of the<br>and  $\delta$ -genes, when expressed in COS-7 cells, did not shan absolute requirement for Ca<sup>2+</sup>, diacylglycerol, a<br>ph 1989). For example, the translational products of the  $\epsilon$ -<br>and  $\delta$ -genes, when expressed in COS-7 cells, did not show<br>an absolute requirement for Ca<sup>2+</sup>, diacylglycerol, and<br>phospholipids (Ono et al., 1987, 1989), and t and  $\delta$ -genes, when expressed in COS-7 cells, did not show<br>an absolute requirement for Ca<sup>2+</sup>, diacylglycerol, and<br>phospholipids (Ono et al., 1987, 1989), and the transla-<br>tional product of the  $\zeta$  gene showed dependen an absolute requirement for Ca<sup>2+</sup>, diacylglycerol, and the phospholipids (Ono et al., 1987, 1989), and the translational product of the  $\zeta$  gene showed dependency on phospholipid but not on Ca<sup>2+</sup> and diacylglycerol (O phospholipids (Ono et al., 1987, 1989), and the translational product of the  $\zeta$  gene showed dependency on phospholipid but not on Ca<sup>2+</sup> and diacylglycerol (Ono et al., 1989). Other studies have indicated that the enzy tional product of the  $\zeta$  gene showed dependency on phospholipid but not on  $Ca^{2+}$  and diacylglycerol (Ono et al., 1989). Other studies have indicated that the enzyme encoded by the  $\epsilon$  gene, when expressed by the bac phospholipid but not on  $Ca^{2+}$  and diacylglycerol (Ono et al., 1989). Other studies have indicated that the enzyme encoded by the  $\epsilon$  gene, when expressed by the baculovirus system, appears to be regulated by phospholip al., 1989). Other studies have<br>encoded by the  $\epsilon$  gene, when e<br>system, appears to be regula<br>possibly, diacylglycerol, but<br>(Schaap and Parker, 1990).<br>b. DISTRIBUTION IN BRAIN coded by the  $\epsilon$  gene, when expressed by the baculovirus<br>stem, appears to be regulated by phospholipids and,<br>ssibly, diacylglycerol, but to be insensitive to  $Ca^{2+}$ <br>chaap and Parker, 1990).<br>b. DISTRIBUTION IN BRAIN. The

system, appears to be regulated by phospholipids and,<br>possibly, diacylglycerol, but to be insensitive to  $Ca^{2+}$ <br>(Schaap and Parker, 1990).<br>b. DISTRIBUTION IN BRAIN. The group A isoenzymes<br>have broad species, tissue, and possibly, diacylglycerol, but to be insensitive to  $Ca^{2+}$  ph<br>
(Schaap and Parker, 1990).<br>
b. DISTRIBUTION IN BRAIN. The group A isoenzymes<br>
have broad species, tissue, and cellular distributions, and<br>
all are highly enri (Schaap and Parker, 1990).<br>
b. DISTRIBUTION IN BRAIN. The group A isoenzymes infl<br>
have broad species, tissue, and cellular distributions, and<br>
all are highly enriched and widely distributed in brain<br>
(Kuo et al., 1980; M b. DISTRIBUTION IN BRAIN. The group A isoenzymes<br>have broad species, tissue, and cellular distributions, and<br>all are highly enriched and widely distributed in brain<br>(Kuo et al., 1980; Minakuchi et al., 1981). Types II and<br> have broad species, tissue, and cellular distributions, and<br>all are highly enriched and widely distributed in brain<br>(Kuo et al., 1980; Minakuchi et al., 1981). Types II and<br>III are found in both neural and peripheral tissu all are highly enriched and widely distributed in brain (Kuo et al., 1980; Minakuchi et al., 1981). Types II and III are found in both neural and peripheral tissues, whereas type I appears to be brain specific (for example (Kuo et al., 1980; Minakuchi et al., 1981). Types II and<br>III are found in both neural and peripheral tissues,<br>whereas type I appears to be brain specific (for examples,<br>see Nishizuka, 1988). Within the brain, the highest III are found in both neural and peripheral tissues, whereas type I appears to be brain specific (for examples,  $G$  and  $G$  are Nishizuka, 1988). Within the brain, the highest protein kinase C activity (measured with hist whereas type I appears to be brain specific (for examples, see Nishizuka, 1988). Within the brain, the highest protein kinase C activity (measured with histone H1 as substrate) was found in cortical regions, including the see Nishizuka, 1988). Within the brain, the highest pro-<br>tein kinase C activity (measured with histone H1 as<br>substrate) was found in cortical regions, including the<br>hippocampus, and in the cerebellum, whereas the lowest<br>a tein kinase C activity (measured with histone H1 asubstrate) was found in cortical regions, including the hippocampus, and in the cerebellum, whereas the lowes activity was found in the brain stem and spinal consumed (Wala substrate) was found in cortical regions, including the hippocampus, and in the cerebellum, whereas the lowest activity was found in the brain stem and spinal cord (Walaas et al., 1983c). Autoradiographic analysis of phorb hippocampus, and in the cerebellum, whereas the lowest<br>activity was found in the brain stem and spinal cord<br>(Walaas et al., 1983c). Autoradiographic analysis of phor-<br>bol ester binding in the CNS showed a comparable en-<br>zy activity was found in the brain stem and spinal cord<br>
(Walaas et al., 1983c). Autoradiographic analysis of phor-<br>
bol ester binding in the CNS showed a comparable en-<br>
zyme distribution (Worley et al., 1986). Certain cell<br> (Walaas et al., 1983c). Autoradiographic analysis of phorbol ester binding in the CNS showed a comparable enzyme distribution (Worley et al., 1986). Certain cell<br>types, such as Purkinje cells and striatonigral cells, may<br> bol ester binding in the CNS showed a compared at al., 1986).<br>
Express, such as Purkinje cells and striatonig<br>
have particularly high concentrations of<br>
(Worley et al., 1986; Walaas et al., 1989f).<br>
Recent immunochemical, me distribution (Worley et al., 1986). Certain cell<br>pes, such as Purkinje cells and striatonigral cells, may<br>we particularly high concentrations of the enzyme<br>Worley et al., 1986; Walaas et al., 1989f).<br>Recent immunochemi types, such as Purkinje cells and striatonigral cells, may<br>have particularly high concentrations of the enzyme<br>(Worley et al., 1986; Walaas et al., 1989f).<br>Recent immunochemical, immunocytochemical, and in<br>situ hybridizati

have particularly high concentrations of the enzyme (Worley et al., 1986; Walaas et al., 1989f).<br>Recent immunochemical, immunocytochemical, and in situ hybridization studies have indicated that different protein kinase C i (Worley et al., 1986; Walaas et al., 1989f).<br>Recent immunochemical, immunocytochemical, and in<br>situ hybridization studies have indicated that different<br>protein kinase C isoenzymes have widespread, but dis-<br>tinct, regional Recent immunochemical, immunocytochemical, and in<br>situ hybridization studies have indicated that different<br>protein kinase C isoenzymes have widespread, but dis-<br>tinct, regional and cellular distributions (Huang et al.,<br>198 situ hybridization studies have indicated that different<br>protein kinase C isoenzymes have widespread, but dis-<br>tinct, regional and cellular distributions (Huang et al., 1<br>1987, 1988; Mochly-Rosen et al., 1987; Kitano et al protein kinase C isoenzymes have widespread, but dis-<br>tinct, regional and cellular distributions (Huang et al., the 1987, 1988; Mochly-Rosen et al., 1987; Kitano et al., compare 1987; Brandt et al., 1987; Hosoda et al., 1 tinct, regional and cellular distributions (Huang et al., <sup>th</sup><br>1987, 1988; Mochly-Rosen et al., 1987; Kitano et al., <sup>co</sup><br>1987; Brandt et al., 1987; Hosoda et al., 1989; Saito et <sup>19</sup><br>al., 1988; Ito et al., 1990). The subc 1987, 1988; Mochly-Rosen et al., 1987; Kitano et 1987; Brandt et al., 1987; Hosoda et al., 1989; Saitdal., 1988; Ito et al., 1990). The subcellular localization the enzymes may also differ, with type I being parassociated 1987; Brandt et al., 1987; Hosoda et al., 1989; Saito et al., 1988; Ito et al., 1990). The subcellular localization of the enzymes may also differ, with type I being partly associated with membranes and type II being predo al., 1988; Ito et al., 1990). The subcellular localization of histographic the enzymes may also differ, with type I being predomi-<br>associated with membranes and type III being predomi-<br>nantly cytosolic under unstimulated c associated with membranes and type III being predon<br>nantly cytosolic under unstimulated conditions (for  $\alpha$ <br>amples, see Kitano et al., 1987; Kose et al., 1988).<br>c. FUNCTIONAL IMPORTANCE IN NERVE CELLS. Prot<br>kinase C appea

hantly cytosonc under unstitutated conditions (for examples, see Kitano et al., 1987; Kose et al., 1988).<br>
c. FUNCTIONAL IMPORTANCE IN NERVE CELLS. Protein<br>
kinase C appears to be involved in a number of physio-<br>
logical a c. FUNCTIONAL IMPORTANCE IN NERVE CELLS. Protein<br>kinase C appears to be involved in a number of physio-<br>logical and pathological functions (Nishizuka, 1986;<br>Woodgett et al., 1987). A variety of brain proteins, in-<br>cluding kinase C appears to be involved in a number of physio-logical and pathological functions (Nishizuka, 1986; Woodgett et al., 1987). A variety of brain proteins, including myelin basic protein (Turner et al., 1982, 1984), MA logical and pathological functions (Nishizuka, 19<br>Woodgett et al., 1987). A variety of brain proteins,<br>cluding myelin basic protein (Turner et al., 1982, 198<br>MAP-2 (Akiyama et al., 1986; Walaas and Nairn, 198<br>tyrosine hydr

Kikkawa et al., 1983; Parker et al., 1986; Baraban, 1987). have been found to be possible physiological substrates<br>The group B enzymes, which are less well character-<br>ized, also appear to be regulated by phospholipids and, BREENGARD<br>associated protein GAP-43 (Aloyo et al., 1983; Coggins<br>and Zwiers, 1989; Nielander et al., 1990), the MARCKS GREENGARD<br>associated protein GAP-43 (Aloyo et al., 1983; Coggins<br>and Zwiers, 1989; Nielander et al., 1990), the MARCKS<br>protein (Wu et al., 1982) (see below), and several other GREENGARD<br>associated protein GAP-43 (Aloyo et al., 1983; Coggins<br>and Zwiers, 1989; Nielander et al., 1990), the MARCKS<br>protein (Wu et al., 1982) (see below), and several other<br>brain proteins (Wrenn et al., 1980; Walaas et associated protein GAP-43 (Aloyo et al., 1983; Coggins<br>and Zwiers, 1989; Nielander et al., 1990), the MARCKS<br>protein (Wu et al., 1982) (see below), and several other<br>brain proteins (Wrenn et al., 1980; Walaas et al., 1983b associated protein GAP-43 (Aloyo et al., 1983; Coggins<br>and Zwiers, 1989; Nielander et al., 1990), the MARCKS<br>protein (Wu et al., 1982) (see below), and several other<br>brain proteins (Wrenn et al., 1980; Walaas et al., 1983b and Zwiers, 1989; Nielander et al., 1990), the MARCKS<br>protein (Wu et al., 1982) (see below), and several other<br>brain proteins (Wrenn et al., 1980; Walaas et al., 1983b,c)<br>have been found to be possible physiological substr protein (Wu et al., 1982) (see below), and several other<br>brain proteins (Wrenn et al., 1980; Walaas et al., 1983b,c)<br>have been found to be possible physiological substrates<br>for the group A protein kinase C isoenzymes. In a brain proteins (Wrenn et al., 1980; Walaas et al., 1983b,c have been found to be possible physiological substrates for the group A protein kinase C isoenzymes. In addition histone H1 and many other nonneuronal proteins are have been found to be possible physiological substrates<br>for the group A protein kinase C isoenzymes. In addition,<br>histone H1 and many other nonneuronal proteins are<br>good substrates for the enzyme (for examples, see Kik-<br>ka for the group A protein kinase C isoenzymes. In addition,<br>histone H1 and many other nonneuronal proteins are<br>good substrates for the enzyme (for examples, see Kik-<br>kawa et al., 1982; Wise et al., 1982a). However, present<br>e histone H1 and many other nonneuronal proteins are<br>good substrates for the enzyme (for examples, see Kik-<br>kawa et al., 1982; Wise et al., 1982a). However, present<br>evidence suggests that distinct isozymic forms of the<br>enzym good substrates for the enzyme (for examples, see Kikkawa et al., 1982; Wise et al., 1982a). However, presen<br>evidence suggests that distinct isozymic forms of thenzyme may have different substrate specificities and<br>therefo kawa et al., 1982; Wise et al., 1982a). However, present evidence suggests that distinct isozymic forms of the enzyme may have different substrate specificities and therefore, may be involved in distinct physiological fun evidence suggests that distinct isozymic forms of the entryme may have different substrate specificities an therefore, may be involved in distinct physiological fun tions (Huang, 1989; Marais et al., 1990). In particula th enzyme may have different substrate specificities and,<br>therefore, may be involved in distinct physiological func-<br>tions (Huang, 1989; Marais et al., 1990). In particular,<br>the  $\epsilon$ -type protein kinase C displayed a substra tions (Huang, 1989; Marais et al., 1990). In particular, the  $\epsilon$ -type protein kinase C displayed a substrate specificity when assayed in vitro which was distinct from that of the group A enzymes, with histones being poor strates for the  $\epsilon$  enzyme (Schaap and Parker, 1990).<br>Analysis of intact nerve terminal preparations has

shown that protein kinase C-catalyzed protein phosficity when assayed in vitro which was distinct from the of the group A enzymes, with histones being poor substrates for the  $\epsilon$  enzyme (Schaap and Parker, 1990).<br>Analysis of intact nerve terminal preparations has shown of the group A enzymes, with histones being poor sub-<br>strates for the  $\epsilon$  enzyme (Schaap and Parker, 1990).<br>Analysis of intact nerve terminal preparations has<br>shown that protein kinase C-catalyzed protein phos-<br>phorylati strates for the  $\epsilon$  enzyme (Schaap and Parker, 1990).<br>Analysis of intact nerve terminal preparations has<br>shown that protein kinase C-catalyzed protein phos-<br>phorylation is activated by depolarization-induced Ca<sup>2+</sup><br>influ Analysis of intact nerve terminal preparations has<br>shown that protein kinase C-catalyzed protein phos-<br>phorylation is activated by depolarization-induced  $Ca^{2+}$ <br>influx (Wu et al., 1982; Dunkley et al., 1986; Wang et al., shown that protein kinase C-catalyzed protein phosphorylation is activated by depolarization-induced Cainflux (Wu et al., 1982; Dunkley et al., 1986; Wang et al. 1988), by addition of tumor-promoting phorbol ester and by a phorylation is activated by depolarization-induced Ca<sup>2+</sup><br>influx (Wu et al., 1982; Dunkley et al., 1986; Wang et al.,<br>1988), by addition of tumor-promoting phorbol esters,<br>and by activation of those receptors that induce p influx (Wu et al., 1982; Dunkley et al., 1986; Wang et al., 1988), by addition of tumor-promoting phorbol esters, and by activation of those receptors that induce phosphatidylinositol turnover (Wang et al., 1988, Audigier 1988), by addition of tumor-promoting phorbol esters,<br>and by activation of those receptors that induce phos-<br>phatidylinositol turnover (Wang et al., 1988, Audigier et<br>al., 1988; J. K. T. Wang, S. M. P. Audigier, and P.<br>Gre and by activation of those receptors that induce phose<br>phatidylinositol turnover (Wang et al., 1988, Audigier e<br>al., 1988; J. K. T. Wang, S. M. P. Audigier, and I<br>Greengard, unpublished observations). Protein kinase C<br>cata phattay intested turnover (wang et al., 1960, Addigier et al., 1988; J. K. T. Wang, S. M. P. Audigier, and P. Greengard, unpublished observations). Protein kinase C-catalyzed protein phosphorylation has also been demonstra al., 1988; J. K. T.<br>Greengard, unpublicatalyzed protein<br>onstrated in brain<br>and Kelly, 1990).<br>Extensive eviden reengard, unpublished observations). Protein kinase C-<br>talyzed protein phosphorylation has also been dem-<br>strated in brain slices containing intact neurons (Yip<br>d Kelly, 1990).<br>Extensive evidence indicates that activators

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onstrated in brain slices containing intact neurons (Yip and Kelly, 1990).<br>
Extensive evidence indicates that activators of protein<br>
kinase C enhance the release of transmitters from var-<br>
ious types of nerve terminals and onstrated in brain slices containing intact neurons (Yip<br>and Kelly, 1990).<br>Extensive evidence indicates that activators of protein<br>kinase C enhance the release of transmitters from var-<br>ious types of nerve terminals and ce and Kelly, 1990).<br>Extensive evidence indicates that activators of protein<br>kinase C enhance the release of transmitters from var-<br>ious types of nerve terminals and cells (for examples, see<br>Knight and Baker, 1983; Zurgil et Extensive evidence indicates that activators of protein<br>kinase C enhance the release of transmitters from var-<br>ious types of nerve terminals and cells (for examples, see<br>Knight and Baker, 1983; Zurgil et al., 1986; Shapira kinase C enhance the release of transmitters from various types of nerve terminals and cells (for examples, see Knight and Baker, 1983; Zurgil et al., 1986; Shapira et al., 1987; Nichols et al., 1987). In other studies, ba ious types of nerve terminals and cells (for examples, Knight and Baker, 1983; Zurgil et al., 1986; Shapira al., 1987; Nichols et al., 1987). In other studies, bapplication of phorbol esters or intracellular injection puri Knight and Baker, 1983; Zurgil et al., 1986; Shapira et al., 1987; Nichols et al., 1987). In other studies, bath application of phorbol esters or intracellular injection of purified protein kinase C led to increases in Ca<sup></sup> al., 1987; Nichols et al., 1987). In other studies, bath application of phorbol esters or intracellular injection of purified protein kinase C led to increases in  $Ca^{2+}$ -dependent action potentials in *Aplysia* bag cell application of phorbol esters or intracellular injection o<br>purified protein kinase C led to increases in Ca<sup>2+</sup>-de<br>pendent action potentials in Aplysia bag cell neurons<br>apparently by recruitment of occult Ca<sup>2+</sup> channel<br>( purified protein kinase C led to increases in  $Ca^{2+}$ -dependent action potentials in *Aplysia* bag cell neurons, apparently by recruitment of occult  $Ca^{2+}$  channels (DeRiemer et al., 1985; Strong et al., 1987; Kaczmarek, apparently by recruitment of occult  $Ca^{2+}$  channels (DeRiemer et al., 1985; Strong et al., 1987; Kaczmarek, 1987). In addition, protein kinase C appears to mediate the inhibitory effect exerted by cholecystokinin on  $Ca^{2$ apparently by recruitment of occult Ca<sup>2+</sup> channels<br>(DeRiemer et al., 1985; Strong et al., 1987; Kaczmarek,<br>1987). In addition, protein kinase C appears to mediate<br>the inhibitory effect exerted by cholecystokinin on Ca<sup>2+</sup> (DeRiemer et al., 1985; Strong et al., 1987; Kaczmarek, 1987). In addition, protein kinase C appears to mediate<br>the inhibitory effect exerted by cholecystokinin on Ca<sup>2+</sup>-conductances in certain *Helix* neurons (Hammond et 1987). In addition, protein kinase C appears to mediate<br>the inhibitory effect exerted by cholecystokinin on  $Ca^{2+}$ -<br>conductances in certain *Helix* neurons (Hammond et al.,<br>1987), while a voltage-sensitive Cl<sup>-</sup> current the inhibitory effect exerted by cholecystokinin on Ca<sup>2+</sup>-<br>conductances in certain *Helix* neurons (Hammond et al.,<br>1987), while a voltage-sensitive Cl<sup>-</sup> current is blocked in<br>hippocampal pyramidal cells (Madison et al., conductances in certain *Helix* neurons (Hammond et al., 1987), while a voltage-sensitive Cl<sup>-</sup> current is blocked in hippocampal pyramidal cells (Madison et al., 1986). Recent work has also shown that injection of purifie 1987), while a voltage-sensitive Cl<sup>-</sup> current is blocked in hippocampal pyramidal cells (Madison et al., 1986). Recent work has also shown that injection of purified protein kinase C into hippocampal pyramidal cells elici hippocampal pyramidal cells (Madison et al., 1986). Recnt work has also shown that injection of purific<br>protein kinase C into hippocampal pyramidal cells elicit<br>(Hu et al., 1987), whereas injection of a peptide inhibit<br>of cent work has also shown that injection of purified<br>protein kinase C into hippocampal pyramidal cells elicits<br>(Hu et al., 1987), whereas injection of a peptide inhibitor<br>of the kinase blocks (Hvalby et al., in preparation) protein kinase C into hippocampal pyramidal cells elicits<br>(Hu et al., 1987), whereas injection of a peptide inhibitor<br>of the kinase blocks (Hvalby et al., in preparation),<br>several features of LTP. The phenomenon of LTP has (Hu et al., 1987), whereas injection of a peptide inhibitor<br>of the kinase blocks (Hvalby et al., in preparation),<br>several features of LTP. The phenomenon of LTP has<br>been used as a model for the early phases of learning and of the kinase blocks (Hvalby et al., in preparation),<br>several features of LTP. The phenomenon of LTP has<br>been used as a model for the early phases of learning and<br>memory in mammalian brain (Nicoll et al., 1988; Mal-<br>enka e been used as a model for the early phases of learning and<br>memory in mammalian brain (Nicoll et al., 1988; Mal-<br>enka et al., 1989b). These few examples, some of which<br>will be discussed further below, suffice to indicate tha been used as a moder for the early phases of learning and<br>memory in mammalian brain (Nicoll et al., 1988; Mal-<br>enka et al., 1989b). These few examples, some of which<br>will be discussed further below, suffice to indicate tha memory in manimalian brain (ivicon et al., 1566, Ma<br>enka et al., 1989b). These few examples, some of which<br>will be discussed further below, suffice to indicate th<br>this protein phosphorylation system is involved in the<br>regu

PROTEIN PHOSPHORYLATION<br>C. Second Messenger-independent Protein Kinases<br>Mammalian brain contains a variety of other protein<br>kinases that can phosphorylate endogenous brain pro-<br>teins on serine and threonine residues (Nairn C. Second Messenger-independent Protein Kinases<br>
Mammalian brain contains a variety of other protein<br>
kinases that can phosphorylate endogenous brain pro-<br>
teins on serine and threonine residues (Nairn et al.,<br>
1985b). Mo Mammalian brain contains a variety of other protein<br>kinases that can phosphorylate endogenous brain pro-<br>teins on serine and threonine residues (Nairn et al.,<br>1985b). Most of these enzymes appear not to be regulated<br>by any kinases that can phosphorylate endogenous brain proteins on serine and threonine residues (Nairn et al., 1985b). Most of these enzymes appear not to be regulated by any of the known second messengers, and in many cases the teins on serine and threonine residues (Nairn et al., 1985b). Most of these enzymes appear not to be regulated by any of the known second messengers, and in many bases their involvement in specific neuronal functions remai 1985b). Most of these enzymes appear not to be regulated<br>by any of the known second messengers, and in many<br>cases their involvement in specific neuronal functions<br>remains to be established. Therefore, although some of<br>the by any of the known second messengers, and in many cases their involvement in specific neuronal functions tion<br>remains to be established. Therefore, although some of  $D$ .<br>them are highly enriched in nervous tissue, indica cases their involuted<br>remains to be est<br>them are highly<br>that they are fun<br>briefly described.<br>Casein kinase mains to be established. Therefore, although some of  $\mu$  and are highly enriched in nervous tissue, indicating at they are functionally important, only a few will be iefly described.<br>*Casein kinase I* and *casein kinase I* 

them are highly enriched in nervous tissue, indicating<br>that they are functionally important, only a few will be<br>briefly described.<br>Casein kinase I and casein kinase II are widespread<br>protein kinases that preferentially ph that they are functionally important, only a few will be briefly described.<br>
Casein kinase I and casein kinase II are widespread<br>
protein kinases that preferentially phosphorylate acidic<br>
proteins like casein and phosviti briefly described.<br>
Casein kinase I and casein kinase II are widespr<br>
protein kinases that preferentially phosphorylate ac<br>
proteins like casein and phosvitin in vitro (Hatha<br>
and Traugh, 1982). Recent studies indicate tha Casein kinase I and casein kinase II are widesprotein kinases that preferentially phosphorylate a proteins like casein and phosvitin in vitro (Hathand Traugh, 1982). Recent studies indicate that DAI 32, a region- and cell protein kinases that preferentially phosphorylate acidic proteins like casein and phosvitin in vitro (Hathaway and Traugh, 1982). Recent studies indicate that DARPP-<br>32, a region- and cell type-specific neuronal phosphopr proteins like casein and phosvitin in vitro (Hathawa<br>and Traugh, 1982). Recent studies indicate that DARPF<br>32, a region- and cell type-specific neuronal phosphory<br>tein (see below), is a good substrate for casein kinase l<br>a and Traugh, 1982). Recent studies indicate that DARPP-<br>32, a region- and cell type-specific neuronal phosphopro-<br>tein (see below), is a good substrate for casein kinase II<br>and that casein kinase II-induced phosphorylation 32, a region- and cell type-specific neuronal phosphoprotein (see below), is a good substrate for casein kinase II and that casein kinase II-induced phosphorylation modifies subsequent cyclic AMP-regulated phosphorylation tein (see below), is a good substrate for casein kinase II<br>and that casein kinase II-induced phosphorylation mod-<br>ifies subsequent cyclic AMP-regulated phosphorylation<br>of this protein (Girault et al., 1989a; 1990). Casein and that casein kinase II-induced phosphorylation modifies subsequent cyclic AMP-regulated phosphorylation of this protein (Girault et al., 1989a; 1990). Casein kinase II, which can be activated by insulin both in periphe ifies subsequent cyclic AMP-regulated phosphorylatiof this protein (Girault et al., 1989a; 1990). Casein kins II, which can be activated by insulin both in periphe tissues (Sommercorn et al., 1987) and in brain (Zorn al., of this protein (Girault et al., 1989a; 1990). Casein kina<br>II, which can be activated by insulin both in peripher<br>tissues (Sommercorn et al., 1987) and in brain (Zorn<br>al., 1989), may, therefore, be involved in specific reg which can be activated by insulin both in peripheral homesues (Sommercorn et al., 1987) and in brain (Zorn et sard, 1989), may, therefore, be involved in specific regulation for the involved in specific regulation for the

Glycogen synthase kin<br>catalyze the *in vitro* pho<br>adhesion molecule N-C<br>involved in regulation of<br>(Mackie et al., 1989b).<br>Several *neurofilamen* talyze the *in vitro* phosphorylation of the neuronal cell<br>hesion molecule N-CAM, suggesting that it may be<br>volved in regulation of cell-cell interactions in the CNS<br>fackie et al., 1989b).<br>Several *neurofilament protein ki* 

adhesion molecule N-CAM, suggesting that it may be<br>involved in regulation of cell-cell interactions in the CNS<br>(Mackie et al., 1989b).<br>Several neurofilament protein kinases, enzymes that<br>al.,<br>can phosphorylate the three n involved in regulation of cell-cell interactions in the CNS 198 (Mackie et al., 1989b).<br>
Several *neurofilament protein kinases*, enzymes that al., can phosphorylate the three neurofilament proteins, also fibs<br>
appear to b Mackie et al., 1989b). and Several *neurofilament protein kinases*, enzymes that al., can phosphorylate the three neurofilament proteins, also fibsoppear to be second messenger independent (Julien and the Mushynski, 1981, Several *neurofilament protein kinases*, enzymes that can phosphorylate the three neurofilament proteins, also appear to be second messenger independent (Julien and Mushynski, 1981, 1982; Julien et al., 1983; Shecket and L can phosphorylate the three neurofilament proteins, appear to be second messenger independent (Julien Mushynski, 1981, 1982; Julien et al., 1983; Shecket Lasek, 1982; Wible et al., 1989). The neurofilament present in neuro appear to be second messenger independent (Julien and the Mushynski, 1981, 1982; Julien et al., 1983; Shecket and from Lasek, 1982; Wible et al., 1989). The neurofilament proteins present in neuronal somata are mostly nonp Lasek, 1982; Wible et al., 1989). The neurofilament proteins present in neuronal somata are mostly nonphosphorylated, whereas the axonally located proteins are heavily phosphorylated (for examples, see Pant et al., 1978; S teins present in neuronal somata are mostly nonphotophorylated, whereas the axonally located proteins an heavily phosphorylated (for examples, see Pant et al 1978; Sternberger and Sternberger, 1983; Matus, 1988a However, t phorylated, whereas the axonally located proteins are meavily phosphorylated (for examples, see Pant et al., dr<br>1978; Sternberger and Sternberger, 1983; Matus, 1988a). of<br>However, the physiological importance of neurofilam VI.D.1). 78; Sternberger and Sternberger, 1983; Matus, 1988a). of independent converted the physiological importance of neurofilament The cosphorylation is not well understood (see section pre (I.D.1).<br>*Myelin basic protein kinase* 

phosphorylation is not well understood (see section pre<br>VI.D.1). act<br>Myelin basic protein kinase has been reported as a phorotein kinase activity independent of the known second gave<br>messengers, highly enriched in myelin f VI.D.1).<br> *Myelin basic protein kinase* has been reported as a<br>
protein kinase activity independent of the known second<br>
messengers, highly enriched in myelin fractions and very<br>
active toward myelin basic protein (Miyamot Myelin basic protein kinase has been reported as a<br>protein kinase activity independent of the known second<br>messengers, highly enriched in myelin fractions and very<br>active toward myelin basic protein (Miyamoto, 1975,<br>1976). protein kinase activity independent of the known second<br>messengers, highly enriched in myelin fractions and very<br>active toward myelin basic protein (Miyamoto, 1975,<br>1976). However, the relationship of this enzyme to pro-<br>t messengers, highly enriched in myelin fractions and very<br>active toward myelin basic protein (Miyamoto, 1975, 7<br>1976). However, the relationship of this enzyme to pro-<br>ance olytically activated fragments of protein kinase C active toward myelin basic protein (Miyamoto, 1975, 1976). However, the relationship of this enzyme to protein and teolytically activated fragments of protein kinase C, The which phosphorylates myelin basic protein in vitr 1976). However, the relationship of this enzyme to protein the dividend fragments of protein kinase C, T which phosphorylates myelin basic protein in vitro and in vivo (Turner et al., 1982, 1984), is not known, and the tim which phos<br>in vivo (Tu<br>functional<br>protein are<br>al., 1982).<br>Pyruvate vivo (Turner et al., 1982, 1984), is not known, and the notional effects of phosphorylation of myelin basic otein are also unclear (for examples, see Agrawal et , 1982).<br>*Pyruvate dehydrogenase kinase*, a mitochondrial en

functional effects of phosphorylation of myelin basic<br>protein are also unclear (for examples, see Agrawal et<br>al., 1982).<br>*Pyruvate dehydrogenase kinase*, a mitochondrial en-<br>zyme, specifically phosphorylates and inactivat protein are also unclear (for examples, see Agrawal et al., 1982).<br> *Pyruvate dehydrogenase kinase*, a mitochondrial en-<br>
zyme, specifically phosphorylates and inactivates the  $\alpha$ -<br>
subunit of pyruvate dehydrogenase (Ree

**PROTEIN PHOSPHORYLATION AND NEURONAL FUNCTION**<br>C. Second Messenger-independent Protein Kinases be under tight metabolic communism orain contains a variety of other protein activated in brain either be activated in the exp C. Second Messenger-independent Protein Kinases<br>Mammalian brain contains a variety of other protein<br>kinases that can phosphorylate endogenous brain pro-<br>mate (Sieghart, 1981) or by repeated electrical stimula-<br>teins on ser AND NEURONAL FUNCTION 311<br>be under tight metabolic control (Randle, 1981), can be<br>activated in brain either by metabolites such as glutaand NEURONAL FUNCTION 33<br>be under tight metabolic control (Randle, 1981), can l<br>activated in brain either by metabolites such as glut<br>mate (Sieghart, 1981) or by repeated electrical stimul AND NEURONAL FUNCTION<br>be under tight metabolic control (Randle, 1981), can<br>activated in brain either by metabolites such as glue<br>mate (Sieghart, 1981) or by repeated electrical stimulation, e.g., in the isolated hippocampa be under tight metabolic control (Randle, 1981), can be activated in brain either by metabolites such as gluta-<br>mate (Sieghart, 1981) or by repeated electrical stimula-<br>tion, e.g., in the isolated hippocampal slice (Browni be under tight metabolic control (Randle, 1981), can be activated in brain either by metabolites such as glutamate (Sieghart, 1981) or by repeated electrical stimulation, e.g., in the isolated hippocampal slice (Browning e activated in brain either by metabolites such as glumate (Sieghart, 1981) or by repeated electrical stimulaion, e.g., in the isolated hippocampal slice (Browning al., 1979, 1981), the latter effect presumably being cau by tion. *D. Tyrosine-specific Protein Kinases* In a metabolic changes induced by the electrical stimula-<br>
In addition to protein serine and threonine kinases, all<br>
In addition to protein serine and threonine kinases, all<br>
sues including brain contain another class of p

tion.<br>
D. Tyrosine-specific Protein Kinases<br>
In addition to protein serine and threonine kinases, all<br>
tissues including brain contain another class of protein<br>
kinase that is probably of great functional importance D. Tyrosine-specific Protein Kinases<br>In addition to protein serine and threonine kinases, all<br>tissues including brain contain another class of protein<br>kinase that is probably of great functional importance<br>(see section V.A In addition to protein serine and threonine kinases, all<br>tissues including brain contain another class of protein<br>kinase that is probably of great functional importance<br>(see section V.A), namely, the tyrosine-specific prot tissues including brain contain another class of protein<br>kinase that is probably of great functional importance<br>(see section V.A), namely, the tyrosine-specific protein<br>kinases (Sefton and Hunter, 1984; Hirano et al., 1988 kinase that is probably of great functional importance<br>(see section V.A), namely, the tyrosine-specific protein<br>kinases (Sefton and Hunter, 1984; Hirano et al., 1988).<br>Two general classes of tyrosine-specific protein kinas (see section V.A), namely, the tyrosine-specific protein kinases (Sefton and Hunter, 1984; Hirano et al., 1988). Two general classes of tyrosine-specific protein kinases have been observed in neuronal preparations, one of kinases (Sefton and Hunter, 1984; Hirano et al., 1988).<br>Two general classes of tyrosine-specific protein kinases<br>have been observed in neuronal preparations, one of<br>which is represented by *protooncogene products* and the<br> *n* general classes of tyrosine-specific protein kinases<br> *1. Protooncogene products* and the<br> *1. Protooncogene products*. The best known of the brain<br> *1. Protooncogene products*. The best known of the brain<br>
otooncogene

tissues (Sommercorn et al., 1987) and in brain (Zorn et sarcoma virus (Bishop, 1982). This tyrosine-specific pro-<br>al., 1989), may, therefore, be involved in specific regula-<br>tory functions in DARPP-32-containing nerve cell tory functions in DARPP-32-containing nerve cells.<br>
Glycogen synthase kinase 3 has recently been found to<br>
catalyze the in vitro phosphorylation of the neuronal cell<br>
and in a modified neuron-specific form, is highly conce catalyze the *in vitro* phosphorylation of the neuronal cell<br>adhesion molecule N-CAM, suggesting that it may be<br>involved in regulation of cell-cell interactions in the CNS<br>involved in regulation of cell-cell interactions i Mushynski, 1981, 1982; Julien et al., 1983; Shecket and<br>Lasek, 1982; Wible et al., 1989). The neurofilament pro-<br>specific form of the enzyme, which has a six-amino acid<br>teins present in neuronal somata are mostly nonphos-<br> phosphorylation is not well understood (see section pre- and postsynaptic functions in mature neurons. The VI.D.1).<br>
WI.D.1).<br>
Myelin basic protein kinase has been reported as a phosphorylation (for examples, see Okada an have been observed in neuronal preparations, one of<br>which is represented by *protooncogene products* and the<br>other by *growth factor receptors*.<br>1. Protooncogene products. The best known of the brain<br>protooncogene product which is represented by *protooncogene products* and the other by *growth factor receptors.*<br>1. Protooncogene *products*. The best known of the brain protooncogene products is pp60<sup>c-src</sup>, the 60-kDa gene product of the pr other by *growth factor receptors*.<br>
1. Protooncogene products. The best known of the brain<br>
protooncogene products is pp60<sup>c-src</sup>, the 60-kDa gene<br>
product of the protooncogene c-src which is the cellular<br>
homolog of v-sr 1. Protooncogene products. The best known of the brain protooncogene products is pp60<sup>c-src</sup>, the 60-kDa gene product of the protooncogene c-src which is the cellular homolog of v-src, the transforming gene of the Rous sa protoontogene protacts is ppoor , the to-kina gene<br>product of the protooncogene c-src which is the cellular<br>homolog of v-src, the transforming gene of the Rous<br>sarcoma virus (Bishop, 1982). This tyrosine-specific pro-<br>tein which is found both in a "nonneuronal," widespread form sarcoma virus (Bishop, 1982). This tyrosine-specific protein kinase (Erikson et al., 1980; Hunter et al., 1981), which is found both in a "nonneuronal," widespread form and in a modified neuron-specific form, is highly con tein kinase (Erikson et al., 1980; Hunter et al., 1981), which is found both in a "nonneuronal," widespread form and in a modified neuron-specific form, is highly concentrated in mammalian brain (Cotton and Brugge, 1983; B which is found both in a "nonneuronal," widespread form<br>and in a modified neuron-specific form, is highly concen-<br>trated in mammalian brain (Cotton and Brugge, 1983;<br>Brugge et al., 1985; Walaas et al., 1988c; Ross et al.,<br> and in a modified neuron-specific form, is highly concentrated in mammalian brain (Cotton and Brugge, 1983; Brugge et al., 1985; Walaas et al., 1988c; Ross et al., 1988). Recent studies have shown that this enzyme, in addi trated in mammalian brain (Cotton and Brugge, 1983;<br>Brugge et al., 1985; Walaas et al., 1988c; Ross et al.,<br>1988). Recent studies have shown that this enzyme, in<br>addition to being enriched in growth cones (Maness et<br>al., 1 Brugge et al., 1985; Walaas et al., 1988c; Ross et al., 1988). Recent studies have shown that this enzyme, in addition to being enriched in growth cones (Maness et al., 1988), is also present in nerve cell bodies and nerve 1988). Recent studies have shown that this enzyme, in addition to being enriched in growth cones (Maness et al., 1988), is also present in nerve cell bodies and nerve fibers and terminals (Walaas et al., 1988c) and represe addition to being enriched in growth cones (Maness<br>al., 1988), is also present in nerve cell bodies and ne<br>fibers and terminals (Walaas et al., 1988c) and represe<br>the major tyrosine kinase in synaptic vesicles purif<br>from a al., 1988), is also present in nerve cell bodies and nerve fibers and terminals (Walaas et al., 1988c) and represents the major tyrosine kinase in synaptic vesicles purified from adult rat brain (Pang et al., 1988a). The n insert and terminals (walaas et al., 1988) and represents<br>the major tyrosine kinase in synaptic vesicles purified<br>from adult rat brain (Pang et al., 1988a). The neuron-<br>specific form of the enzyme, which has a six-amino ac From adult rat brain (Fang et al., 1988). The neuron-<br>specific form of the enzyme, which has a six-amino acid<br>insert (Levy et al., 1987; Martinez et al., 1987), has a<br>more restricted brain distribution but is present in d insert (Levy et al., 1987; Martinez et al., 1987), has a more restricted brain distribution but is present in dendrites, somata, axons, and axon terminals of several types of neurons (Walaas et al., 1988c; Sugrue et al., 1 more restricted brain distribution but is present in dendrites, somata, axons, and axon terminals of several types of neurons (Walaas et al., 1988c; Sugrue et al., 1990). These data indicate that  $pp60^{\circ-m}$  may be involve drites, somata, axons, and axon terminals of several types<br>of neurons (Walaas et al., 1988c; Sugrue et al., 1990).<br>These data indicate that  $pp60^{\circ\text{-src}}$  may be involved in both<br>pre- and postsynaptic functions in mature n These data indicate that  $pp60^{c\text{-}src}$  may be involved in both These data indicate that pp60<sup>c-src</sup> may be involved in both<br>pre- and postsynaptic functions in mature neurons. The<br>activity of pp60<sup>c-src</sup> appears to be regulated by enzyme<br>phosphorylation (for examples, see Okada and Na pre- and postsynaptic functivity of pp60<sup>c-src</sup> apper<br>phosphorylation (for exagawa, 1989), with phosph<br>being strongly inhibitory<br>The endogenous subst phosphorylation (for examples, see Okada and Naka-

al., 1982).<br>
Reed and Yeaman, 1987). This kinase, which appears to reparations of both synaptophysin (Pang et al., 1988a,b;<br>
Reed and Yeaman, 1987). This kinase, which appears to review, see De Camilli and Jahn, 1990), in gawa, 1989), with phosphorylation on tyrosine residues<br>being strongly inhibitory.<br>The endogenous substrates for this enzyme in brain<br>and its role(s) in neuronal function are not yet known.<br>The enrichment of the c-*src* gen gawa, 1989), with phosphorylation on tyrosine residues<br>being strongly inhibitory.<br>The endogenous substrates for this enzyme in brain<br>and its role(s) in neuronal function are not yet known.<br>The enrichment of the c-*src* gen being strongly inhibitory.<br>The endogenous substrates for this enzyme in brain<br>and its role(s) in neuronal function are not yet known.<br>The enrichment of the c-src gene product in nerve ter-<br>minals and somata of postmitotic The endogenous substrates for this enzyme in brain<br>and its role(s) in neuronal function are not yet known.<br>The enrichment of the c-src gene product in nerve ter-<br>minals and somata of postmitotic neurons suggests that<br>the e and its role(s) in neuronal function are not yet known<br>The enrichment of the c-src gene product in nerve ter<br>minals and somata of postmitotic neurons suggests tha<br>the enzyme may be involved in pleiotropic functions no<br>rest The enrichment of the c-src gene product in nerve ter-<br>minals and somata of postmitotic neurons suggests that<br>the enzyme may be involved in pleiotropic functions not<br>restricted to growth and proliferation. The enrichment<br>o minais and somata or postmitotic neurons suggests that<br>the enzyme may be involved in pleiotropic functions not<br>restricted to growth and proliferation. The enrichment<br>of the enzyme in synaptic vesicles and the prominent<br>tyr restricted to growth and proliferation. The enrichment of the enzyme in synaptic vesicles and the prominent of the enzyme in synaptic vesicles and the prominent<br>tyrosine phosphorylation obtained in synaptic vesicle<br>preparations of both synaptophysin (Pang et al., 1988a,b;<br>Barnekow et al., 1990) and p29 (Baumert et al., 1990),<br>tw tyrosine phosphorylation obtained in synaptic vesicle<br>preparations of both synaptophysin (Pang et al., 1988a,b;<br>Barnekow et al., 1990) and p29 (Baumert et al., 1990),<br>two intrinsic synaptic vesicle membrane proteins (for<br>r

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Solution 12<br>synaptic vesicle functions may be regulated by tyrosine<br>phosphorylation. In fact, it has recently been found that WALAAS AND<br>synaptic vesicle functions may be regulated by tyrosine<br>phosphorylation. In fact, it has recently been found that<br>the *c-src* protein is largely responsible for the endogenous<br>phosphorylation of synaptophysin on synaptic vesicle functions may be regulated by tyrosine<br>phosphorylation. In fact, it has recently been found that<br>the c-*src* protein is largely responsible for the endogenous<br>phosphorylation of synaptophysin on tyrosine r synaptic vesicle functions may be regulated<br>phosphorylation. In fact, it has recently been<br>the c-src protein is largely responsible for the<br>phosphorylation of synaptophysin on tyrosi<br>(Pang et al., 1988a; Barnekow et al., 1 osphorylation. In fact, it has recently been found that e c-src protein is largely responsible for the endogenous osphorylation of synaptophysin on tyrosine residues ang et al., 1988a; Barnekow et al., 1990). In other stud the c-*src* protein is largely responsible for the endogenous<br>phosphorylation of synaptophysin on tyrosine residues<br>(Pang et al., 1988a; Barnekow et al., 1990).<br>In other studies, a link between this class of enzymes<br>and ac

phosphorylation of synaptophysin on tyrosine residues<br>(Pang et al., 1988a; Barnekow et al., 1990).<br>In other studies, a link between this class of enzymes<br>and activation of membrane receptors has been obtained.<br>A pp60<sup>c-src</sup> (Fang et al., 1988), Barnekow et al., 1990).<br>In other studies, a link between this class of enzymes<br>and activation of membrane receptors has been obtained.<br>A pp60<sup>c-sm</sup>-related tyrosine kinase termed pp56<sup>kk</sup>, present<br>in In other studies, a link between this class of enzymes<br>and activation of membrane receptors has been obtained.<br>A pp60<sup>c-src</sup>-related tyrosine kinase termed pp56<sup>kk</sup>, present<br>in T-lymphocytes (Barber et al., 1989), has bee A pp60<sup>c-src</sup>-related tyrosine kinase termed pp56<sup>kk</sup>, present<br>in T-lymphocytes (Barber et al., 1989), has been found<br>to be activated by the CD4 or CD8 transmembrane<br>proteins involved in transmembrane signaling in these<br>c in T-lymphocytes (Barber et al., 1989), has been found<br>to be activated by the CD4 or CD8 transmembrane<br>protein phosphatase-2E  $Ca^{2+}/c$ almodulin Narrow<br>proteins involved in transmembrane signaling  $\overline{C}$ <br>cells (Veillette In 1-lymphocytes (Balber et al., 1989), has been lound<br>to be activated by the CD4 or CD8 transmembrane<br>proteins involved in transmembrane signaling in these<br>cells (Veillette et al., 1989). Activation of these signaling<br>sy to be activated by the CD4 or CD6 transmembrane<br>proteins involved in transmembrane signaling in these<br>cells (Veillette et al., 1989). Activation of these signaling<br>systems in intact T-lymphocytes apparently induces<br>pp56<sup>k</sup> cells (Veillette et al., 1989). Activation of these signaling<br>systems in intact T-lymphocytes apparently induces<br> $pp56^{k}$ -catalyzed tyrosine phosphorylation of a subunit<br>of the T-cell antigen receptor (Barber et al., 1989 systems in intact T-lymphocytes apparently induces<br>pp56<sup>kk</sup>-catalyzed tyrosine phosphorylation of a subunit<br>of the T-cell antigen receptor (Barber et al., 1989). In<br>contrast, this tyrosine kinase appears itself to be unde of the T-cell antigen receptor (Barber et al., 1989). In (section III.B), is able to activate  $pp56<sup>lck</sup>$  (Mustelin et of the T-cell antigen receptor (Barber et al., 1989). In contrast, this tyrosine kinase appears itself to be under inhibitory control by tyrosine phosphorylation, because left the membrane protein CD45, a tyrosine phospha contrast, this tyrosine kinase appears itself to be under<br>inhibitory control by tyrosine phosphorylation, because<br>the membrane protein CD45, a tyrosine phosphatase<br>(section III.B), is able to activate pp56<sup>kk</sup> (Mustelin e known. ection III.B), is able to activate pp56<sup>kk</sup> (Mustelin, 1989). Whether pp60<sup>c-grc</sup>-related proteins are involusional similar regulation mechanisms in neural cells is town.<br>2. *Growth factor receptors*. The other class of ty

al., 1989). Whether pp60<sup>c-arc</sup>-related proteins are involved<br>in similar regulation mechanisms in neural cells is not<br>known.<br>2. Growth factor receptors. The other class of tyrosine-<br>specific protein kinases is intrinsic t known.<br>
2. *Growth factor receptors*. The other class of tyrosine-<br>
specific protein kinases is intrinsic to receptors for a<br>
number of hormones, mitogens, and growth factors (for<br>
review, see Yarden and Ullrich, 1988). F 2. Growth factor receptors. The other class of tyrosine-<br>specific protein kinases is intrinsic to receptors for a<br>number of hormones, mitogens, and growth factors (for<br>review, see Yarden and Ullrich, 1988). For example, b specific protein kinases is intrinsic to receptors for a<br>number of hormones, mitogens, and growth factors (for<br>review, see Yarden and Ullrich, 1988). For example, brain<br>contains receptors for insulin and insulin-like growt number of hormones, mitogens, and growth factors (for review, see Yarden and Ullrich, 1988). For example, brain contains receptors for insulin and insulin-like growth factor I (somatomedin C), both of which display tyrosin review, see rarden and Olinch, 1988). For example, brain<br>contains receptors for insulin and insulin-like growth<br>factor I (somatomedin C), both of which display tyrosine<br>kinase activities (Jacobs et al., 1983; Rees-Jones et factor I (somatomedin C), both of which display tyrosine Co<br>kinase activities (Jacobs et al., 1983; Rees-Jones et al., tas<br>1984; Gammeltoft et al., 1985; Adamo et al., 1989). Ty-<br>rosine phosphorylation of these receptors kinase activities (Jacobs et al., 1983; Rees-Jones et al., 1984; Gammeltoft et al., 1985; Adamo et al., 1989). Tyrosine phosphorylation of these receptors following ligand binding appears to represent the initial step in t messengers (for examples, see Rosen, 1987; Yarden and signal transduction pathways used by the relevant first signal transduction pathways used by the relevant first changes are Rosen, 1987; Yarden and tive Ullrich, 1988) **III. Phosphoprotein Phosphatases in Brain Sengers (for examples, see Rosen, 1987; Yarden and ich, 1988) (see further discussion in section V.A.3).<br><b>III. Phosphoprotein Phosphatases in Brain**<br>*III. Phosphoprotein Phosphata* messengers (for examples, see Rosen, 1987; Yarden<br>Ullrich, 1988) (see further discussion in section V.A<br>III. Phosphoprotein Phosphatases in Brain<br>A. Serine/Threonine-specific Protein Phosphatases<br>Although protein phosphory

and III. Phosphoprotein Phosphatases in Brain<br>Serine/Threonine-specific Protein Phosphatases al.<br>Although protein phosphorylation systems in the brain as<br>pear in many cases to be regulated by activation of tin III. Phosphoprotein Phosphatases in Brain<br>A. Serine/Threonine-specific Protein Phosphatases<br>Although protein phosphorylation systems in the brain<br>appear in many cases to be regulated by activation of ti<br>protein kinases, pr A. Serine/Threonine-specific Protein Phosphatases<br>Although protein phosphorylation systems in the brain<br>appear in many cases to be regulated by activation of<br>protein kinases, protein phosphatases also constitute<br>targets fo At though protein phosphorylation systems in the brain<br>appear in many cases to be regulated by activation of<br>protein kinases, protein phosphatases also constitute<br>targets for regulatory agents. The protein phosphatases<br>in Although protein phosphorylation systems in the brain<br>appear in many cases to be regulated by activation of<br>protein kinases, protein phosphatases also constitute<br>targets for regulatory agents. The protein phosphatases<br>invo appear in many cases to be regulated by activation of tin protein kinases, protein phosphatases also constitute et at targets for regulatory agents. The protein phosphatases and involved in cellular regulation that dephos protein kinases, protein phosphatases also constitute<br>targets for regulatory agents. The protein phosphatases<br>involved in cellular regulation that dephosphorylate<br>serine and/or threonine residues have been divided into<br>two targets for regulatory agents. The protein phosphatases and involved in cellular regulation that dephosphorylate linearine and/or threonine residues have been divided into photom major types and further subclassified into involved in cellular regulation that dephosphorylate<br>serine and/or threonine residues have been divided into<br>two major types and further subclassified into four en-<br>zymatic activities (table 5), all of which have been foun serine ana/or threonine residues have been divided into<br>two major types and further subclassified into four en-<br>zymatic activities (table 5), all of which have been found<br>in brain (Ingebritsen and Cohen, 1983a,b; Ingebrits zymatic activities (table 5), all of which have been found<br>in brain (Ingebritsen and Cohen, 1983a,b; Ingebritsen et<br>al., 1983). More recent evidence, mainly gained from<br>molecular cloning studies, indicates that a large num al., 1983). More recent evidence, mainly gained from hamolecular cloning studies, indicates that a large number of isozymic forms of these enzymes exist (for reviews, N<br>see Cohen, 1989; Cohen and Cohen, 1989; Shenolikar kn molecular cloning studies, indicates that a large number<br>of isozymic forms of these enzymes exist (for reviews,<br>see Cohen, 1989; Cohen and Cohen, 1989; Shenolikar<br>and Nairn, 1991; Guerini et al., 1990). However, the basic<br> of isozymic forms of these enzymes exist (for reviews,<br>see Cohen, 1989; Cohen and Cohen, 1989; Shenolikar k<br>and Nairn, 1991; Guerini et al., 1990). However, the basic 1<br>classification scheme (Ingebritsen and Cohen, 1983a,b see Conen, 1989; Conen and Conen, 1989; Shenonkar Kiand Nairn, 1991; Guerini et al., 1990). However, the basic 19 classification scheme (Ingebritsen and Cohen, 1983a,b) ties follows that the properties of the main phosphat

TABLE 5<br>TABLE 5<br>fic protein phosph *Serine/threonine-specific protein phosphatases in brain\**

<b>Enzyme</b>	Regulator	Substrate specificity
Protein phosphatase-1	Inhibitor-1, inhibitor-2, DARPP-32	<b>Broad</b>
Protein phosphatase-2A	Unknown. (G-sub- strate)	<b>Broad</b>
Protein phosphatase-2B	$Ca2+/calmodulin$	Narrow
Protein phosphatase-2C	$Mg^{2+}$	Broad

\* The major classes of protein phosphatase activities in neural and Cohen (1983a,b) and Shenolikar and Nairn (1991). Further details are

phosphatases, particularly in nonneuronal tissues, the peripheral tissues are presented. Data compiled from ingebritsen and<br>Cohen (1983a,b) and Shenolikar and Nairn (1991). Further details are<br>described in the text, section III.<br>phosphatases, particularly in nonneuronal tissue described in the text, section III.<br>phosphatases, particularly in nonneuronal tissues, the<br>reader is referred to several recent reviews of this topic<br>for more detail (Li, 1982; Yang, 1986; Cohen, 1989; Cohen<br>and Cohen, 198 and Cohen, 1989; Shenolikar and Nairn, 1991).<br>Type 1 phosphatase (protein phosphatase-1) seleclosphatases, particularly in nonneuronal tissues, the ader is referred to several recent reviews of this top r more detail (Li, 1982; Yang, 1986; Cohen, 1989; Cohen d Cohen, 1989; Shenolikar and Nairn, 1991). Type 1 phosp

in similar regulation mechanisms in neural cells is not<br>
known.<br>
2. Growth factor receptors. The other class of tyrosine-<br>
2. Growth factor receptors. The other class of tyrosine-<br>
sinase and is inhibited by certain heatreader is referred to several recent reviews of this topic<br>for more detail (Li, 1982; Yang, 1986; Cohen, 1989; Cohen<br>and Cohen, 1989; Shenolikar and Nairn, 1991).<br>Type 1 phosphatase (*protein phosphatase-1*) selec-<br>tively for more detail (Li, 1982; Yang, 1986; Cohen, 1989; Cohen<br>and Cohen, 1989; Shenolikar and Nairn, 1991).<br>Type 1 phosphatase (*protein phosphatase-1*) selec-<br>tively dephosphorylates the  $\beta$ -subunit of phosphorylase<br>kinase and Cohen, 1989; Shenolikar and Nairn, 1991).<br>Type 1 phosphatase (*protein phosphatase-1*) selectively dephosphorylates the  $\beta$ -subunit of phosphorylase<br>kinase and is inhibited by certain heat-stable inhibitor<br>proteins, Type 1 phosphatase (*protein phosphatase-1*) selectively dephosphorylates the  $\beta$ -subunit of phosphorylase kinase and is inhibited by certain heat-stable inhibitor proteins, and type 2 phosphatases (*protein phosphatases* subury dephosphorylates the  $p$ -subunit of phosphorylase<br>kinase and is inhibited by certain heat-stable inhibitor<br>proteins, and type 2 phosphatases (*protein phosphatases*<br>-2A, -2B, and -2C) selectively dephosphorylate th these and is inhibited by certain heat-stable inhibitor<br>proteins, and type 2 phosphatases (*protein phosphatases*<br>-2A, -2B, and -2C) selectively dephosphorylate the  $\alpha$ -<br>subunit of phosphorylase kinase and are insensitiv -2A, -2B, and -2C) selectively dephosphorylate the  $\alpha$ -subunit of phosphorylase kinase and are insensitive to these heat-stable inhibitor proteins (Ingebritsen and Cohen, 1983a,b). Type 1, type 2A, and type 2B phosphatas -2A, -2D, and -2C) selectively dephosphorylate the  $\alpha$ -<br>subunit of phosphorylase kinase and are insensitive to<br>these heat-stable inhibitor proteins (Ingebritsen and<br>Cohen, 1983a,b). Type 1, type 2A, and type 2B phospha-<br> these heat-stable inhibitor proteins (Ingebritsen and  $\frac{5}{9}$  Cohen, 1983a,b). Type 1, type 2A, and type 2B phosphatases are inhibited by NaF and inorganic phosphate (Ingebritsen and Cohen, 1983a,b; Shenolikar and Nairn Cohen, 1983a,b). Type 1, type 2A, and type 2B phosphatases are inhibited by NaF and inorganic phosphate (Ingebritsen and Cohen, 1983a,b; Shenolikar and Nairn, 1991). Other protein phosphatases, with more narrow substrate s tases are inhibited by NaF and inorganic phosphate (Ingebritsen and Cohen, 1983a,b; Shenolikar and Nairn, 1991). Other protein phosphatases, with more narrow substrate specificity, that have been characterized include pyr (Ingebritsen and Cohen, 1983a,b; Shenolikar and Nairn, 1991). Other protein phosphatases, with more narrow substrate specificity, that have been characterized include pyruvate dehydrogenase phosphatase, which is activated 1991). Other protein phosphatases, with more narrow substrate specificity, that have been characterized include pyruvate dehydrogenase phosphatase, which is activated by  $Ca^{2+}$  (Reed et al., 1985), and the branched chain substrate specificity, that have been characterized in-<br>clude pyruvate dehydrogenase phosphatase, which is ac-<br>tivated by Ca<sup>2+</sup> (Reed et al., 1985), and the branched<br>chain  $\alpha$ -keto acid dehydrogenase phosphatase (Damuni clude pyruvate dehydrogenase phosphatase, which is activated by  $Ca^{2+}$  (Reed et al., 1985), and the branched chain  $\alpha$ -keto acid dehydrogenase phosphatase (Damuni and Reed, 1987), which appears to be regulated through t tivated by  $Ca^{2+}$  (Reed et al., 1985), and the branched<br>chain  $\alpha$ -keto acid dehydrogenase phosphatase (Damuni<br>and Reed, 1987), which appears to be regulated through<br>the binding of a heat-stable inhibitor protein (Reed e chain  $\alpha$ -keto acid denyarogenase phosphatase (Damuni<br>and Reed, 1987), which appears to be regulated through<br>the binding of a heat-stable inhibitor protein (Reed et<br>al., 1985). Protein phosphatase activities have also be and Reed, 1967), which appears to be regulated through<br>the binding of a heat-stable inhibitor protein (Reed  $\epsilon$ <br>al., 1985). Protein phosphatase activities have also bee<br>reported in mitochondria and myelin fractions, as w al., 1985). Protein phosphatase activities have also been reported in mitochondria and myelin fractions, as well as in partially purified preparations of rhodopsin, nicotinic acetylcholine receptors, and microtubules (Gord al., 1985). Protein phosphatase activities have also been<br>reported in mitochondria and myelin fractions, as well<br>as in partially purified preparations of rhodopsin, nico-<br>tinic acetylcholine receptors, and microtubules (Go reported in mitochondria and myelin fractions, as w<br>as in partially purified preparations of rhodopsin, nit<br>tinic acetylcholine receptors, and microtubules (Gord<br>et al., 1979; Miyamoto and Kakiuchi, 1975; McNama<br>and Appel, as in partially purified preparations of rhodopsin, nicotinic acetylcholine receptors, and microtubules (Gordon et al., 1979; Miyamoto and Kakiuchi, 1975; McNamara and Appel, 1977; Teichberg and Changeux, 1977; Cough-<br>lin tinic acetylcholine receptors, and K<br>et al., 1979; Miyamoto and K<br>and Appel, 1977; Teichberg an<br>lin et al., 1980). The identit<br>phosphatases are not known.<br>The presence of these enzyn al., 1979; Miyamoto and Kakiuchi, 1975; McNamara<br>d Appel, 1977; Teichberg and Changeux, 1977; Cough-<br>i et al., 1980). The identities of the latter types of<br>losphatases are not known.<br>The presence of these enzymes in brain

and Appel, 1977; Teichberg and Changeux, 1977; Couplin et al., 1980). The identities of the latter types phosphatases are not known.<br>The presence of these enzymes in brain indicates the physiological importance in dephosph lin et al., 1980). The identities of the latter types of<br>phosphatases are not known.<br>The presence of these enzymes in brain indicates their<br>physiological importance in dephosphorylating endoge-<br>nous phosphoproteins. Phosph of phosphatase -2B is more restricted (Shenolikar and I he presence of these enzymes in orain indicates their<br>physiological importance in dephosphorylating endoge-<br>nous phosphoproteins. Phosphatase-1, -2A, and -2C all<br>have relatively broad substrate specificities, whereas tha physiological importance in dephosphorylating endogenous phosphoroteins. Phosphatase-1, -2A, and -2C all have relatively broad substrate specificities, whereas that of phosphatase -2B is more restricted (Shenolikar and Nai nave relatively broad substrate specificities, whereas that<br>of phosphatase -2B is more restricted (Shenolikar and<br>Nairn, 1991). Despite this, protein phosphatase-2B, also<br>known as calcineurin (Stewart et al., 1982; Yang et Nairn, 1991). Despite this, protein phosphatase-2B, also<br>known as calcineurin (Stewart et al., 1982; Yang et al.,<br>1982), has been found to dephosphorylate several iden-<br>tified phosphoproteins in brain, including phosphatas known as calcineurin (Stewart et al., 1982; Tang et al., 1982), has been found to dephosphorylate several identified phosphoproteins in brain, including phosphatase inhibitor-1 and DARPP-32 (see below) with high efficiency



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protein phosphoneylation-<br>inhibitor-1 and of DARPP-32 are potent inhibitors of<br>protein phosphatase-1 (see below). This suggests that<br>phosphatase-2B indirectly regulates the activity of phos-PROTEIN PHOSPHORYLAT<br>inhibitor-1 and of DARPP-32 are potent inhibitors of<br>protein phosphatase-1 (see below). This suggests the<br>phosphatase-2B indirectly regulates the activity of phosphatase-1, thereby extending its influe inhibitor-1 and of DARPP-32 are potent inhibitors<br>protein phosphatase-1 (see below). This suggests t<br>phosphatase-2B indirectly regulates the activity of ph<br>phatase-1, thereby extending its influence to phosp<br>proteins which inhibitor-1 and of DARPP-32 are potent inhibito<br>protein phosphatase-1 (see below). This suggests<br>phosphatase-2B indirectly regulates the activity of p<br>phatase-1, thereby extending its influence to phospha<br>proteins which ar protein ph<br>phosphatas<br>phatase-1,<br>proteins wl<br>2B itself.<br>1. Reguld osphatase-2B indirectly regulates the activity of phos-<br>atase-1, thereby extending its influence to phospho-<br>Thoteins which are not direct substrates for phosphatase-<br>is itself.<br>*1. Regulation of activity*. Phosphatases-1,

phatase-1, thereby extending its influence to phospho-<br>proteins which are not direct substrates for phosphatase-<br>2B itself.<br>1. Regulation of activity. Phosphatases-1, -2A, and -2B<br>appear to be targets for regulation in bra proteins which are not direct substrates for phosphatase 2B itself.<br>2B itself.<br>1. Regulation of activity. Phosphatases-1, -2A, and -2E<br>appear to be targets for regulation in brain. Regulation<br>of type-1 phosphatase appears 2D itsen.<br>
1. Regulation of activity. Phosphatases-1, -2A, and -2B<br>
appear to be targets for regulation in brain. Regulation<br>
of type-1 phosphatase appears particularly interesting.<br>
Although little is known about phosphat I. Regulation of activity. I hospitalases-1, -2N, and -2B of appear to be targets for regulation in brain. Regulation has of type-1 phosphatase appears particularly interesting. being Although little is known about phospha more and the digets for regulation in brain, regulation increases of type-1 phosphatase appears particularly interesting. brain heural tissues (Shenolikar and Nairn, 1991), brain effecontains both phosphatase inhibitor-1 a Athough fitte is known about phosphatase inhibitor-2 that<br>in neural tissues (Shenolikar and Nairn, 1991), brain efficontains both phosphatase inhibitor-1 and DARPP-32 ito<br>(Walaas and Greengard, 1984; Nairn et al., 1988), t in neural tissues (Shenolikar and Nairn, 1991), brain<br>contains both phosphatase inhibitor-1 and DARPP-32<br>(Walaas and Greengard, 1984; Nairn et al., 1988), two<br>closely related proteins that, during phosphorylation by<br>cyclic contains both phosphatase inhibitor-1 and DARPP-32 (Walaas and Greengard, 1984; Nairn et al., 1988), two closely related proteins that, during phosphorylation by cyclic AMP-dependent protein kinase, become inhibitors of pr (Walaas and Greengard, 1984; Nairn et al., 1988), two<br>closely related proteins that, during phosphorylation by<br>cyclic AMP-dependent protein kinase, become inhibitors<br>of protein phosphatase-1 (Hemmings et al., 1984a, 1990). closely related proteins that, during phosphorylation by<br>cyclic AMP-dependent protein kinase, become inhibitors for<br>of protein phosphatase-1 (Hemmings et al., 1984a, 1990). va<br>Phosphatase inhibitor-1 and DARPP-32 share par cyclic AMP-dependent protein kinase, become inhibitors<br>of protein phosphatase-1 (Hemmings et al., 1984a, 1990).<br>Phosphatase inhibitor-1 and DARPP-32 share partial<br>sequence homology and heat and acid stability (Aitken<br>et al sequence homology and heat and acid stability (Aitken et al., 1982; Hemmings et al., 1984c; Williams et al., 1986) and appear to be colocalized in a number of brain cells, particularly in the basal ganglia (Nairn et al., 1 1986) and appear to be colocalized in a number of brain eral, 1982; Hemmings et al., 1984c; Williams et al., 1986) and appear to be colocalized in a number of brain leads, particularly in the basal ganglia (Nairn et al., 1988). In Phosphatase inhibitor-1 is also present in many 1986) and appear to be colocalized in a number of brain<br>cells, particularly in the basal ganglia (Nairn et al., 1988). P<br>Phosphatase inhibitor-1 is also present in many periph-<br>eral, nonneuronal tissues (for examples, see cells, particularly in the basal ganglia (Nairn et al., 1988).<br>Phosphatase inhibitor-1 is also present in many peripheral, nonneuronal tissues (for examples, see Elbrecht et<br>al., submitted). In contrast, DARPP-32 appears g Phosphatase inhibitor-1 is also present in many periph-<br>eral, nonneuronal tissues (for examples, see Elbrecht et<br>al., submitted). In contrast, DARPP-32 appears generally<br>to be restricted to neuronal and peripheral cells t eral, nonneuronal tissues (for examples, see Elbrecht e<br>al., submitted). In contrast, DARPP-32 appears generall<br>to be restricted to neuronal and peripheral cells tha<br>contain the D1 subclass of dopamine receptor, such a<br>the al., submitted). In contrast, DARPP-32 appears generally<br>to be restricted to neuronal and peripheral cells that<br>contain the D1 subclass of dopamine receptor, such as<br>the medium-sized spiny neurons of the neostriatum (Ouito be restricted to neuronal and peripheral cells that<br>contain the D1 subclass of dopamine receptor, such as<br>the medium-sized spiny neurons of the neostriatum (Oui-<br>met et al., 1984b), parathyroid cells, brown fat cells, a contain the D1 subclass of dopamine receptor, such as  $\frac{D}{2}$ <br>the medium-sized spiny neurons of the neostriatum (Oui-<br>the endition-sized spiny neurons of the neostriatum (Oui-<br>the tet al., 1984b), parathyroid cells, bro the medium-sized spiny neutons of the neostriatum (Current et al., 1984b), parathyroid cells, brown fat cells, and renal tubular cells (Brown et al., 1977; Meister et al., 1988, 1989), where it appears to mediate certain o met et al., 1984b), parathyroid cells, brown fat cells, and phatase-1. (DARPP-32 is further discussed in section V.<br>
renal tubular cells (Brown et al., 1977; Meister et al., C, and NMDA-induced dephosphorylation of MAP-2 i 1987a,b,c).

effects of dopamine acting on dopamine D1 receptors (for review, see Walaas et al., 1986a; Hemmings et al., 1987a,b,c).<br>
Characterization of the type-2 phosphatases has shown that phosphatase-2A does not require divalent (for review, see Walaas et al., 1986a; Hemmings et al., 1987a,b,c).<br>
1987a,b,c).<br>
Characterization of the type-2 phosphatases has al., idualing the shown that phosphatase-2A does not require divalent  $T_{0}$  cations, phosp 1987a,b,c).<br>Characterization of the type-2 phosphatases has<br>shown that phosphatase-2A does not require divalent<br>cations, phosphatase-2B requires  $Ca^{2+}/calmodulin$ , and<br>phosphatase-2C requires  $Mg^{2+}$  for activity (Ingebritsen<br> Characterization of the type-2 phosphatases has<br>shown that phosphatase-2A does not require divalent<br>cations, phosphatase-2B requires  $Ca^{2+}/calmodulin$ , and<br>phosphatase-2C requires  $Mg^{2+}$  for activity (Ingebritsen<br>and Cohen, 1 shown that phosphatase-2A does not require divalent<br>cations, phosphatase-2B requires  $Ca^{2+}/c$ almodulin, and<br>phosphatase-2C requires  $Mg^{2+}$  for activity (Ingebritsen<br>and Cohen, 1983a,b; Klee and Cohen, 1988; Shenolikar<br>a phosphatase-2C requires Mg<sup>2+</sup> for activity (Ingebrits and Cohen, 1983a,b; Klee and Cohen, 1988; Shenolik and Nairn, 1991). Phosphatase-2A may also be regulat by G-substrate, a well-characterized cytosolic protein 23 kDa, and Cohen, 1983a,b; Klee and Cohen, 1988; Shenolikar cand Nairn, 1991). Phosphatase-2A may also be regulated a by G-substrate, a well-characterized cytosolic protein of p 23 kDa, which is a specific substrate for cyclic G and Nairn, 1991). Phosphatase-2A may also be regulated by G-substrate, a well-characterized cytosolic protein of 23 kDa, which is a specific substrate for cyclic GMP dependent protein kinase (Schlichter et al., 1978). This by G-substrate, a well-characterized cytosolic protein 23 kDa, which is a specific substrate for cyclic GM dependent protein kinase (Schlichter et al., 1978). The protein, which is enriched in Purkinje cells in the cellum 23 kDa, which is a specific substrate for cyclic GMP-<br>dependent protein kinase (Schlichter et al., 1978). This pro<br>protein, which is enriched in Purkinje cells in the cere-<br>bellum (Detre et al., 1984), shares some physico dependent protein kinase (Schlichter et al., 1978). This<br>protein, which is enriched in Purkinje cells in the cere-<br>bellum (Detre et al., 1984), shares some physicochemical, fou<br>primary structural, and functional properties protein, which is enriched in Purkinje cells in the cerebellum (Detre et al., 1984), shares some physicochemical, primary structural, and functional properties with DARPP-32 and phosphatase inhibitor-1 (Aswad and Greengard bellum (Detre et al., 1984), shares some physicochemical, for firmary structural, and functional properties with fr<br>DARPP-32 and phosphatase inhibitor-1 (Aswad and ty<br>Greengard, 1981a,b; Aitken et al., 1981; Hemmings et al primary structural, and functional properties with<br>DARPP-32 and phosphatase inhibitor-1 (Aswad and<br>Greengard, 1981a,b; Aitken et al., 1981; Hemmings et al.,<br>1984b,c), including being a good substrate for protein<br>phosphatas DARPP-32 and phosphatase inhibitor-1 (Aswad and type Greengard, 1981a,b; Aitken et al., 1981; Hemmings et al., 19819-1984b,c), including being a good substrate for protein Ophosphatase-2B (King et al., 1984). However, in c Greengard, 1981a,b; Aitken et al., 1981; Hemmings et al., 1989).<br>
1984b,c), including being a good substrate for protein One of the brain protein tyrosine phosphatases, des-<br>
phosphatase-2B (King et al., 1984). However, in 1984b,c), including being a good substrate for protein<br>phosphatase-2B (King et al., 1984). However, in contrast<br>to DARPP-32, G-substrate is not phosphorylated by<br>cyclic AMP-dependent protein kinase or casein kinase<br>II. Whe phosphadase-2B (King et al., 1964). However, in contra<br>to DARPP-32, G-substrate is not phosphorylated b<br>cyclic AMP-dependent protein kinase or casein kina<br>II. When phosphorylated by cyclic GMP-dependent pr<br>tein kinase, G-s to DARPP-32, G-substrate is not phosphorylated by cyclic AMP-dependent protein kinase or casein kinase II. When phosphorylated by cyclic GMP-dependent protein kinase, G-substrate is an efficient inhibitor of phosphatase-2A cyclic AMP-dependent protein kinase or casein kinase<br>II. When phosphorylated by cyclic GMP-dependent pro-<br>tein kinase, G-substrate is an efficient inhibitor of phos-<br>phatase-2A (A. C. Nairn, P. Simonelli, H. C. Li and P.<br>G 11. When phosphorylated by cyclic GMP-dependent protein kinase, G-substrate is an efficient inhibitor of phosphatase-2A (A. C. Nairn, P. Simonelli, H. C. Li and P. Greengard, unpublished results). Therefore, neuronal cells

inhibitor-1 and of DARPP-32 are potent inhibitors of inhibitors, some of which appear to be neuron specific.<br>protein phosphatase-1 (see below). This suggests that It appears probable that additional phosphatase inhibi-<br>pho AND NEURONAL FUNCTION<br>inhibitors, some of which appear to be neuron specific.<br>It appears probable that additional phosphatase inhibi-IND NEURONAL FUNCTION<br>
Inhibitors, some of which appear to be neuron speci:<br>
It appears probable that additional phosphatase inhit<br>
itors will be found in brain. AND NEURONAL FUNCTION 313<br>
inhibitors, some of which appear to be neuron specific.<br>
It appears probable that additional phosphatase inhibi-<br>
tors will be found in brain.<br>
The data summarized above indicate that the activit

Phosphatase inhibitor-1 and DARPP-32 share partial found to decrease (Halpain et al., 1990), phosphorylation<br>sequence homology and heat and acid stability (Aitken of DARPP-32 in situ. These changes occurred on that<br>et al., It appears probable that additional phosphatase inhibitors will be found in brain.<br>The data summarized above indicate that the activities<br>of certain phosphatases in brain are regulated, directly<br>or indirectly, by second me It appears probable that additional phosphatase inhibitors will be found in brain.<br>
The data summarized above indicate that the activities<br>
of certain phosphatases in brain are regulated, directly<br>
or indirectly, by secon The data summarized above indicate that the activities<br>of certain phosphatases in brain are regulated, directly<br>or indirectly, by second messengers such as cyclic AMP,<br>cyclic GMP, and  $Ca^{2+}$  and that these regulatory sys I he data summarized above mulcate that the activities<br>of certain phosphatases in brain are regulated, directly<br>or indirectly, by second messengers such as cyclic AMP,<br>cyclic GMP, and Ca<sup>2+</sup> and that these regulatory syste or indirectly, by second messengers such as cyclic AM<br>cyclic GMP, and  $Ca^{2+}$  and that these regulatory syste<br>have distinct cellular and regional distributions in t<br>brain. Indeed, recent data indicate that certain neu<br>tra or munectly, by second messengers such as cyclic  $GMP$ , and  $Ca^{2+}$  and that these regulatory system<br>have distinct cellular and regional distributions in the brain. Indeed, recent data indicate that certain neuron<br>transmit have distinct cellular and regional distributions in the brain. Indeed, recent data indicate that certain neuro-<br>transmitters may produce some of their physiological<br>effects in brain by regulating protein phosphatase inhib brain. Indeed, recent data indicate that certain neuro-<br>transmitters may produce some of their physiological<br>effects in brain by regulating protein phosphatase inhib-<br>itors in specific cells, in some cases by molecular mec brain. Indeed, fecent data mulcate that certain heuto-<br>transmitters may produce some of their physiological<br>effects in brain by regulating protein phosphatase inhib-<br>itors in specific cells, in some cases by molecular mech rransmitters may produce some of their physiological<br>effects in brain by regulating protein phosphatase inhib-<br>itors in specific cells, in some cases by molecular mech-<br>anisms that may be specific to nervous tissue. For ex enects in brain by regulating protein phosphatase inhibitors in specific cells, in some cases by molecular mech<br>anisms that may be specific to nervous tissue. For ex<br>ample, activation of dopamine D1 receptors has been<br>foun riors in specific cens, in some cases by molecular mechanisms that may be specific to nervous tissue. For example, activation of dopamine D1 receptors has been found to increase (Walaas et al., 1983a), whereas activation o amisms that may be specific to hervous tissue. For example, activation of dopamine D1 receptors has been<br>found to increase (Walaas et al., 1983a), whereas activation of the NMDA type of glutamate receptor has been<br>found to ample, activation of dopamine D1 receptors has been<br>found to increase (Walaas et al., 1983a), whereas acti-<br>vation of the NMDA type of glutamate receptor has been<br>found to decrease (Halpain et al., 1990), phosphorylation<br>o phosphorylation site that is preferentially phosphorylation of the NMDA type of glutamate receptor has found to decrease (Halpain et al., 1990), phosphorylation of DARPP-32 in situ. These changes occurred on phosphorylatio vation of the NMDA type of glutamate receptor has been<br>found to decrease (Halpain et al., 1990), phosphorylation<br>of DARPP-32 in situ. These changes occurred on that<br>phosphorylation site that is preferentially phosphory-<br>la phosphorylation<br>of DARPP-32 in situ. These changes occurred on that<br>phosphorylation site that is preferentially phosphory-<br>lated by cyclic AMP-dependent protein kinase and de-<br>phosphorylated by phosphatase-2B in vitro and phosphorylation site that is preferentially phosphory-<br>lated by cyclic AMP-dependent protein kinase and de-<br>phosphorylated by phosphatase-2B in vitro and that<br>determines the potency of DARPP-32 as an inhibitor of<br>phosphata lated by cyclic AMP-dependent protein kinase and de-<br>phosphorylated by phosphatase-2B in vitro and that<br>determines the potency of DARPP-32 as an inhibitor of<br>phosphatase-1 (Hemmings et al., 1984a,c, 1990). There-<br>fore, the phosphorylated by phosphatase-2B in vitro and that phosphorylated by phosphatase-2B in vitro and that<br>determines the potency of DARPP-32 as an inhibitor of<br>phosphatase-1 (Hemmings et al., 1984a,c, 1990). There-<br>fore, the neurotransmitters dopamine and glutamate may<br>achieve determines the potency of DARPP-32 as an inhibitor of<br>phosphatase-1 (Hemmings et al., 1984a,c, 1990). There-<br>fore, the neurotransmitters dopamine and glutamate may<br>achieve some of their actions in these cells through<br>DARPP phosphatase-1 (Hemmings et al., 1964a,c, 1990). Ther<br>fore, the neurotransmitters dopamine and glutamate machieve some of their actions in these cells throug<br>DARPP-32 phosphorylation and dephosphorylation an<br>thus, through r Frore, the neurotransmitters dopamine and glutamate may<br>achieve some of their actions in these cells through<br>DARPP-32 phosphorylation and dephosphorylation and,<br>thus, through regulation of the activity of protein phos-<br>pha DANT P-32 phosphorylation at<br>thus, through regulation of the<br>phatase-1. (DARPP-32 is furt<br>C, and NMDA-induced dephation VI.D.1.) *B. Tyrosine-specific Protein Phosphatases*<br>*B. Tyrosine-specific Protein Phosphatases*<br>*B. Tyrosine-specific Protein Phosphatases*<br>Protein phosphatases specific for phosph and NMDA-induced dephosphorylation of MAP-2 is<br>scussed in section VI.D.1.)<br>Tyrosine-specific Protein Phosphatases<br>Protein phosphatases specific for phosphotyrosine res-<br>ues have also been found in various tissues (Foulkes

Characterization of the type-2 phosphatases has<br>shown that phosphatase-2A does not require divalent Topks and Characterization. 1985; Okada et al., 1986;<br>In the shown that phosphatase-2A does not require divalent Topks and cations, phosphatase-2B requires Ca<sup>--</sup>/caimoduin, and<br>phosphatase-specific phosphatases<br>phosphatase-2C requires  $Mg^{2+}$  for activity (Ingebritsen<br>and Cohen, 1983a,b; Klee and Cohen, 1988; Shenolikar<br>and Nairn, 1991). Ph Protein phosphatases specific for phosphotyrosine res-B. Tyrosine-specific Protein Phosphatases<br>Protein phosphatases specific for phosphotyrosine res-<br>idues have also been found in various tissues (Foulkes et<br>al., 1983; Brunati and Pinna, 1985; Okada et al., 1986;<br>Tonks and C Protein phosphatases specific for phosphotyrosine residues have also been found in various tissues (Foulkes et al., 1983; Brunati and Pinna, 1985; Okada et al., 1986; Tonks and Charbonneau, 1989; Tonks et al., 1989). In on Protein phosphatases specific for phosphotyrosine residues have also been found in various tissues (Foulkes et al., 1983; Brunati and Pinna, 1985; Okada et al., 1986; Tonks and Charbonneau, 1989; Tonks et al., 1989). In on idues have also been found in various tissues (Foulkes et al., 1983; Brunati and Pinna, 1985; Okada et al., 1986; Tonks and Charbonneau, 1989; Tonks et al., 1989). In one study, seven forms of tyrosine-specific phosphatase al., 1983; Brunati and Pinna, 1985; Okada et al., 1986;<br>Tonks and Charbonneau, 1989; Tonks et al., 1989). In<br>one study, seven forms of tyrosine-specific phosphatases<br>were separated from bovine brain extracts and partially<br> Tonks and Charbonneau, 1969; Tonks et al., 1969). Tone study, seven forms of tyrosine-specific phosphatases were separated from bovine brain extracts and partial characterized (Jones et al., 1989). These activities cou all one study, seven forms of tyrosine-specific phosphatase<br>were separated from bovine brain extracts and partiall<br>characterized (Jones et al., 1989). These activities could<br>all be distinguished from the major serine/threonin<br> characterized (Jones et al., 1989). These activities could<br>all be distinguished from the major serine/threonine<br>phosphatases by their relative sensitivity to vanadate,<br>NaF, inorganic phosphate, and the heat-stable inhibito all be distinguished from the major serine/threonine all be distinguished from the major serine/threonine<br>phosphatases by their relative sensitivity to vanadate,<br>NaF, inorganic phosphate, and the heat-stable inhibitor<br>proteins described above (Jones et al., 1989). Two heat-<br> phosphatases by their relative sensitivity to vaniable.<br>NaF, inorganic phosphate, and the heat-stable inhibitor<br>proteins described above (Jones et al., 1989). Two heat-<br>stable tyrosine phosphatase inhibitor proteins were a type-1 serine/threonine phosphatases (Ingebritsen, 1989). found in the brain extracts, both of which were distinct<br>from the heat-stable inhibitor proteins regulating the<br>type-1 serine/threonine phosphatases (Ingebritsen,<br>1989).<br>One of the brain protein tyrosine phosphatases, des-

irom the heat-stable inhibitor proteins regulating the<br>type-1 serine/threonine phosphatases (Ingebritsen,<br>1989).<br>One of the brain protein tyrosine phosphatases, des-<br>ignated PTP-5 (Jones et al., 1989), displayed a number<br>o type-1 serine/threonine phosphatases (ingebritsen,<br>1989).<br>One of the brain protein tyrosine phosphatases, des-<br>ignated PTP-5 (Jones et al., 1989), displayed a number<br>of similarities with the major phosphotyrosine protein<br>p 1989).<br>
One of the brain protein tyrosine phosphatases, des-<br>
ignated PTP-5 (Jones et al., 1989), displayed a number<br>
of similarities with the major phosphotyrosine protein<br>
phosphatase previously purified from both solubl ignated PTP-5 (Jones et al., 1989), displayed a number<br>of similarities with the major phosphotyrosine protein<br>phosphatase previously purified from both soluble and<br>particulate fractions from human placenta (Tonks et al.,<br>1 of similarities with the major phosphotyrosine pro<br>phosphatase previously purified from both soluble<br>particulate fractions from human placenta (Tonks et<br>1988b). The latter enzyme has recently been found<br>have similarities i phosphatase previously purified from both soluble<br>particulate fractions from human placenta (Tonks et<br>1988b). The latter enzyme has recently been found<br>have similarities in primary structure with the intra<br>lular domain of particulate fractions from numan placenta (1 onks et al., 1988b). The latter enzyme has recently been found to have similarities in primary structure with the intracel-<br>lular domain of the CD45 transmembrane glycopro-<br>tein

<sup>314</sup> **WALAAS AND GREENGARD** matopoietic lineages (Charbonneau et al., 1988; Tonks WALAAS A<br>matopoietic lineages (Charbonneau et al., 1988; Toni<br>et al., 1988a). CD45 is known to regulate signal trans-<br>duction and lymphocyte activation by specific associ WALAAS<br>matopoietic lineages (Charbonneau et al., 1988; Tor<br>et al., 1988a). CD45 is known to regulate signal tra<br>duction and lymphocyte activation by specific assoc<br>tion with lymphocyte receptors (Ledbetter et al., 198 matopoietic lineages (Charbonneau et al., 1988; Tonks<br>et al., 1988a). CD45 is known to regulate signal trans-<br>duction and lymphocyte activation by specific associa-<br>tion with lymphocyte receptors (Ledbetter et al., 1989).<br> matopoietic lineages (Charbonneau et al., 1988; Tonlet al., 1988a). CD45 is known to regulate signal tranduction and lymphocyte activation by specific assocition with lymphocyte receptors (Ledbetter et al., 1989)<br>CD45 may, et al., 1988a). CD45 is known to regulate signal trans-<br>duction and lymphocyte activation by specific associa-<br>tion with lymphocyte receptors (Ledbetter et al., 1989).<br>CD45 may, therefore, represent a prototype of mem-<br>bra duction and lymphocyte activation by specific associa-<br>tion with lymphocyte receptors (Ledbetter et al., 1989). nun<br>CD45 may, therefore, represent a prototype of mem-<br>ductorane-associated, receptor-linked tyrosine phosphat tion with lymphocyte receptors (Ledbetter et al., 1989).<br>CD45 may, therefore, represent a prototype of mem-<br>brane-associated, receptor-linked tyrosine phosphatases<br>that could mediate or modulate signal transduction by<br>acti CD45 may, therefore, represent a prototype of mem-<br>brane-associated, receptor-linked tyrosine phosphatases<br>that could mediate or modulate signal transduction by<br>activating protein tyrosine dephosphorylation (Tonks et<br>al., brane-associated, receptor-linked tyrosine phosphatases<br>that could mediate or modulate signal transduction by<br>activating protein tyrosine dephosphorylation (Tonks et<br>al., 1990; Streuli et al., 1989). Moreover, the membrane that could mediate or modulate signal transduction by<br>activating protein tyrosine dephosphorylation (Tonks et<br>al., 1990; Streuli et al., 1989). Moreover, the membrane<br>organization of CD45 is similar to that of growth facto activating protein tyrosine dephosphorylation (Tonks et al., 1990; Streuli et al., 1989). Moreover, the membrane organization of CD45 is similar to that of growth factor receptors with tyrosine kinase activity, such as the and France and Cohen, 1990). Moreover, the membrane<br>organization of CD45 is similar to that of growth factor<br>receptors with tyrosine kinase activity, such as the epi-<br>dermal growth factor receptor (Yarden and Ullrich, 1988 receptors with tyrosine kinase activity, such as the epi-<br>dermal growth factor receptor (Yarden and Ullrich, 1988; the<br>Carpenter and Cohen, 1990). Putative phosphorylation a<br>sites for both protein kinase C and casein kinas dermal growth factor receptor (Yarden and Ullrich, 1988;<br>Carpenter and Cohen, 1990). Putative phosphorylation<br>sites for both protein kinase C and casein kinase II are<br>also present in the intracellular domain of both CD45<br>a Carpenter and Cohen, 1990). Putative phosphorylation<br>sites for both protein kinase C and casein kinase II are<br>also present in the intracellular domain of both CD45<br>and the epidermal growth factor receptor (Hunter et al., 1 sites for both protein kinase C and casein kinase II<br>also present in the intracellular domain of both Cl<br>and the epidermal growth factor receptor (Hunter et<br>1984; Cochet et al., 1984; Davis and Czech, 1986; To<br>et al., 1989 also present in the intracellular domain of both CD-<br>and the epidermal growth factor receptor (Hunter et a<br>1984; Cochet et al., 1984; Davis and Czech, 1986; Ton<br>et al., 1989). Hence, phosphotyrosine protein phosph<br>tases su and the epidermal growth factor receptor (Hunter et al., 1984; Cochet et al., 1984; Davis and Czech, 1986; Tonks<br>et al., 1989). Hence, phosphotyrosine protein phospha-<br>tases such as CD45 may be regulated directly by extra-1984; Cochet et al., 1984; Davis and Czech, 1986; Tonks<br>et al., 1989). Hence, phosphotyrosine protein phospha-<br>tases such as CD45 may be regulated directly by extra-<br>cellular ligands and, indirectly, by phosphorylation ca et al., 1989). Hence, phosphotyrosine protein phosp<br>tases such as CD45 may be regulated directly by ex<br>cellular ligands and, indirectly, by phosphorylation<br>alyzed by protein kinase C or casein kinase II. T<br>would represent result as CD40 may be regulated unectly by extra-<br>cellular ligands and, indirectly, by phosphorylation cat-<br>alyzed by protein kinase C or casein kinases II. This<br>would represent a parallel to the growth factor receptor-<br>as would represent a parallel to the growth factor receptor-<br>associated tyrosine-specific protein kinases discussed<br>above. Whether such membrane-bound tyrosine phos-<br>phatases exist in brain is not yet known. **IV. Phosphoproteins and Presynaptic Function**<br> **IV. Phosphoproteins and Presynaptic Function**<br> **IV. Phosphoproteins and Presynaptic Function**<br> **Many physiological processes in brain are regulated by** ove. Whether such membrane-bound tyrosine phos-<br>atases exist in brain is not yet known. (All<br>IV. Phosphoproteins and Presynaptic Function pho<br>Many physiological processes in brain are regulated by<br>otein phosphorylation. Th

phatases exist in brain is not yet known.<br>IV. Phosphoproteins and Presynaptic Function<br>Many physiological processes in brain are regulated b<br>protein phosphorylation. These include neuronal excit-<br>ability, receptor-mediated IV. Phosphoproteins and Presynaptic Function<br>Many physiological processes in brain are regulated<br>protein phosphorylation. These include neuronal exc<br>ability, receptor-mediated signal transduction, neuro-<br>transmitter biosyn Many physiological processes in brain are regulated by protein phosphorylation. These include neuronal excitability, receptor-mediated signal transduction, neuro-transmitter biosynthesis and release, regulation of inter-me Many physiological processes in brain are regulated by<br>protein phosphorylation. These include neuronal excit-<br>ability, receptor-mediated signal transduction, neuro-<br>transmitter biosynthesis and release, regulation of inter protein phosphorylation. These include neuronal excitability, receptor-mediated signal transduction, neuro-<br>transmitter biosynthesis and release, regulation of inter-<br>mediary metabolism, and regulation of neuronal growth,<br> ability, receptor-mediated signal transduction, neuro-<br>transmitter biosynthesis and release, regulation of inter-<br>mediary metabolism, and regulation of neuronal growth,<br>differentiation, and morphology (for review, see Nest phosphoproteins involved in regulation of inter-<br>mediary metabolism, and regulation of neuronal growth,<br>differentiation, and morphology (for review, see Nestler<br>and Greengard, 1984). In this section, examples of major<br>phos differentiation, and morphology (for review, see Nestler<br>
and Greengard, 1984). In this section, examples of major<br>
phosphoproteins that appear to be involved in regulation<br>
of the physiology of axon terminals are reviewed phosphoproteins that appear to be involved in regulation of the physiology of axon terminals are reviewed, and phosphoproteins involved in regulation of the response of postsynaptic cells to neurotransmitters are reviewed *A. Regulation of Neurotransmitter Synthesis and*<br>*A. Regulation of Neurotransmitters are reviews*<br>*A. Regulation of Neurotransmitter Synthesis and*<br>*Release* 

# *Release*

**1. Regulation of Neurotransmitter Synthesis and<br>
<b>1. Tyrosine hydroxylase and regulation of neurotr**<br> *1. Tyrosine hydroxylase and regulation of neurotr*<br> *itter synthesis.* The activity of tyrosine hydroxy *A. Regulation of Neurotransmitter Synthesis and<br><i>Release*<br>*1. Tyrosine hydroxylase and regulation of neurotrans*<br>*mitter synthesis.* The activity of tyrosine hydroxylase<br>the rate-limiting enzyme in the biosynthesis of the 1. Tyrosine hydroxylase and regulation of neurotransmitter synthesis. The activity of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of the cat-echolamine neurotransmitters (dopamine, noradrena-Release<br>1. Tyrosine hydroxylase and regulation of neurotr<br>mitter synthesis. The activity of tyrosine hydroxy<br>the rate-limiting enzyme in the biosynthesis of the<br>echolamine neurotransmitters (dopamine, noradr<br>line, adrenali 1. Tyrosine hydroxylase and regulation of neurotrans-<br>mitter synthesis. The activity of tyrosine hydroxylase,<br>the rate-limiting enzyme in the biosynthesis of the cat-<br>echolamine neurotransmitters (dopamine, noradrena-<br>lin mitter synthesis. The activity of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of the cateorholamine neurotransmitters (dopamine, noradrena-<br>line, adrenaline), is subject to regulation by multiple pro the rate-limiting enzyme in the biosynthesis of the cecholamine neurotransmitters (dopamine, noradreline, adrenaline), is subject to regulation by multiprotein kinases (for a recent review, see Zigmond et 1989), whereas pr echolamine neurotransmitters (dopamine, noradrena-<br>line, adrenaline), is subject to regulation by multiple<br>protein kinases (for a recent review, see Zigmond et al.,<br>1989), whereas protein phosphatase-2A may be respon-<br>sibl line, adrenaline), is subject to regulation by multiple Kaprotein kinases (for a recent review, see Zigmond et al., It is 1989), whereas protein phosphatase-2A may be responsible for dephosphorylation of the enzyme (Haavi protein kinases (for a recent review, see Zigmond et al. 1989), whereas protein phosphatase-2A may be responsible for dephosphorylation of the enzyme (Haavik et al. 1989). Tyrosine hydroxylase was originally found to bacti 1989), whereas protein phosphatase-2A may be respon-<br>sible for dephosphorylation of the enzyme (Haavik et al., yl<br>1989). Tyrosine hydroxylase was originally found to be<br>activated (Morgenroth et al., 1978) and directly phos 1989). Tyrosine nyuroxylase was originally found to be<br>activated (Morgenroth et al., 1975) and directly phos-<br>phorylated (Joh et al., 1978; Edelman et al., 1981) by the is a<br>cyclic AMP-dependent protein kinase II, protein phorylated (Joh et al., 1978; Edelman et al., 1981) by the cyclic AMP-dependent protein kinase and was later reported also to be a substrate for CaM kinase II, protein kinase C, cyclic GMP-dependent protein kinase, and add

receptors with tyrosine kinase activity, such as the epi-<br>nus (Haycock, 1990). Such data support the hypothesis<br>dermal growth factor receptor (Yarden and Ullrich, 1988; that the NH<sub>2</sub>-terminal region of the enzyme constit <sup>SREENGARD</sup><br>Fujisawa et al., 1984; McTigue et al., 1985; Roskoski et<br>al., 1987; Vulliet et al., 1985; Haycock et al., 1982; Hay-BREENGARD<br>Fujisawa et al., 1984; McTigue et al., 1985; Roskoski e<br>al., 1987; Vulliet et al., 1985; Haycock et al., 1982; Hay<br>cock, 1990). In intact chromaffin cells and PC12 cells, GREENGARD<br>Fujisawa et al., 1984; McTigue et al., 1985; Roskoski et<br>al., 1987; Vulliet et al., 1985; Haycock et al., 1982; Hay-<br>cock, 1990). In intact chromaffin cells and PC12 cells, a<br>number of extracellular stimuli have Fujisawa et al., 1984; McTigue et al., 1985; Roskoski et al., 1987; Vulliet et al., 1985; Haycock et al., 1982; Haycock, 1990). In intact chromaffin cells and PC12 cells, a number of extracellular stimuli have been found t Fujisawa et al., 1984; McTigue et al., 1985; Roskoski et al., 1987; Vulliet et al., 1985; Haycock et al., 1982; Haycock, 1990). In intact chromaffin cells and PC12 cells, a number of extracellular stimuli have been found t al., 1987; Vulliet et al., 1985; Haycock et al., 1982; Haycock, 1990). In intact chromaffin cells and PC12 cells, a<br>number of extracellular stimuli have been found to in-<br>duce multisite phosphorylation and activation of th cock, 1990). In intact chromaffin cells and PC12 cells, a<br>number of extracellular stimuli have been found to in-<br>duce multisite phosphorylation and activation of the<br>enzyme (for examples, see Haycock et al., 1982; Nose et<br> number of extracellular stimuli have been found to in-<br>duce multisite phosphorylation and activation of the<br>enzyme (for examples, see Haycock et al., 1982; Nose et<br>al., 1985; Tachikawa et al., 1986). Analysis of the mech-<br> duce multisite phosphorylation and activation of the<br>enzyme (for examples, see Haycock et al., 1982; Nose et<br>al., 1985; Tachikawa et al., 1986). Analysis of the mech-<br>anisms involved in intact cells indicated that four ser enzyme (for examples, see Haycock et al., 1982; Nose<br>al., 1985; Tachikawa et al., 1986). Analysis of the mec<br>anisms involved in intact cells indicated that four seri<br>residues became phosphorylated in situ and that all<br>the and, 1990, 1 achinawa et an., 1990). Such data four serine residues became phosphorylated in situ and that all of these occurred within 40 amino acids of the NH<sub>2</sub> terminus (Haycock, 1990). Such data support the hypothesi residues became phosphorylated in situ and that all of these occurred within 40 amino acids of the  $NH_2$  terminus (Haycock, 1990). Such data support the hypothesis that the  $NH_2$ -terminal region of the enzyme constitutes nus (Haycock, 1990). Such data support the hypothesis<br>that the  $NH_2$ -terminal region of the enzyme constitutes<br>a regulatory domain which, in the dephosphorylated<br>state, inhibits the catalytic domain; phosphorylation of<br>th nus (Haycock, 1990). Such data support the hypothesis<br>that the  $NH_2$ -terminal region of the enzyme constitutes<br>a regulatory domain which, in the dephosphorylated<br>state, inhibits the catalytic domain; phosphorylation of<br>th that the NH<sub>2</sub>-terminal regional values<br>a regulatory domain whis<br>state, inhibits the catalytic<br>the NH<sub>2</sub>-terminal region<br>straints (Haycock, 1990).<br>Comparisons between tl regulatory domain which, in the dephosphorylated<br>ate, inhibits the catalytic domain; phosphorylation of<br>e NH<sub>2</sub>-terminal region then relieves inhibitory con-<br>raints (Haycock, 1990).<br>Comparisons between the results obtained

state, inhibits the catalytic domain; phosphorylation of<br>the NH<sub>2</sub>-terminal region then relieves inhibitory con-<br>straints (Haycock, 1990).<br>Comparisons between the results obtained following<br>in situ phosphorylation in PC12 the NH<sub>2</sub>-terminal region then relieves inhibitory constraints (Haycock, 1990).<br>
Comparisons between the results obtained following<br>
in situ phosphorylation in PC12 cells and that obtained<br>
with purified components in vit straints (Haycock, 1990).<br>
Comparisons between the results obtained following<br>
in situ phosphorylation in PC12 cells and that obtained<br>
with purified components in vitro suggest that cyclic<br>
AMP-dependent protein kinase a Comparisons between the results obtained following<br>in situ phosphorylation in PC12 cells and that obtained<br>with purified components in vitro suggest that cyclic<br>AMP-dependent protein kinase and protein kinase C<br>both phosph in situ phosphorylation in PC12 cells and that obtained<br>with purified components in vitro suggest that cyclic<br>AMP-dependent protein kinase and protein kinase C<br>both phosphorylate a common site (Ser-40) in the en-<br>zyme (Alb with purified components in vitro suggest that cyclic AMP-dependent protein kinase and protein kinase C both phosphorylate a common site (Ser-40) in the en-<br>zyme (Albert et al., 1984; Campbell et al., 1986; Griffith and S AMP-dependent protein kinase and protein kinase C<br>both phosphorylate a common site (Ser-40) in the en-<br>zyme (Albert et al., 1984; Campbell et al., 1986; Griffith<br>and Schulman, 1987; Haycock, 1990) and activate it by<br>decre both phosphorylate a common site (Ser-40) in the erayme (Albert et al., 1984; Campbell et al., 1986; Griffit and Schulman, 1987; Haycock, 1990) and activate it is decreasing the  $K_m$  of the enzyme for the pterin cofacts ( and Schulman, 1987; Haycock, 1990) and activate it by decreasing the  $K_m$  of the enzyme for the pterin cofactor (Albert et al., 1984). CaM kinase II, in contrast, phos-<br>phorylates a distinct site (Ser-19) which also is ph decreasing the  $K_m$  of the enzyme for the pterin cofactor (Albert et al., 1984). CaM kinase II, in contrast, phosphorylates a distinct site (Ser-19) which also is phosphorylated in situ, and this phosphorylation apparentl (Albert et al., 1984). CaM kinase II, in contrast, phosphorylates a distinct site (Ser-19) which also is phosphorylated in situ, and this phosphorylation apparently activates the enzyme by increasing the  $V_{max}$  only in th phorylates a distinct site (Ser-19) which also is phos-<br>phorylated in situ, and this phosphorylation apparently<br>activates the enzyme by increasing the V<sub>max</sub> only in the<br>presence of an "activator" protein (Yamauchi et al., phorylated in situ, and this phosphorylation apparently<br>activates the enzyme by increasing the V<sub>max</sub> only in the<br>presence of an "activator" protein (Yamauchi et al., 1981;<br>Atkinson et al., 1987; Ichimura et al., 1987). Ot activates the enzyme by increasing the  $V_{\text{max}}$  only in the presence of an "activator" protein (Yamauchi et al., 1981; Atkinson et al., 1987; Ichimura et al., 1987). Other serine residues (Ser-8, Ser-31) on tyrosine hydr presence of an "activator" protein (Yamauchi et al., 1981)<br>Atkinson et al., 1987; Ichimura et al., 1987). Other serin<br>residues (Ser-8, Ser-31) on tyrosine hydroxylase hav<br>also been found to be phosphorylated in situ, but t Atkinson et al., 1987; Ichimura et al., 1987). Other serine residues (Ser-8, Ser-31) on tyrosine hydroxylase have also been found to be phosphorylated in situ, but the kinase(s) responsible for the latter reactions are pre residues (Ser-8, Ser-31) on tyrosine hydroxylase has also been found to be phosphorylated in situ, but the kinase(s) responsible for the latter reactions are preently less well characterized (see Haycock, 1990). Thus regul also been found to be phosphorylated in situ, but the<br>kinase(s) responsible for the latter reactions are pres-<br>ently less well characterized (see Haycock, 1990). Thus,<br>the regulation of this key enzyme in neurotransmitter<br> ently less well characterized (see Haycock, 1990). Thus,<br>the regulation of this key enzyme in neurotransmitter<br>synthesis appears to be achieved through a complicated<br>interplay between different protein phosphorylation<br>path the regulation of this key enzyme in neurotransmitter synthesis appears to be achieved through a complicated interplay between different protein phosphorylation pathways, the identities of which are dependent on the recept synthesis appears<br>interplay betwee<br>pathways, the ide<br>receptor types pr<br>cells and tissues.<br>Less extensive terplay between different protein phosphorylation<br>thways, the identities of which are dependent on the<br>ceptor types present and may be different in distinct<br>lls and tissues.<br>Less extensive evidence indicates that other enz pathways, the identities of which are dependent on the receptor types present and may be different in distinc<br>cells and tissues.<br>Less extensive evidence indicates that other enzyme<br>involved in neurotransmitter biosynthesis

receptor types present and may be different in distinct<br>cells and tissues.<br>Less extensive evidence indicates that other enzymes<br>involved in neurotransmitter biosynthesis, such as tryp-<br>tophan hydroxylase and phenylalanine cells and tissues.<br>Less extensive evidence indicates that other enzymes<br>involved in neurotransmitter biosynthesis, such as tryp-<br>tophan hydroxylase and phenylalanine hydroxylase, are<br>also regulated by protein phosphorylati Less extensive evidence indicates that other enzymes<br>involved in neurotransmitter biosynthesis, such as tryp-<br>tophan hydroxylase and phenylalanine hydroxylase, are<br>also regulated by protein phosphorylation (Hamon et al.,<br>1 involved in neurotransmitter biosynthesis, such as tryp-<br>tophan hydroxylase and phenylalanine hydroxylase, are<br>also regulated by protein phosphorylation (Hamon et al.,<br>1978; Kuhn et al., 1978, 1980; Kaufman et al., 1981;<br>K also regulated by protein phosphorylation (Hamon et al., 1978; Kuhn et al., 1978, 1980; Kaufman et al., 1981; Kaufman, 1987; Døskeland et al., 1984; Schulman, 1988).<br>It may be expected that other neurotransmitter-synthe-si 1978; Kuhn et al., 1978, 1980; Kaufman et al., 1981; ylation. aufman, 1987; Døskeland et al., 1984; Schulman, 1988).<br> *2. Synapsins and regulated by protein phosphoration*.<br> *2. Synapsins and regulation of neurotransmitter release.*<br>
<sup>2.</sup> -dependent transmitter release from nerve ter

It may be expected that other neurotransmitter-synthe-<br>sizing enzymes are also regulated by protein phosphor-<br>ylation.<br>2. Synapsins and regulation of neurotransmitter release.<br> $Ca^{2+}$ -dependent transmitter release from ne sizing enzymes are also regulated by protein phosphor-<br>ylation.<br>2. Synapsins and regulation of neurotransmitter release.<br>Ca<sup>2+</sup>-dependent transmitter release from nerve terminals<br>is subject to multiple regulatory mechanism 2. Synapsins and regulation of neurotransmitter release.<br>Ca<sup>2+</sup>-dependent transmitter release from nerve terminals<br>is subject to multiple regulatory mechanisms in both<br>vertebrate and invertebrate neurons (for review, see  $Ca<sup>2+</sup>$ -dependent transmitter release from nerve terminals<br>is subject to multiple regulatory mechanisms in both<br>vertebrate and invertebrate neurons (for review, see Au-<br>gustine et al., 1987), and it has become increasi vertebrate and invertebrate neurons (for review, see Augustine et al., 1987), and it has become increasingly clear that both CaM kinase II and protein kinase C are importantly involved in the regulation of this phenomenon.

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**PROTEIN PHOSPHORYLATION AND NEURONAL FUNCTION** <sup>315</sup>

PROTEIN PHOSPHORYLATION<br>Activators of protein kinase C, for example, significantly<br>increase the release of both amino acid and monoamine<br>transmitters from rat brain synaptosomes and other **PROTEIN PHOSPHORYLATION**<br>
Activators of protein kinase C, for example, significantly<br>
increase the release of both amino acid and monoamine<br>
transmitters from rat brain synaptosomes and other<br>
preparations (Shapira et al. Activators of protein kinase C, for example, significantly increase the release of both amino acid and monoamine transmitters from rat brain synaptosomes and other preparations (Shapira et al., 1987; Nichols et al., 1987). increase the release of both amino acid and monoamine creasurement<br>transmitters from rat brain synaptosomes and other Superparations (Shapira et al., 1987; Nichols et al., 1987). ta<br>Likewise, injection of CaM kinase II int transmitters from rat brain synaptosomes and ot<br>preparations (Shapira et al., 1987; Nichols et al., 199<br>Likewise, injection of CaM kinase II into the presynal<br>digit of the squid giant axon potently increases<br>amount of tran preparations (Shapira et al., 1987; Nichols et al., 1987).<br>Likewise, injection of CaM kinase II into the presynaptic<br>digit of the squid giant axon potently increases the<br>amount of transmitter released in response to depola Likewise, injection of CaM kinase II into the presynaptic digit of the squid giant axon potently increases the amount of transmitter released in response to depolarization-induced Ca<sup>2+</sup> influx (Llinás et al., 1985, in pre digit of the squid giant axon potently increases the ter amount of transmitter released in response to depolari-<br>zation-induced  $Ca^{2+}$  influx (Llinás et al., 1985, in press;). and Recent studies have shown similar effect amount of transmitter released in response to depola<br>zation-induced  $Ca^{2+}$  influx (Llinás et al., 1985, in press<br>Recent studies have shown similar effects following los<br>ing of permeabilized synaptosomes from rat brain wi zation-induced  $Ca^{2+}$  influx (Llinás et al., 1985, in press;). a<br>Recent studies have shown similar effects following load-<br>ing of permeabilized synaptosomes from rat brain with<br>this kinase (Nichols et al., 1990). The rel Recent studies have shown similar effects following loading of permeabilized synaptosomes from rat brain with ithis kinase (Nichols et al., 1990). The release of neuro-<br>transmitters is thus one of the neuronal functions fo ing of permeabilized syn<br>this kinase (Nichols et a<br>transmitters is thus one<br>which there is particularl<br>by protein phosphorylatic<br>Several studies of pro is kinase (Nichols et al., 1990). The release of neuro-<br>
ansmitters is thus one of the neuronal functions for<br>
rotion there is particularly strong evidence for regulation<br>
in protein phosphorylation.<br>
Several studies of pr

transmitters is thus one of the heuronal functions if<br>which there is particularly strong evidence for regulatie<br>by protein phosphorylation.<br>Several studies of protein phosphorylation in ner<br>terminals have been performed (f which there is particularly strong evidence for regulation<br>by protein phosphorylation. the<br>Several studies of protein phosphorylation in nerve<br>terminals have been performed (for examples, see Krue-<br>ser et al., 1977; Robins by protein phosphorylation.<br>
Several studies of protein phosphorylation in ner<br>
terminals have been performed (for examples, see Kringer et al., 1977; Robinson and Dunkley, 1983; Dunkl<br>
et al., 1986; Wang et al., 1988). St Several studies of protein phosphorylation in nerveterminals have been performed (for examples, see Krue ger et al., 1977; Robinson and Dunkley, 1983; Dunkley et al., 1986; Wang et al., 1988). Studies of intact synap tosom terminals have been performed (for examples, see Kruger et al., 1977; Robinson and Dunkley, 1983; Dunkle et al., 1986; Wang et al., 1988). Studies of intact synaptosome preparations prelabeled with radioactive inouganic ph ger et al., 1977; Robinson and Dunkley, 1983; Dunkley<br>et al., 1986; Wang et al., 1988). Studies of intact synap-<br>tosome preparations prelabeled with radioactive inor-<br>ganic phosphate show that both depolarization-induced<br>C et al., 1986; Wang et al., 1988). Studies of intact synaptosome preparations prelabeled with radioactive inor-<br>tosome preparations prelabeled with radioactive inor-<br>ganic phosphate show that both depolarization-induced an<br> ussome preparations prelabered with radioactive inor-<br>ganic phosphate show that both depolarization-induced<br>Ca<sup>2+</sup> influx and addition of the tumor-promoting phorbol<br>esters which activate protein kinase C result in the<br>pho  $Ca^{2+}$  influx and addition of the tumor-promoting phoesters which activate protein kinase C result in phosphorylation of a number of proteins (Wang et 1988). Detailed two-dimensional electrophoretic anal has shown that t esters which activate protein kinase C result in the phosphorylation of a number of proteins (Wang et al., 1988). Detailed two-dimensional electrophoretic analysis has shown that the major substrates for the depolarizatio phosphorylation of a number of proteins (Wang et al., 1988). Detailed two-dimensional electrophoretic analysis has shown that the major substrates for the depolarization-induced,  $Ca^{2+}$ -dependent protein phosphorylation s 1988). Detailed two-dimensional electrophoretic analysis<br>has shown that the major substrates for the depolariza-<br>tion-induced,  $Ca^{2+}$ -dependent protein phosphorylation<br>seen in such isolated nerve terminals comprise six m mas shown that the major substrates for the depolarization-induced, Ca<sup>2+</sup>-dependent protein phosphorylation seen in such isolated nerve terminals comprise six major phosphoproteins (table 6). These include four synaptic v seen in such isolated nerve terminals comprise six major creased neurotransmitter release (Llinás et al., 1985, in phosphoproteins (table 6). These include four synaptic press; Nichols et al., 1990).<br>vesicle-associated pro phosphoproteins (table 6). These include four synaptic press; Nichols et al., 1990).<br>
vesicle-associated proteins, the synapsins, which are sub-<br>
strates for CaM kinases and which are described in this mentary DNA for the phosphoproteins (table 6). These include four synaptic press;<br>vesicle-associated proteins, the synapsins, which are sub-<br>strates for CaM kinases and which are described in this menta<br>section, and proteins with apparent mol vesicle-associated proteins, the synapsins, which are substrates for CaM kinases and which are described in the section, and proteins with apparent molecular masses 87 and 48 kDa which are substrates for protein kinase and section, and proteins with apparent molecular masses of 87 and 48 kDa which are substrates for protein kinase C and which are described in the following two sections.<br>The *synapsins* are a family of neuron-specific synapti

section, and proteins with apparent molecular masses of 87 and 48 kDa which are substrates for protein kinase C and which are described in the following two sections.<br>The synapsins are a family of neuron-specific synaptic 87 and 48 kDa which are substrates for protein kinase C ogy,<br>and which are described in the following two sections. have<br>The *synapsins* are a family of neuron-specific synaptic min<br>vesicle-associated proteins (for reviews and which are described in the following two sections. have The *synapsins* are a family of neuron-specific synaptic minvesicle-associated proteins (for reviews, see De Camilli ing and Greengard, 1986; De Camilli et al., 1 The synapsins are a family of neuron-specific synaptic<br>vesicle-associated proteins (for reviews, see De Camilli<br>and Greengard, 1986; De Camilli et al., 1990), which in<br>mammalian brain consist of synapsin Ia and synapsin Ib vesicie-associated proteins (for reviews, see De Camili in<br>and Greengard, 1986; De Camilli et al., 1990), which in co<br>mammalian brain consist of synapsin Ia and synapsin Ib<br>(collectively referred to as synapsin IIa II<br>and and Greengard, 1986; De Camilli et al., 1990), which in communalian brain consist of synapsin Ia and synapsin Ib the (collectively referred to as synapsin I and previously termed proteins Ia and Ib, respectively) and synap mammalian brain consist of synapsin Ia and synapsin (collectively referred to as synapsin I and previou<br>termed proteins Ia and Ib, respectively) and synapsin<br>and synapsin IIb (collectively referred to as synapsin<br>and previ (collectively referred to as synapsin I and previously termed proteins Ia and Ib, respectively) and synapsin IIa I<br>and synapsin IIb (collectively referred to as synapsin II tand previously termed proteins IIIa and IIIb, r termed proteins Ia and Ib, respectively) and synapsin<br>and synapsin IIb (collectively referred to as synapsin<br>and previously termed proteins IIIa and IIIb, resp<br>tively). All of the synapsins are major substrates<br>cyclic AMPand synapsin Tib (conectively referred to as synapsin and previously termed proteins IIIa and IIIb, respectively). All of the synapsins are major substrates for cyclic AMP-regulated and  $Ca^{2+}/cal$  calmodulin-regulate protei and previously termed proteins IIIa and IIIb, respectively). All of the synapsins are major substrates for cyclic AMP-regulated and  $Ca^{2+}/calodundulin-regulared$  protein kinases (Ueda et al., 1973; Ueda and Greengard 1977; Forn and Green tively). All of the synapsins are major substrates for<br>cyclic AMP-regulated and Ca<sup>2+</sup>/calmodulin-regulated<br>protein kinases (Ueda et al., 1973; Ueda and Greengard,<br>1977; Forn and Greengard, 1978; Huttner and Greengard,<br>197 cyclic AMP-regulated and Ca<sup>2+</sup>/calmodulin-regulated protein kinases (Ueda et al., 1973; Ueda and Green<br>1977; Forn and Greengard, 1978; Huttner and Green<br>1979; Kennedy and Greengard, 1981; Walaas e<br>1983c; Nairn and Greenga protein kinases (Ueda et al., 1973; Ueda and Greengard, 1977; Forn and Greengard, 1978; Huttner and Greengard, 1981; Walaas et al., 1983c; Nairn and Greengard, 1987). Cyclic AMP-dependent protein kinase and CaM kinase I bo 1977; Forn and Greengard, 1978; Huttner and Greeng<br>1979; Kennedy and Greengard, 1981; Walaas et<br>1983c; Nairn and Greengard, 1987). Cyclic AMP-depe<br>ent protein kinase and CaM kinase I both phosphory<br>a single serine residue 1979; Kennedy and Greengard, 1981; Walaas et al., family a<br>1983c; Nairn and Greengard, 1987). Cyclic AMP-depend- nerve te<br>ent protein kinase and CaM kinase I both phosphorylate sonal co<br>a single serine residue (site 1) in 1983c; Nairn and Greengard, 1987). Cyclic AMP-depend-<br>ent protein kinase and CaM kinase I both phosphorylate<br>a single serine residue (site 1) in the collagenase-resistant ta<br>"head" region of both synapsin I and synapsin II ent protein kinase and CaM kinase I both phosphorylate<br>a single serine residue (site 1) in the collagenase-resistant<br>"head" region of both synapsin I and synapsin II. CaM<br>kinase II, in contrast, phosphorylates a pair of se a single serine residue (site 1) in the collagenase-resistant<br>"head" region of both synapsin I and synapsin II. CaM<br>kinase II, in contrast, phosphorylates a pair of serine<br>residues in the collagenase-sensitive "tail" regio kinase II, in contrast, phosphorylates a pair of serine residues in the collagenase-sensitive "tail" region of syn-<br>apsin I (sites 2 and 3) (Ueda and Greengard, 1977;<br>Huttner and Greengard, 1979; Huttner et al., 1981) but<br> sidues in the collagenase-sensitive "tail" region of sysin I (sites 2 and 3) (Ueda and Greengard, 19<br>uttner and Greengard, 1979; Huttner et al., 1981) l<br>es not phosphorylate synapsin II (Südhof et al., 198<br>A variety of phy

Activators of protein kinase C, for example, significantly ulations of intact nerve cell preparations produce in-<br>increase the release of both amino acid and monoamine creases in the state of phosphorylation of synapsin I. ulations of intact nerve call preparations produce in-AND NEURONAL FUNCTION 315<br>ulations of intact nerve cell preparations produce in-<br>creases in the state of phosphorylation of synapsin I.<br>Such manipulations include electrical stimulation of in-AND NEURONAL FUNCTION 315<br>
ulations of intact nerve cell preparations produce in-<br>
creases in the state of phosphorylation of synapsin I.<br>
Such manipulations include electrical stimulation of in-<br>
tact nerve fibers (Nestle ulations of intact nerve cell preparations produce increases in the state of phosphorylation of synapsin I.<br>Such manipulations include electrical stimulation of intact nerve fibers (Nestler and Greengard, 1982a,b; Tsou<br>and tereases in the state of phosphorylation of synapsin<br>Such manipulations include electrical stimulation of ir<br>tact nerve fibers (Nestler and Greengard, 1982a,b; Tso<br>and Greengard, 1982), depolarization of isolated nerv<br>term Such manipulations include electrical stimulation of intact nerve fibers (Nestler and Greengard, 1982a,b; Tsou<br>and Greengard, 1982), depolarization of isolated nerve<br>terminals (Krueger et al., 1977; Huttner and Greengard,<br> cact herve meas (resader and Greengard, 1982a,0, 180d<br>and Greengard, 1982), depolarization of isolated nerve<br>terminals (Krueger et al., 1977; Huttner and Greengard,<br>1979; Wang et al., 1988), application of cyclic AMP<br>analo terminals (Krueger et al., 1977; Huttner and Greengard, 1979; Wang et al., 1988), application of cyclic AMP analogs or depolarization of brain slices (Forn and Greengard, 1978), the use of convulsants and tranquilizers on 1979; Wang et al., 1988), application of cyclic AMP<br>analogs or depolarization of brain slices (Forn and<br>Greengard, 1978), the use of convulsants and tranquil-<br>izers on intact animals (Strömbom et al., 1979), and<br>applicatio analogs or depolarization of brain slices (Forn<br>Greengard, 1978), the use of convulsants and transizers on intact animals (Strömbom et al., 1979),<br>application of neurotransmitter candidates such as<br>rotonin (Dolphin and Gre Greengard, 1978), the use of convulsants and tranqui<br>izers on intact animals (Strömbom et al., 1979), an<br>application of neurotransmitter candidates such as se<br>rotonin (Dolphin and Greengard, 1981a,b), noradrena<br>line (Moble izers on intact animals (Strömbom et al., 1979), and<br>application of neurotransmitter candidates such as se-<br>rotonin (Dolphin and Greengard, 1981a,b), noradrena-<br>line (Mobley and Greengard, 1985), and dopamine (Nes-<br>tler an rotonin (Dolphin and Greengard, 1981a,b), noradrena-<br>line (Mobley and Greengard, 1985), and dopamine (Nes-<br>tler and Greengard, 1980; Treiman and Greengard, 1985;<br>Walaas et al., 1989e) to peripheral nervous tissue or<br>slices line (Mobley and Greengard, 1985), and dopamine (Nesthe internal Greengard, 1980; and dopamine (ives-<br>tler and Greengard, 1980; Treiman and Greengard, 1985;<br>Walaas et al., 1989e) to peripheral nervous tissue or<br>slices from defined brain regions. In each of these sys-<br>tems, Let and Creengard, 1500, 11eman and Creengard, 1500,<br>Walaas et al., 1989e) to peripheral nervous tissue or<br>slices from defined brain regions. In each of these sys-<br>tems, treatments that are known to increase the levels<br>of of cyclic AMP in the tissue have been found to increase<br>the state of phosphorylation of site 1 both in synapsin I<br>and, where analyzed, in synapsin II. Treatments that slices from defined brain regions. In each of these sys-<br>tems, treatments that are known to increase the levels<br>of cyclic AMP in the tissue have been found to increase<br>the state of phosphorylation of site 1 both in synapsi tems, treatments that are known to increase the levels<br>of cyclic AMP in the tissue have been found to increase<br>the state of phosphorylation of site 1 both in synapsin I<br>and, where analyzed, in synapsin II. Treatments that of cyclic AMP in the tissue have been found to increase<br>the state of phosphorylation of site 1 both in synapsin I<br>and, where analyzed, in synapsin II. Treatments that<br>increase intracellular levels of  $Ca^{2+}$ , in contrast, the state of phosphorylation of site 1 both in synapsin I and, where analyzed, in synapsin II. Treatments that increase intracellular levels of  $Ca^{2+}$ , in contrast, have been found to increase the state of phosphorylatio and, where analyzed, in synapsin II. I reatments that<br>increase intracellular levels of  $Ca^{2+}$ , in contrast, have<br>been found to increase the state of phosphorylation of<br>both sites 1, 2, and 3 in synapsin I and, where anal increase intracellular levels of  $Ca^{2+}$ , in contrast, hippen found to increase the state of phosphorylation both sites 1, 2, and 3 in synapsin I and, where analyz of the site in synapsin II that corresponds to site 1 syn been found to increase the state of phosphorylation of both sites 1, 2, and 3 in synapsin I and, where analyzed, of the site in synapsin II that corresponds to site 1 in synapsin I. Those manipulations that caused  $Ca^{2+}$ both sites 1, 2, and 3 in synapsin I and, where analyzed,<br>of the site in synapsin II that corresponds to site 1 in<br>synapsin I. Those manipulations that caused  $Ca^{2+}$ -de-<br>pendent phosphorylation of synapsin I also caused of the site in synapsin II the<br>synapsin I. Those manipula<br>pendent phosphorylation of<br>creased neurotransmitter re<br>press; Nichols et al., 1990).<br>Analysis of the nucleotide Hapsin 1. Those mainpulations that caused Ca<br>
ndent phosphorylation of synapsin I also caused<br>
eased neurotransmitter release (Llinás et al., 1985,<br>
ess; Nichols et al., 1990).<br>
Analysis of the nucleotide sequences of clon

pendent phosphorylation of synapsin I also caused in-<br>creased neurotransmitter release (Llinás et al., 1985, in<br>press; Nichols et al., 1990).<br>Analysis of the nucleotide sequences of cloned comple-<br>mentary DNA for the four reased neutotransmitter refease (Emilas et al., 1960, in<br>press; Nichols et al., 1990).<br>Analysis of the nucleotide sequences of cloned comple-<br>mentary DNA for the four synapsins has revealed that<br>synapsins Ia and Ib display Analysis of the nucleotide sequences of cloned commentary DNA for the four synapsins has revealed t synapsins Ia and Ib display extensive sequence hon ogy, as do synapsins IIa and IIb. Synapsins I and II and the have comm mentary Division the four synapsins has reveated synapsins Ia and Ib display extensive sequence hor ogy, as do synapsins IIa and IIb. Synapsins I and II have common domains, composed of similar NH<sub>2</sub>-minal regions, which c synapsins Ia and Ib display extensive sequence homology, as do synapsins IIa and IIb. Synapsins I and II also<br>have common domains, composed of similar  $NH_2$ -ter-<br>minal regions, which contain the serine residue compris-<br>in ogy, as do synapsins IIa and IIb. Synapsins I and II also<br>have common domains, composed of similar  $NH_2$ -ter-<br>minal regions, which contain the serine residue compris-<br>ing phosphorylation site 1, and central regions which<br> minal regions, which contain the serine residue comprising phosphorylation site 1, and central regions which contain both charged and hydrophobic areas. In addition, they also have variable domains located in the COOH-<br>ter ing phosphorylation site 1, and central regions which contain both charged and hydrophobic areas. In addition, they also have variable domains located in the COOH-<br>terminal regions: synapsins Ia and Ib, but not synapsins<br>IIa or IIb, have long, extremely basic "tails" which co contain both charged and hydrophobic areas. In addition,<br>they also have variable domains located in the COOH-<br>terminal regions: synapsins Ia and Ib, but not synapsins<br>IIa or IIb, have long, extremely basic "tails" which co rminal regions: synapsins Ia and Ib, but not synapsins<br>a or IIb, have long, extremely basic "tails" which con-<br>in the serine residues comprising phosphorylation sites<br>and 3 (Südhof et al., 1989).<br>Synapsins Ia, Ib, IIa, and tain the serine residues comprising phosphorylation sites 2 and 3 (Südhof et al., 1989).<br>Synapsins Ia, Ib, IIa, and IIb are all enriched in a majority of nerve terminals in brain (De Camilli et al.,

"head" region of both synapsin I and synapsin II. CaM IIb than do most CNS regions (Walaas et al., 1988a).<br>
kinase II, in contrast, phosphorylates a pair of serine Moreover, all mossy fiber terminals of the hippocampal<br>
re 1983a,b; Walaas et al., 1988a), although the relative amounts of the four distinct isoforms of this protein 2 and 3 (Suddiot et al., 1989).<br>
Synapsins Ia, Ib, IIa, and IIb are all enriched in a<br>
majority of nerve terminals in brain (De Camilli et al.,<br>
1983a,b; Walaas et al., 1988a), although the relative<br>
amounts of the four di Synapsins 1a, 10, 11a, and 11b are an emiched in a<br>majority of nerve terminals in brain (De Camilli et al.,<br>1983a,b; Walaas et al., 1988a), although the relative<br>amounts of the four distinct isoforms of this protein<br>family majority of nerve terminals in brain (De Camilli et al., 1983a,b; Walaas et al., 1988a), although the relative amounts of the four distinct isoforms of this protein family appear to vary among different populations of nerv 1983a,b; Walaas et al., 1988a), although the relative amounts of the four distinct isoforms of this protein family appear to vary among different populations of nerve terminals (Südhof et al., 1989; E. Mugnaini, pe sonal c amounts of the four distinct isoforms of this protein<br>family appear to vary among different populations of<br>nerve terminals (Südhof et al., 1989; E. Mugnaini, per-<br>sonal communication). For example, the posterior pitui-<br>tar family appear to vary among different populations of<br>nerve terminals (Südhof et al., 1989; E. Mugnaini, per-<br>sonal communication). For example, the posterior pitui-<br>tary and olfactory bulb contain relatively less of synaps nerve terminals (Südhof et al., 1989; E. Mugnaini, per<br>sonal communication). For example, the posterior pitui<br>tary and olfactory bulb contain relatively less of synapsii<br>IIb than do most CNS regions (Walaas et al., 1988a)<br> sonal communication). For example, the posterior pitui-<br>tary and olfactory bulb contain relatively less of synapsin<br>IIb than do most CNS regions (Walaas et al., 1988a).<br>Moreover, all mossy fiber terminals of the hippocampa tary and olfactory bulb contain relatively less of synapsin<br>IIb than do most CNS regions (Walaas et al., 1988a).<br>Moreover, all mossy fiber terminals of the hippocampal<br>granule cells contain all four synapsins, whereas Purk IIb than do most CNS regions (Walaas et al., 1988a).<br>Moreover, all mossy fiber terminals of the hippocampal<br>granule cells contain all four synapsins, whereas Purkinje<br>cell axon terminals do not contain detectable amounts<br>o Moreover, all mossy fiber terminals of the hippocampal<br>granule cells contain all four synapsins, whereas Purkinje<br>cell axon terminals do not contain detectable amounts<br>of synapsin IIa (Südhof et al., 1989). In the vertebra granue cens contain an iour synapsins, whereas rurking<br>cell axon terminals do not contain detectable amounts<br>of synapsin IIa (Südhof et al., 1989). In the vertebrate<br>retina, further differences have been observed. In this<br>

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WALAAS AND GREENGARD<br>TABLE 6<br>*Characteristics of proteins phosphorylated in isolated nerve terminals by depolarization-induced Ca<sup>2+</sup> influx\** 



from: De Camilli et al. (1990), Stumpo et al. (1989), Wang et al. (1988), Albert et al. (1987), Aderem et al. (1988), Graff et al. (1989b), Katz et al. (1989b), Katz et al. (1985), Cuimet et al. (1990), Liu and Storm (1990

ent. One is represented by conventional synapses, which The synapsins appear to be associated with the exter-<br>are formed mostly by amacrine cells, and another is nal surface of small, electron-lucent synaptic vesicles, represented by ribbon synapses, which are formed by represented by conventional synapses, which<br>ent. One is represented by conventional synapses, which Tare formed mostly by amacrine cells, and another is nal<br>represented by ribbon synapses, which are formed by i.e.,<br>photore ent. One is represented by conventional synapses, which are formed mostly by amacrine cells, and another is represented by ribbon synapses, which are formed by photoreceptors and bipolar cells (Mandell et al., 1990). These ent. One is represented by conventional synapses, which are formed mostly by amacrine cells, and another is represented by ribbon synapses, which are formed by photoreceptors and bipolar cells (Mandell et al., 1990). These represented by ribbon synapses, which are formed<br>photoreceptors and bipolar cells (Mandell et al., 19<br>These synapses differed in their content of synaps<br>with only conventional synapses containing these  $\mu$ <br>teins. Moreover photoreceptors and bipolar cells (Mandell et al., 1990). rotr<br>These synapses differed in their content of synapsins, I is<br>with only conventional synapses containing these pro-<br>teins. Moreover, the synapsin isoforms were di with only conventional synapses containing these pro-<br>these synaptic vesicles through its tail region, and the<br>teins. Moreover, the synapsin isoforms were differen-<br>tially distributed within the synapses formed by ama-<br>in teins. Moreover, the synapsin isoforms were differentially distributed within the synapses formed by amacrine cells, with synapsin I apparently being present in all amacrine nerve terminals and synapsins IIa and IIb specif tially distributed within the synapses formed by ama-<br>crine cells, with synapsin I apparently being present in<br>all amacrine nerve terminals and synapsins IIa and IIb<br>specifically enriched in a subset of amacrine nerve ter crine cells, with synapsin I apparently being present in all amacrine nerve terminals and synapsins IIa and IIb specifically enriched in a subset of amacrine nerve terminals only. No correlation between the expression of all amacrine nerve terminals and synapsins IIa and IIb<br>specifically enriched in a subset of amacrine nerve ter-<br>minals only. No correlation between the expression of<br>synapsin II and identified neurotransmitter types was<br>e specifically enriched in a subset of amacrine nerve ter-<br>minals only. No correlation between the expression of<br>synapsin II and identified neurotransmitter types was<br>evident. Thus, the presence or absence of synapsin II in minals only. No correlation between the expression of synapsin II and identified neurotransmitter types was evident. Thus, the presence or absence of synapsin II in the retina may correlate with some other property of conv 1990). evident. Thus, the presence or absence or synapsin II in<br>
the retina may correlate with some other property of<br>
conventional presynaptic terminals (Mandell et al.,  $C_i$ <br>
1990).<br>
Considerable evidence indicates that the sy

conventional presynaptic terminals (Mandell et al., 1990).<br>
Considerable evidence indicates that the synapsins are<br>
involved in regulation of neurotransmitter release. Thus,<br>
microinjection of dephosphosynapsin I into pres 1990).<br>Considerable evidence indicates that the synapsins are<br>involved in regulation of neurotransmitter release. Thus,<br>microinjection of dephosphosynapsin I into presynaptic<br>nerve terminals of the squid giant axon inhibit Considerable evidence indicates that the synapsins<br>involved in regulation of neurotransmitter release. T<br>microinjection of dephosphosynapsin I into presyna<br>nerve terminals of the squid giant axon inhibi<br>whereas injection o involved in regulation of neurotransmitter release. Thus,<br>microinjection of dephosphosynapsin I into presynaptic<br>nerve terminals of the squid giant axon inhibited,<br>whereas injection of CaM kinase II promoted, transmit-<br>te microinjection of dephosphosynapsin I into presynaptic nerve terminals of the squid giant axon inhibited, whereas injection of CaM kinase II promoted, transmitter release at this synapse (Llinás et al., 1985; Llinas et al. merve terminals of the squid giant axon inhibited,<br>whereas injection of CaM kinase II promoted, transmitter<br>release at this synapse (Llinás et al., 1985; Llinas et<br>al., in press;). Similar observations have been reported<br>f whereas injection of Calvi kinase 11 promoted, tranter release at this synapse (Llinás et al., 1985; Llin<br>al., in press;). Similar observations have been rep<br>for the goldfish Mauthner cell (Hackett et al., 1990)<br>cell biolo ter release at this synapse (Linnas et al., 1985; Linnas et al., in press;). Similar observations have been reported Per for the goldfish Mauthner cell (Hackett et al., 1990). The synall biological basis for such regulatio al., in press;). Similar obset<br>for the goldfish Mauthner ce<br>cell biological basis for suc<br>mitter release by synapsin I<br>investigated in some detail.

The synapsins appear to be associated with the exter-The synapsins appear to be associated with the exter-<br>nal surface of small, electron-lucent synaptic vesicles,<br>i.e., those vesicles that contain classical, nonpeptide neu-The synapsins appear to be associated with the external surface of small, electron-lucent synaptic vesicles i.e., those vesicles that contain classical, nonpeptide neu-<br>rotransmitters (De Camilli et al., 1983b, 1990). Syna The synapsins appear to be associated with the external surface of small, electron-lucent synaptic vesicles, i.e., those vesicles that contain classical, nonpeptide neu-<br>rotransmitters (De Camilli et al., 1983b, 1990). Syn I he synapsins appear to be associated with the exter-<br>
nal surface of small, electron-lucent synaptic vesicles,<br>
i.e., those vesicles that contain classical, nonpeptide neu-<br>
rotransmitters (De Camilli et al., 1983b, 1990 nal surface of small, electron-lucent synaptic vesicles,<br>i.e., those vesicles that contain classical, nonpeptide neu-<br>rotransmitters (De Camilli et al., 1983b, 1990). Synapsin<br>I is bound to a specific, high-affinity satura i.e., those vesicles that contain classical, nonpeptide neu-<br>rotransmitters (De Camilli et al., 1983b, 1990). Synapsin<br>I is bound to a specific, high-affinity saturable site on<br>these synaptic vesicles through its tail regi Fortansmitters (De Camilii et al., 1983b, 1990). Synapid<br>I is bound to a specific, high-affinity saturable site<br>these synaptic vesicles through its tail region, and t<br>central hydrophobic domain appears to be partly buri<br>in ner et al., 1983; Schiebler et al., 1986; Bähler et al., 1989; chese synaptic vesteles through its tan region, and the<br>central hydrophobic domain appears to be partly buried<br>in the lipid environment of the vesicle membrane (Hutt-<br>ner et al., 1983; Schiebler et al., 1986; Bähler et al. tentral hydrophoot domain appears to be partly buried<br>in the lipid environment of the vesicle membrane (Hutt-<br>ner et al., 1983; Schiebler et al., 1986; Bähler et al., 1989;<br>Benfenati et al., 1989a,b, 1991). Phosphorylation ner et al., 1983; Schiebler et al., 1986; Bähler et al., 1989;<br>Benfenati et al., 1989a,b, 1991). Phosphorylation of the<br>tail domain of the protein by CaM kinase II has been<br>found under certain conditions to reduce the stre Benfenati et al., 1989a,b, 1991). Phosphorylation of the tail domain of the protein by CaM kinase II has been found under certain conditions to reduce the strength of binding of synapsin I to vesicles (Huttner et al., 1983 Earl domain of the protein by CaM kinase II has been<br>found under certain conditions to reduce the strength of<br>binding of synapsin I to vesicles (Huttner et al., 1983;<br>Schiebler et al., 1986). Thus, the interaction between<br> Nutle of Synapsin 1 to vesteles (Hutther et al., 1988),<br>hiebler et al., 1986). Thus, the interaction between<br>napsin I and synaptic vesicles may be regulated by<br>M kinase II.<br>Synapsin I also interacts with cytoskeletal eleme

schlebler et al., 1980). Thus, the interaction between<br>synapsin I and synaptic vesicles may be regulated by<br>CaM kinase II.<br>Synapsin I also interacts with cytoskeletal elements<br>such as actin, microtubules, and spectrin in v Calvi kinase 11.<br>
Synapsin I also interacts with cytoskeletal elements<br>
such as actin, microtubules, and spectrin in vitro (Bähler<br>
and Greengard, 1987; Bähler et al., 1989; Bennett et al.,<br>
1985; Goldenring et al., 1986; Synapsin 1 also interacts with cytoskeretar elements<br>such as actin, microtubules, and spectrin in vitro (Bähler<br>and Greengard, 1987; Bähler et al., 1989; Bennett et al.,<br>1985; Goldenring et al., 1986; Petrucci and Morrow, and Greengard, 1987, Damer et al., 1989, Demiett et al.,<br>1985; Goldenring et al., 1986; Petrucci and Morrow, 1987;<br>Steiner et al., 1987). In fact, dephosphosynapsin I causes<br>the bundling of F-actin (Bähler and Greengard, 1 rood, coldening et al., 1980, I erracti and Morrow, 1987,<br>Steiner et al., 1987). In fact, dephosphosynapsin I causes<br>the bundling of F-actin (Bähler and Greengard, 1987;<br>Petrucci and Morrow, 1987). Evidence indicates that<br> Stemer et al., 1967). In lact, dephosphosynapsin I cause<br>the bundling of F-actin (Bähler and Greengard, 198<br>Petrucci and Morrow, 1987). Evidence indicates the<br>synapsin I contains two binding sites for actin, that Ca<br>kinase the bunding of r-actin (Bainer and Greengard, 1567,<br>Petrucci and Morrow, 1987). Evidence indicates that<br>synapsin I contains two binding sites for actin, that CaM<br>kinase II-catalyzed phosphorylation of the protein inhib-<br>it Petrucci and Morrow, 1987). Evidence indicates that<br>synapsin I contains two binding sites for actin, that CaM<br>kinase II-catalyzed phosphorylation of the protein inhib-<br>its actin binding to one of these sites, and that this

PHARMACOLOGICAL REVIEWS

from taking place (Bähler and Greengard, 1987; Petrucci and Morrow, 1987; Bähler et al., 1989). PROTEIN PH<br>from taking place (Bähler and Greengard<br>and Morrow, 1987; Bähler et al., 1989).<br>It has been proposed that a tertiary

**INTER PHOSPHORYLATI**<br>Iom taking place (Bähler and Greengard, 1987; Petruce<br>Iom Morrow, 1987; Bähler et al., 1989).<br>It has been proposed that a tertiary complex, com-<br>Ised of actin/synapsin I/synaptic vesicle, exists and from taking place (Bähler and Greengard, 1987; Petrucci tein<br>and Morrow, 1987; Bähler et al., 1989). from from It has been proposed that a tertiary complex, com-<br>prised of actin/synapsin I/synaptic vesicle, exists and tert from taking place (Bähler and Greengard, 1987; Petrucci to and Morrow, 1987; Bähler et al., 1989). f<br>It has been proposed that a tertiary complex, com-<br>prised of actin/synapsin I/synaptic vesicle, exists and that this comp and Morrow, 1987; Bähler et al., 1989).<br>It has been proposed that a tertiary complex, com-<br>prised of actin/synapsin I/synaptic vesicle, exists and<br>that this complex, by tethering the synaptic vesicle, keeps<br>it in a reserve It has been proposed that a tertiary complex, com-<br>prised of actin/synapsin I/synaptic vesicle, exists and ter<br>that this complex, by tethering the synaptic vesicle, keeps dis<br>it in a reserve pool (Benfenati et al., 1991). prised of actin/synapsin I/synaptic vesicle, exists and that this complex, by tethering the synaptic vesicle, keeps it in a reserve pool (Benfenati et al., 1991). Disruption to this complex would allow vesicles to move fro that this complex, by tethering the synaptic vesicle, keep<br>it in a reserve pool (Benfenati et al., 1991). Disruptio<br>of this complex would allow vesicles to move from suca<br>reserve pool to a releasable pool. Such a disruptio it in a reserve pool (Benfenati et al., 1991). Disruption the of this complex would allow vesicles to move from such 1<br>a reserve pool to a releasable pool. Such a disruption m<br>could be achieved either through a decrease in of this complex would allow vesicles to move from such 1<br>a reserve pool to a releasable pool. Such a disruption n<br>could be achieved either through a decrease in the inter-<br>action between synapsin I and synaptic vesicle or a reserve pool to a releasable pool. Such a disruption mot<br>could be achieved either through a decrease in the inter-<br>action between synapsin I and synaptic vesicle or (Ro<br>through a decrease in the interaction between synap could be achieved either through a decrease in the in<br>action between synapsin I and synaptic vesicle<br>through a decrease in the interaction between syna<br>I and actin. Computer modeling of synapsin I bindir<br>synaptic vesicles action between synapsin I and synaptic vesicle or<br>through a decrease in the interaction between synapsin<br>I and actin. Computer modeling of synapsin I binding to<br>synaptic vesicles and F-actin, based upon the experimen-<br>tall through a decrease in the interaction between synapsin all and actin. Computer modeling of synapsin I binding to synaptic vesicles and F-actin, based upon the experimentally determined binding constants, indicates that dis I and actin. Computer modeling of synapsin I binding to<br>synaptic vesicles and F-actin, based upon the experimentally determined binding constants, indicates that dis-<br>sociation of a synapsin I/synaptic vesicle binary compl synaptic vesicles and F-actin, based<br>tally determined binding constant<br>sociation of a synapsin I/synaptic of<br>from actin could account for the somplex (Benfenati et al., 1991).<br>Synapsin II is also a major subst lly determined binding constants, indicates that<br>ciation of a synapsin I/synaptic vesicle binary com<br>om actin could account for the severing of the ter<br>mplex (Benfenati et al., 1991).<br>Synapsin II is also a major substrate

sociation of a synapsin I/synaptic vesicle binary complex im<br>from actin could account for the severing of the tertiary<br>complex (Benfenati et al., 1991).<br>Synapsin II is also a major substrate for  $Ca^{2+}$ -depending the phos from actin could account for the severing of the tertiary<br>complex (Benfenati et al., 1991).<br>Synapsin II is also a major substrate for  $Ca^{2+}$ -depend-<br>ent protein phosphorylation in nerve terminals (Wang<br>et al., 1988). Syn complex (Benfenati et al., 1991).<br>
Synapsin II is also a major substrate for  $Ca^{2+}$ -dependent protein phosphorylation in nerve terminals (Wang 's<br>
et al., 1988). Synapsin II can be phosphorylated on that<br>
serine residue Synapsin II is also a major substrate for  $Ca^{2+}$ -depent protein phosphorylation in nerve terminals (Wast al., 1988). Synapsin II can be phosphorylated on the serine residue that corresponds to site 1 in synapsin and this ent protein phosphorylation in nerve terminals (Wang<br>et al., 1988). Synapsin II can be phosphorylated on that<br>serine residue that corresponds to site 1 in synapsin I,<br>and this reaction can be catalyzed by either cyclic AMP et al., 1988). Synapsin II can be phosphorylated on that<br>serine residue that corresponds to site 1 in synapsin I,<br>and this reaction can be catalyzed by either cyclic AMP-<br>dependent protein kinase or CaM kinase I (Huang et serine residue that corresponds to site 1 in synapsin I, gate<br>and this reaction can be catalyzed by either cyclic AMP-1986<br>dependent protein kinase or CaM kinase I (Huang et al., prot<br>1982; Browning et al., 1987; Nairn and and this reaction can be catalyzed by either cyclic AMP-<br>dependent protein kinase or CaM kinase I (Huang et al.,<br>1982; Browning et al., 1987; Nairn and Greengard, 1987).<br>Synapsin II can also be phosphorylated in intact cel dependent protein kinase or CaM kinase I (Huang et a<br>1982; Browning et al., 1987; Nairn and Greengard, 198<br>Synapsin II can also be phosphorylated in intact cells<br>response to any of several neurotransmitters and stime<br>that 1982; Browning et al., 1987; Nairn and Greengard, 1987)<br>Synapsin II can also be phosphorylated in intact cells ir<br>response to any of several neurotransmitters and stimul<br>that increase cyclic AMP or Ca<sup>2+</sup> levels in nerve t Synapsin II can also be phosphorylated in intact cells in response to any of several neurotransmitters and stimuli that increase cyclic AMP or Ca<sup>2+</sup> levels in nerve terminals (Forn and Greengard, 1978; Tsou and Greengard, response to any<br>that increase c<br>nals (Forn ano<br>1982; Haycock<br>et al., 1989e).<br>Studies in v at increase cyclic AMP or Ca<sup>2+</sup> levels in nerve termi-<br>ls (Forn and Greengard, 1978; Tsou and Greengard, of<br>82; Haycock et al., 1988b; Wang et al., 1988; Walaas fa<br>al., 1989e). (I<br>Studies in which recombinant DNA technolo

nals (Forn and Greengard, 1978; Tsou and Greengard, of<br>1982; Haycock et al., 1988b; Wang et al., 1988; Walaas fa<br>et al., 1989e). (I<br>Studies in which recombinant DNA technology was bind<br>used have indicated that synapsin II 1982; Haycock et al., 1988b; Wang et al., 1988; Walaas fact al., 1989e). (Fig. 2016).<br>
Studies in which recombinant DNA technology was brused have indicated that synapsin II can bind to a protein brused have indicated tha et al., 1989e). (Represents the NH<sub>2</sub>-terminal region, although the extreme NH<sub>2</sub> is to the NH<sub>2</sub>-terminal region, although the extreme NH<sub>2</sub> its terminus appears unnecessary for such binding (Thiel et aly Studies in which recombinant DNA technology was<br>used have indicated that synapsin II can bind to a protein<br>in small synaptic vesicles through a domain located close<br>to the NH<sub>2</sub>-terminal region, although the extreme NH<sub>2</sub> used have indicated that synapsin II can bind to a protein<br>in small synaptic vesicles through a domain located close<br>to the  $NH_2$ -terminal region, although the extreme  $NH_2$ <br>iterminus appears unnecessary for such binding in small synaptic vesicles through a domain located close<br>to the  $NH_2$ -terminal region, although the extreme  $NH_2$  is<br>terminus appears unnecessary for such binding (Thiel et<br>al., 1990). Because the region of synapsin II t to the NH<sub>2</sub>-terminal region, although the extreme NH<sub>2</sub> it<br>terminus appears unnecessary for such binding (Thiel et<br>al., 1990). Because the region of synapsin II that binds<br>pto synaptic vesicles is common to synapsins I a terminus appears unnecessar<br>al., 1990). Because the region<br>to synaptic vesicles is comme<br>seems likely that the binding<br>also applies to synapsin I.<br>Much less is known abou 1990). Because the region of synapsin II that binds<br>synaptic vesicles is common to synapsins I and II, it<br>tems likely that the binding observed with synapsin II in<br>the possible functions of high<br>Much less is known about th

to synaptic vesicles is common to synapsins I and II, it<br>seems likely that the binding observed with synapsin II<br>also applies to synapsin I.<br>Much less is known about the possible functions of<br>synapsin II than of synapsin I seems likely that the binding observed with synapsin II<br>also applies to synapsin I.<br>Much less is known about the possible functions of<br>synapsin II than of synapsin I. In view of the structural<br>similarities (common domains) also applies to synapsin I. The possible functions of hydrograpsin II than of synapsin I. In view of the structural the similarities (common domains), as well as the structural be differences (variable domains), between sy Much less is known about the possible functions of hyperpapsin II than of synapsin I. In view of the structural the similarities (common domains), as well as the structural be differences (variable domains), between synaps synapsin II than of synapsin I. In view of the structural the similarities (common domains), as well as the structural be differences (variable domains), between synapsin I and my synapsin II, it will be of great interest similarities (common domains), as well as the struct<br>differences (variable domains), between synapsin I<br>synapsin II, it will be of great interest to determine w<br>functions are held in common and which functions<br>unique to th differences (var<br>synapsin II, it w<br>functions are h<br>unique to these<br>ciated proteins.<br>3. MARCKS ( mapsin II, it will be of great interest to determine wh<br>nctions are held in common and which functions<br>nique to these two subclasses of synaptic vesicle-as<br>ated proteins.<br>3. *MARCKS* (80 to 87 kDa) protein. Following depol

unique to these two subclasses of synaptic vesicle-asso-<br>ciated proteins.<br>3. MARCKS (80 to 87 kDa) protein. Following depolar-<br>ization-induced  $Ca^{2+}$  influx or application of phorbol<br>esters to isolated nerve terminals, a unique to these two subclasses of synaptic vesicle-asso-<br>ciated proteins. p<br>ciated proteins. and  $\frac{1}{2}$ <br>3. MARCKS (80 to 87 kDa) protein. Following depolar-<br>ization-induced Ca<sup>2+</sup> influx or application of phorbol ti<br>es ciated proteins.<br>
3. MARCKS (80 to 87 kDa) protein. Following depolaization-induced Ca<sup>2+</sup> influx or application of phore<br>
esters to isolated nerve terminals, an 80- to 87-kiprotein rapidly becomes phosphorylated through 3. MARCKS (80 to 87 kDa) protein. Following depolarization-induced  $Ca^{2+}$  influx or application of phorbol esters to isolated nerve terminals, an 80- to 87-kDa protein rapidly becomes phosphorylated through activation of ization-induced  $Ca^{2+}$  influx or application of phorbol the esters to isolated nerve terminals, an 80- to 87-kDa for<br>protein rapidly becomes phosphorylated through activa-ble<br>tion of protein kinase C (Wu et al., 1982; Wa esters to isolated nerve terminals, an 80- to 87-kD<br>protein rapidly becomes phosphorylated through active<br>tion of protein kinase C (Wu et al., 1982; Wang et al<br>1988). The phosphorylation of this protein has bee<br>found to co tion of protein kinase C (Wu et al., 1982; Wang et al., known. Given the ubiquitous presence of this protein in<br>1988). The phosphorylation of this protein has been both neuronal and nonneuronal cells, an involvement in<br>fou induced increase in release of transmitter from such

**PROTEIN PHOSPHORYLATION AND NEURONAL FUNCTION**<br>**d** Greengard, 1987; Petrucci tein, which recently has been purified to homogeneity AND NEURONAL FUNCTION 317<br>tein, which recently has been purified to homogeneity<br>from bovine (Albert et al., 1987) and rat (Patel and AND NEURONAL FUNCTION 317<br>tein, which recently has been purified to homogeneity<br>from bovine (Albert et al., 1987) and rat (Patel and<br>Kligman, 1987) brain and characterized, is not a nerve AND NEURONAL FUNCTION 317<br>
tein, which recently has been purified to homogeneity<br>
from bovine (Albert et al., 1987) and rat (Patel and<br>
Kligman, 1987) brain and characterized, is not a nerve<br>
terminal-specific protein. Rat tein, which recently has been purified to homogeneity<br>from bovine (Albert et al., 1987) and rat (Patel and<br>Kligman, 1987) brain and characterized, is not a nerve<br>terminal-specific protein. Rather, it appears to be widely<br>d tein, which recently has been purified to homogeneity<br>from bovine (Albert et al., 1987) and rat (Patel and<br>Kligman, 1987) brain and characterized, is not a nerve<br>terminal-specific protein. Rather, it appears to be widely<br>d from bovine (Albert et al., 1987) and rat (Patel and Kligman, 1987) brain and characterized, is not a nerve terminal-specific protein. Rather, it appears to be widely distributed in both neurons and glial cells throughout Kligman, 1987) brain and characterized, is not a nerve<br>terminal-specific protein. Rather, it appears to be widely<br>distributed in both neurons and glial cells throughout<br>the brain (Walaas et al., 1983b,c, 1989f; Ouimet et a terminal-specific protein. Rather, it appears to be widely distributed in both neurons and glial cells throughout the brain (Walaas et al., 1983b,c, 1989f; Ouimet et al., 1990), being particularly enriched in growth cones, distributed in both neurons and glial cells throughout<br>the brain (Walaas et al., 1983b,c, 1989f; Ouimet et al.,<br>1990), being particularly enriched in growth cones, the<br>motile structures that form the tips of advancing neur the brain (Walaas et al., 1983b,c, 1989f; Ouimet et al., 1990), being particularly enriched in growth cones, the motile structures that form the tips of advancing neurites (Katz et al., 1985). It is also found in nonneural motile structures that form the tips of advancing neurites<br>(Katz et al., 1985). It is also found in nonneural tissues<br>(Rozengurt et al., 1983; Albert et al., 1986; Blackshear et<br>al., 1986).<br>Analysis of the biochemical prop otile structures that form the tips of advancing neurites<br>
(atz et al., 1985). It is also found in nonneural tissues<br>
cozengurt et al., 1983; Albert et al., 1986; Blackshear et<br>
, 1986).<br>
Analysis of the biochemical proper

(Katz et al., 1985). It is also found in nonneural tissues<br>(Rozengurt et al., 1983; Albert et al., 1986; Blackshear et<br>al., 1986).<br>Analysis of the biochemical properties of the protein<br>and of complementary DNA clones has r and of complementary DNA clones has revealed that the protein consists of a single polypeptide chain of approximately  $M_r$  32,000, which contrasts with the apparent molecular masses of 68 to 87 kDa observed on different sodium dodecyl sulfate-polyacrylamide gel electrophoreand of complementary DNA clones has revealed the<br>protein consists of a single polypeptide chain of app<br>imately  $M_r$  32,000, which contrasts with the app<br>molecular masses of 68 to 87 kDa observed on diff<br>sodium dodecyl sul protein consists of a single polypeptide chain of approximately  $M_r$  32,000, which contrasts with the apparent molecular masses of 68 to 87 kDa observed on different sodium dodecyl sulfate-polyacrylamide gel electrophores imately  $M_r$  32,000, which contrasts with the apparent<br>molecular masses of 68 to 87 kDa observed on different<br>sodium dodecyl sulfate-polyacrylamide gel electrophore-<br>sis systems (Blackshear et al., 1986; Aderem et al., 19 molecular masses of 68 to 87 kDa observed on differen<br>sodium dodecyl sulfate-polyacrylamide gel electrophore<br>sis systems (Blackshear et al., 1986; Aderem et al., 1988)<br>The protein contains a high proportion of alanine, i<br>d sodium dodecyl sulfate-polyacrylamide gel electrophore-<br>sis systems (Blackshear et al., 1986; Aderem et al., 1988).<br>The protein contains a high proportion of alanine, it<br>displays an acidic isoelectric point, and it is high sis systems (Blackshear et al., 1986; Aderem et al., 1988).<br>The protein contains a high proportion of alanine, it<br>displays an acidic isoelectric point, and it is highly elon-<br>gated and heat stable (Albert et al., 1987; Stu The protein contains a high proportion of alanine, it<br>displays an acidic isoelectric point, and it is highly elon-<br>gated and heat stable (Albert et al., 1987; Stumpo et al.,<br>1989). Moreover, the protein can be phosphorylat displays an acidic isoelectric point, and it is highly elongated and heat stable (Albert et al., 1987; Stumpo et al., 1989). Moreover, the protein can be phosphorylated by protein kinase C on as many as four serine residue gated and heat stable (Albert et al., 1987; Stumpo et al<br>1989). Moreover, the protein can be phosphorylated b<br>protein kinase C on as many as four serine residue<br>(Stumpo et al., 1989; Graff et al., 1989a), whereas othe<br>kina 1989). Moreover, the protein can be phosphorylated by<br>protein kinase C on as many as four serine residues<br>(Stumpo et al., 1989; Graff et al., 1989a), whereas other<br>kinases appear ineffective both in vitro and in situ (Wa-<br> protein kinase C on as many as four serine residues<br>(Stumpo et al., 1989; Graff et al., 1989a), whereas other<br>kinases appear ineffective both in vitro and in situ (Wa-<br>laas et al., 1983: Albert et al., 1986; Blackshear et (Stumpo et al., 1989; Graff et al., 1989a), whereas other<br>kinases appear ineffective both in vitro and in situ (Wa-<br>laas et al., 1983c; Albert et al., 1986; Blackshear et al.,<br>1986). The protein is also phosphorylated in a kinases appear ineffective both in vitro and in situ (Wa-<br>laas et al., 1983c; Albert et al., 1986; Blackshear et al.,<br>1986). The protein is also phosphorylated in a number<br>of peripheral tissues and cells by a variety of g laas et al., 1983c; Albert et al., 1986; Blackshear et al., 1986). The protein is also phosphorylated in a number of peripheral tissues and cells by a variety of growth factors and hormones that activate protein kinase C ( 1986). The protein is also phosphorylated in a numb<br>of peripheral tissues and cells by a variety of growt<br>factors and hormones that activate protein kinase<br>(Rozengurt et al., 1983; Blackshear et al., 1986). In ra<br>brain, th of peripheral tissues and cells by a variety of growth<br>factors and hormones that activate protein kinase C<br>(Rozengurt et al., 1983; Blackshear et al., 1986). In rat<br>brain, the protein is enriched in both synaptosomal mem-<br> factors and hormones that activate protein kinase C<br>(Rozengurt et al., 1983; Blackshear et al., 1986). In rat<br>brain, the protein is enriched in both synaptosomal mem-<br>branes and cytosol (Albert et al., 1986). The subcellul (Rozengurt et al., 1983; Blackshear et al., 1986). In 1<br>brain, the protein is enriched in both synaptosomal mer<br>branes and cytosol (Albert et al., 1986). The subcellul<br>distribution of the protein appears to be determined<br>i brain, the protein is enriched in both synaptosomal mem-<br>branes and cytosol (Albert et al., 1986). The subcellular<br>distribution of the protein appears to be determined by<br>its phosphorylation state, because protein kinase C branes and cytosol (Albert et al., 1986). The subcellular<br>distribution of the protein appears to be determined by<br>its phosphorylation state, because protein kinase C-cat-<br>alyzed phosphorylation was able both to release the distribution of the protein appears to be determined by<br>its phosphorylation state, because protein kinase C-cat-<br>alyzed phosphorylation was able both to release the<br>protein from synaptosomal membranes in vitro and to<br>trans its phosphorylation state, because protein kinase C-cat-<br>alyzed phosphorylation was able both to release the<br>protein from synaptosomal membranes in vitro and to<br>translocate the protein from membranes to cytosol in<br>intact s alyzed phosphorylation was able both to release the<br>protein from synaptosomal membranes in vitro and to<br>translocate the protein from membranes to cytosol in<br>intact synaptosomes (Wang et al., 1989). The deduced<br>primary stru protein from synaptosomal membranes in vitro and to<br>translocate the protein from membranes to cytosol in<br>intact synaptosomes (Wang et al., 1989). The deduced<br>primary structure of the protein does not show any<br>hydrophobic d translocate the protein from membranes to cytosol in<br>intact synaptosomes (Wang et al., 1989). The deduced<br>primary structure of the protein does not show any<br>hydrophobic domains (Stumpo et al., 1989). Therefore,<br>the membran intact synaptosomes (Wang et al., 1989). The deduced<br>primary structure of the protein does not show any<br>hydrophobic domains (Stumpo et al., 1989). Therefore,<br>the membrane association of the protein is believed to<br>be caused primary structure of the protein does not show any<br>hydrophobic domains (Stumpo et al., 1989). Therefore,<br>the membrane association of the protein is believed to<br>be caused by fatty acid acylation of the protein with<br>myristic hydrophobic domains (Stumpo et al., 1989). Therefore,<br>the membrane association of the protein is believed to<br>be caused by fatty acid acylation of the protein with<br>myristic acid, an acylation that has been demonstrated<br>in m the membrane association of the protein is believed to<br>be caused by fatty acid acylation of the protein with<br>myristic acid, an acylation that has been demonstrated<br>in macrophages and muscle cells (Aderem et al., 1988;<br>Jame be caused by fatty acid acylation of the protein with<br>myristic acid, an acylation that has been demonstrated<br>in macrophages and muscle cells (Aderem et al., 1988;<br>James and Olson, 1989). Finally, the protein appears to<br>be myristic acid, an acylation that has been demonstrated<br>in macrophages and muscle cells (Aderem et al., 1988;<br>James and Olson, 1989). Finally, the protein appears to<br>be able to bind calmodulin, and this binding can be<br>preve in macrophages and muscle cells (Aderem et al., 1988;<br>James and Olson, 1989). Finally, the protein appears to<br>be able to bind calmodulin, and this binding can be<br>prevented by protein kinase C-catalyzed phosphorylation<br>(Gra be able to bind calmodulin, and this binding can be able to bind calmodulin, and this binding can levented by protein kinase C-catalyzed phosphorylatic iraff et al., 1989b). The protein has been designate MARCKS protein (Stumpo et al., 1989). The function of the MARCKS prot

prevented by protein kinase C-catalyzed phosphorylation (Graff et al., 1989b). The protein has been designated the MARCKS protein (Stumpo et al., 1989). The function of the MARCKS protein, and the possible relationship to (Graff et al., 1989b). The protein has been designated<br>the MARCKS protein (Stumpo et al., 1989).<br>The function of the MARCKS protein, and the possi-<br>ble relationship to cellular release mechanisms, is un-<br>known. Given the u the MARCKS protein (Stumpo et al., 1989).<br>The function of the MARCKS protein, and the possi-<br>ble relationship to cellular release mechanisms, is un-<br>known. Given the ubiquitous presence of this protein in<br>both neuronal and The function of the MARCKS protein, and the possi-<br>ble relationship to cellular release mechanisms, is un-<br>known. Given the ubiquitous presence of this protein in<br>both neuronal and nonneuronal cells, an involvement in<br>wide ble relationship to cellular release mechanisms,<br>known. Given the ubiquitous presence of this pro<br>both neuronal and nonneuronal cells, an involver<br>widespread functions not restricted to nerve term<br>to be expected. Recent ul known. Given the ubiquitous presence of this protein in<br>both neuronal and nonneuronal cells, an involvement in<br>widespread functions not restricted to nerve terminals is<br>to be expected. Recent ultrastructural immunocytochem

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<sup>318</sup> **WALAAS AND GREENGARD** enriched in both dendrites and axons of certain neurons wallas and<br>enriched in both dendrites and axons of certain neurons<br>and in glial cells (Ouimet et al., 1990). In these cell types,<br>both membrane-associated and cytosolic immunoreactivwaLA<br>enriched in both dendrites and axons of certain ne<br>and in glial cells (Ouimet et al., 1990). In these cell<br>both membrane-associated and cytosolic immunore<br>ity could be seen. Moreover, a particularly heavy re enriched in both dendrites and axons of certain neurons and in glial cells (Ouimet et al., 1990). In these cell types, reaction both membrane-associated and cytosolic immunoreactiv- City could be seen. Moreover, a particul enriched in both dendrites and axons of certain neurons<br>and in glial cells (Ouimet et al., 1990). In these cell types<br>both membrane-associated and cytosolic immunoreactiv-<br>ity could be seen. Moreover, a particularly heavy and in glial cells (Ouimet et al., 1990). In these cell types, respective the membrane-associated and cytosolic immunoreactively could be seen. Moreover, a particularly heavy reaction 43 product was associated with microtu both membrane-associated and cytosolic immunoreactivity could be seen. Moreover, a particularly heavy reaction product was associated with microtubules in certain dendrites. Thus, it appears possible that, in neurons, the functions. oduct was associated with microtubules in certain den-<br>ites. Thus, it appears possible that, in neurons, the et a<br>otein could be involved in both pre- and postsynaptic l<br>nctions.<br>In other studies, MARCKS has been observed

drites. Thus, it appears possible that, in neurons,<br>protein could be involved in both pre- and postsyna<br>functions.<br>In other studies, MARCKS has been observed t<br>able to bind actin and to be associated with membr<br>bound actin protein could be involved in both pre- and postsynaptic<br>functions.<br>In other studies, MARCKS has been observed to be<br>nable to bind actin and to be associated with membrane-<br>bound actin filaments associated with focal adhesi functions.<br>In other studies, MARCKS has been observed to be<br>able to bind actin and to be associated with membrane-<br>bound actin filaments associated with focal adhesion<br>plaques at the plasma membrane in nonstimulated cul-<br>t In other studies, MARCKS has been observed to be able to bind actin and to be associated with membrane-<br>bound actin filaments associated with focal adhesion<br>plaques at the plasma membrane in nonstimulated cul-<br>tured neutro able to bind actin and to be associated with membrain bound actin filaments associated with focal adhesiplaques at the plasma membrane in nonstimulated curred neutrophils and macrophages (Rosen et al., 199<br>Following protei bound actin filaments associated with focal adhesion (*A* plaques at the plasma membrane in nonstimulated cultured neutrophils and macrophages (Rosen et al., 1990). on Following protein kinase C-catalyzed phosphorylation, plaques at the plasma membrane in nonstimulated cultured neutrophils and macrophages (Rosen et al., 1990). on<br>Following protein kinase C-catalyzed phosphorylation, 4<br>the actin-MARCKS complex was released from these b<br>membr tured neutrophils and macrophages (Rosen et al., 1990)<br>Following protein kinase C-catalyzed phosphorylation<br>the actin-MARCKS complex was released from thes<br>membrane plaques (Rosen et al., in preparation). Thes<br>data support Following protein kinase C-catalyzed phosphorylation<br>the actin-MARCKS complex was released from thes<br>membrane plaques (Rosen et al., in preparation). Thes<br>data support the possibility that MARCKS may be func<br>tionally invol the actin-MARCKS comembrane plaques (R<br>data support the possitionally involved in r<br>membrane interactions.<br>4. GAP-43 (B-50, F. embrane plaques (Rosen et al., in preparation). These apptate approximate the possibility that MARCKS may be functionally involved in regulation of cytoskeleton-plasma embrane interactions.<br>4. *GAP-43 (B-50, F1, pp46, p57,* 

data support the possibility that MARCKS may be func-<br>tionally involved in regulation of cytoskeleton-plasma<br>membrane interactions.<br>4. GAP-43 (B-50, F1, pp46, p57, neuromodulin). The in<br>other major protein phosphorylated tionally involved in regulation of cytoskeleton-plasma<br>membrane interactions.<br>4.  $GAP-43$  ( $B-50$ ,  $F1$ ,  $pp46$ ,  $p57$ , neuromodulin). The<br>other major protein phosphorylated by  $Ca^{2+}$  influx or<br>protein kinase C activators membrane interactions. Lotson, Eq. 3. 1988; Meanwood Minkley, The in other major protein phosphorylated by  $Ca^{2+}$  influx or protein kinase C activators in nerve terminals (Wang et mal., 1988; Dekker et al., 1990) is a pr 4.  $GAP-43$  ( $B-50$ ,  $F1$ ,  $pp46$ ,  $p57$ , neuromodulin).<br>
other major protein phosphorylated by  $Ca^{2+}$  influ<br>
protein kinase C activators in nerve terminals (Wa<br>
al., 1988; Dekker et al., 1990) is a protein that, d<br>
sodium other major protein phosphorylated by  $Ca^{2+}$  influx or protein kinase C activators in nerve terminals (Wang et mal., 1988; Dekker et al., 1990) is a protein that, during 19 sodium dodecyl sulfate-polyacrylamide gel elect protein kinase C activators in nerve terminals (Wang et m<br>al., 1988; Dekker et al., 1990) is a protein that, during 19<br>sodium dodecyl sulfate-polyacrylamide gel electrophore-re<br>sis, usually displays an approximate molecula al., 1988; Dekker et al., 1990) is a protein that, duesdom dodecyl sulfate-polyacrylamide gel electrophers, usually displays an approximate molecular mateum 48 to 49 kDa and appears to be identical with the prodesignated G sodium dodecyl sulfate-polyacrylamide gel electrophore-<br>sis, usually displays an approximate molecular mass of<br>48 to 49 kDa and appears to be identical with the protein<br>designated GAP-43, B-50, F1, pp46, p57, or neuromodu-48 to 49 kDa and appears to be identical with the protein designated GAP-43, B-50, F1, pp46, p57, or neuromodulin (Benowitz and Routtenberg, 1987; Chan et al., 1986; Meiri et al., 1986; Nielander et al., 1987). This protei 48 to 49 kDa and appears to be identical with the protein pro<br>designated GAP-43, B-50, F1, pp46, p57, or neuromodu-<br>lin (Benowitz and Routtenberg, 1987; Chan et al., 1986; We<br>Meiri et al., 1986; Nielander et al., 1987). Th designated GAP-43, B-50, F1, pp46, p57, or neurom<br>lin (Benowitz and Routtenberg, 1987; Chan et al., 1<br>Meiri et al., 1986; Nielander et al., 1987). This pro<br>which has been extensively characterized, represen<br>neuron-specific lin (Benowitz and Routtenberg, 1987; Chan et al., 1986; W.<br>Meiri et al., 1986; Nielander et al., 1987). This protein, ce<br>which has been extensively characterized, represents a<br>neuron-specific (Kristjansson et al., 1982), m Meiri et al., 1986; Nielander et al., 1987). This protein,<br>which has been extensively characterized, represents a<br>neuron-specific (Kristjansson et al., 1982), membrane-<br>associated phosphoprotein whose expression is greatly which has been extensively characterized, represents a<br>neuron-specific (Kristjansson et al., 1982), membrane-<br>associated phosphoprotein whose expression is greatly<br>increased during neuronal development and regeneration<br>(Ja neuron-specific (Kristjansson et al., 1982), membrane-<br>associated phosphoprotein whose expression is greatly<br>increased during neuronal development and regeneration<br>(Jacobson et al., 1986; Larrivee and Grafstein, 1987;<br>Sken associated phosphoprotein whose expression is great<br>increased during neuronal development and regeneratio<br>(Jacobson et al., 1986; Larrivee and Grafstein, 198<br>Skene, 1989). GAP-43 shares a number of propertie<br>with the MARCK increased during neuronal development and regeneration (Jacobson et al., 1986; Larrivee and Grafstein, 1987; Skene, 1989). GAP-43 shares a number of properties with the MARCKS protein. It is one of the most abundant protei (Jacobson et al., 1986; Larrivee and Grafstein, 1987; Skene, 1989). GAP-43 shares a number of properties with the MARCKS protein. It is one of the most abundant proteins in neuronal growth cones (Katz et al., 1985; Hyman a with the MARCKS protein. It is one of the most abundant proteins in neuronal growth cones (Katz et al., 1985; Hyman and Pfenninger, 1987; De Graan et al., with the MARCKS protein. It is one of the most abundant proteins in neuronal growth cones (Katz et al., 1985; Hyman and Pfenninger, 1987; De Graan et al., 1985; Skene et al., 1986). Analyses of the biochemical properties o dant proteins in neuronal growth cones (Katz et al., neuronal 1985; Hyman and Pfenninger, 1987; De Graan et al., ker 1985; Skene et al., 1986). Analyses of the biochemical aga properties of the purified protein and of com 1985; Hyman and Pfenninger, 1987; De Graan et al., 1985; Skene et al., 1986). Analyses of the biochemical properties of the purified protein and of complementary DNA clones have revealed that the protein consists of a hig properties of the purified protein and of complementary DNA clones have revealed that the protein consists of a highly acidic polypeptide chain of approximately  $M_r$ properties of the purified protein and of complementary<br>DNA clones have revealed that the protein consists of a<br>highly acidic polypeptide chain of approximately  $M_r$ <br>24,000, which contrasts with the apparent molecular<br>mas DNA clones have revealed that the protein consists of a highly acidic polypeptide chain of approximately  $M_r$  24,000, which contrasts with the apparent molecular mass of 43 to 57 kDa observed on various sodium dodecyl sul highly acidic polypeptide chain of approximately  $M_r$ <br>24,000, which contrasts with the apparent molecular<br>mass of 43 to 57 kDa observed on various sodium dodecyl<br>sulfate-polyacrylamide gel electrophoresis systems (Basi<br>et mass of 43 to 57 kDa observed on various sodium dodecyl<br>sulfate-polyacrylamide gel electrophoresis systems (Basi<br>et al., 1987; Benowitz et al., 1987; Karns et al., 1987;<br>Kosik et al., 1988). Moreover, the protein can be ph sulfate-polyacrylamide gel electrophoresis systems (Basi sulfate-polyacrylamide gel electrophoresis systems (Basi can et al., 1987; Benowitz et al., 1987; Karns et al., 1987; 198<br>Kosik et al., 1988). Moreover, the protein can be phos-<br>the phorylated by protein kinase C (Aloyo et et al., 1987; Benowitz et al., 1987; Karns et al., 1987; 1988<br>Kosik et al., 1988). Moreover, the protein can be phos-<br>phorylated by protein kinase C (Aloyo et al., 1983), gest<br>apparently on a single serine residue (Coggins Kosik et al., 1988). Moreover, the protein can be phophorylated by protein kinase C (Aloyo et al., 1983) apparently on a single serine residue (Coggins an Zwiers, 1989; Nielander et al., 1990), both in vitro and is situ. A phorylated by protein kinase C (Aloyo et al., 1983), apparently on a single serine residue (Coggins and Zwiers, 1989; Nielander et al., 1990), both in vitro and in situ. Although the protein behaves as an integral membrane apparently on a single serine residue (Coggins and Zwiers, 1989; Nielander et al., 1990), both in vitro and in situ. Although the protein behaves as an integral membrane protein during subcellular fractionation (Mahler et Zwiers, 1989; Nielander et al., 1990), both in vitro and in<br>situ. Although the protein behaves as an integral mem-<br>brane protein during subcellular fractionation (Mahler<br>et al., 1982), the deduced primary structure does no situ. Although the protein behaves as an integral membrane protein during subcellular fractionation (Mahler et al., 1982), the deduced primary structure does not contain any hydrophobic domains (for examples, see Basi et a brane protein during subcellular fractionation (Mahler<br>et al., 1982), the deduced primary structure does not<br>contain any hydrophobic domains (for examples, see Basi<br>et al., 1987; Karns et al., 1987; Wakim et al., 1987).<br>In

GREENGARD<br>acid (Skene and Virag, 1989) appears to be at least partly<br>responsible for the membrane localization of GAP-43. FREENGARD<br>acid (Skene and Virag, 1989) appears to be at least partly<br>responsible for the membrane localization of GAP-43.<br>Other studies have indicated a tight association of GAP-GREENGARD<br>acid (Skene and Virag, 1989) appears to be at least part<br>responsible for the membrane localization of GAP-4<br>Other studies have indicated a tight association of GAI<br>43 with actin-rich submembranous cytoskeleton st acid (Skene and Virag, 1989) appears to be at least part<br>responsible for the membrane localization of GAP-4<br>Other studies have indicated a tight association of GAl<br>43 with actin-rich submembranous cytoskeleton stru<br>tures i acid (Skene and Virag, 1989) appears to be at least partly<br>responsible for the membrane localization of GAP-43.<br>Other studies have indicated a tight association of GAP-<br>43 with actin-rich submembranous cytoskeleton struc-<br> responsible fo<br>0ther studies<br>43 with actin<br>tures in neuro<br>et al., 1990).<br>Recent com ther studies have indicated a tight association of GAP-<br>
With actin-rich submembranous cytoskeleton struc-<br>
res in neurons (Meiri and Gordon-Weeks, 1990; Moss<br>
al., 1990).<br>
Recent comparison of primary structures has shown

43 with actin-rich submembranous cytoskeleton struc-<br>tures in neurons (Meiri and Gordon-Weeks, 1990; Moss<br>et al., 1990).<br>Recent comparison of primary structures has shown<br>that GAP-43 is identical with p57 or neuromodulin, tures in neurons (Meiri and Gordon-Weeks, 1990; Mos<br>et al., 1990).<br>Recent comparison of primary structures has show<br>that GAP-43 is identical with p57 or neuromodulin,<br>neuronal protein that has the unusual property of bind<br> et al., 1990).<br>Recent comparison of primary structures has shown<br>that GAP-43 is identical with p57 or neuromodulin, a<br>neuronal protein that has the unusual property of bind-<br>ing calmodulin with high affinity in the absenc Recent comparison of primary structures has shown<br>that GAP-43 is identical with p57 or neuromodulin, a<br>neuronal protein that has the unusual property of bind-<br>ing calmodulin with high affinity in the absence of  $Ca^{2+}$ <br>(A that GAP-43 is identical with p57 or neuromodulin, a<br>neuronal protein that has the unusual property of bind-<br>ing calmodulin with high affinity in the absence of  $Ca^{2+}$ <br>(Alexander et al., 1987; Wakim et al., 1987). As in neuronal protein that has the unusual property of bind ing calmodulin with high affinity in the absence of Ca (Alexander et al., 1987; Wakim et al., 1987). As in the case of the MARCKS protein, binding of calmodulin wis on ing calmodulin with high affinity in the absence of  $Ca^{2+}$ <br>(Alexander et al., 1987; Wakim et al., 1987). As in the<br>case of the MARCKS protein, binding of calmodulin was<br>only observed with the dephosphorylated form of  $GAP$ (Alexander et al., 1987; Wakim et al., 1987). As in the case of the MARCKS protein, binding of calmodulin was only observed with the dephosphorylated form of GAP-43 (Liu and Storm, 1990). Despite various similarities betw case of the MARCKS protein, binding of calmodulin was<br>only observed with the dephosphorylated form of GAP-<br>43 (Liu and Storm, 1990). Despite various similarities<br>between the two proteins (Table 6), GAP-43 does not<br>appear t **MARCKS** protein. (Liu and Storm, 1990). Despite various similarities<br>tween the two proteins (Table 6), GAP-43 does not<br>pear to have any sequence homology with the<br>ARCKS protein.<br>The functions of GAP-43 remain essentially unknown.<br>calizatio

between the two proteins (Table 6), GAP-43 does not<br>appear to have any sequence homology with the<br>MARCKS protein.<br>The functions of GAP-43 remain essentially unknown.<br>Localization studies of this neuron-specific protein hav appear to have any sequence homology with the<br>MARCKS protein.<br>The functions of GAP-43 remain essentially unknown.<br>Localization studies of this neuron-specific protein have<br>indicated that it is specifically enriched in axon MARCKS protein.<br>The functions of GAP-43 remain essentially unknown.<br>Localization studies of this neuron-specific protein have<br>indicated that it is specifically enriched in axons and<br>presynaptic terminals, and it has not be The functions of GAP-43 remain essentially unknow<br>Localization studies of this neuron-specific protein ha<br>indicated that it is specifically enriched in axons as<br>presynaptic terminals, and it has not been found<br>mature dendr Localization studies of this neuron-specific protein have<br>indicated that it is specifically enriched in axons and<br>presynaptic terminals, and it has not been found in<br>mature dendrites (Goslin et al., 1988; Gordon-Weeks,<br>198 indicated that it is specifically enriched in axons and<br>presynaptic terminals, and it has not been found in<br>mature dendrites (Goslin et al., 1988; Gordon-Weeks,<br>1989). Its increased expression during axonal growth and<br>rege presynaptic terminals, and it has not been found in<br>mature dendrites (Goslin et al., 1988; Gordon-Weeks,<br>1989). Its increased expression during axonal growth and<br>regeneration (Meiri et al., 1988) and its high levels in<br>fet mature dendrites (Goslin et al., 1988; Gordon-Weeks, 1989). Its increased expression during axonal growth and regeneration (Meiri et al., 1988) and its high levels in fetal growth cones has led to the hypothesis that the p 1989). Its increased expression during axonal growth regeneration (Meiri et al., 1988) and its high levels fetal growth cones has led to the hypothesis that protein may be involved in additions to rapidly grow neuronal str regeneration (Meiri et al., 1988) and its high levels in fetal growth cones has led to the hypothesis that the protein may be involved in additions to rapidly growing neuronal structures and in membrane retrieval (Gordon W protein may be involved in additions to rapidly growing<br>neuronal structures and in membrane retrieval (Gordon-<br>Weeks, 1989). Expression of the protein in nonneuronal<br>cells has been reported to induce filopodia generation,<br> protein may be involved in additions to rapidly growing<br>neuronal structures and in membrane retrieval (Gordon-<br>Weeks, 1989). Expression of the protein in nonneuronal<br>cells has been reported to induce filopodia generation,<br> neuronal structures and in membrane retrieval (Gordon-Weeks, 1989). Expression of the protein in nonneuronal cells has been reported to induce filopodia generation, supporting a role in such phenomena (Zuber et al., 1989). Weeks, 1989). Expression of the protein in nonneu cells has been reported to induce filopodia general supporting a role in such phenomena (Zuber et al., 1 Other studies have indicated that phosphorylatic GAP-43 may inhibit cells has been reported to induce filopodia generation,<br>supporting a role in such phenomena (Zuber et al., 1989).<br>Other studies have indicated that phosphorylation of<br>GAP-43 may inhibit phosphatidylinositol phosphoryla-<br>t supporting a role in such phenomena (Zuber et al., 1989).<br>Other studies have indicated that phosphorylation of<br>GAP-43 may inhibit phosphatidylinositol phosphoryla-<br>tion (Jolles et al., 1980; Van Dongen et al., 1985) and<br>t Other studies have indicated that phosphorylation of GAP-43 may inhibit phosphatidylinositol phosphorylation (Jolles et al., 1980; Van Dongen et al., 1985) and that GTP binding to the brain-enriched  $G_0$  protein may be m GAP-43 may inhibit phosphatidylinositol phosphorylation (Jolles et al., 1980; Van Dongen et al., 1985) and that GTP binding to the brain-enriched  $G_0$  protein may be modulated by GAP-43 (Strittmatter et al., 1990). Phosp tion (Jolles et al., 1980; Van Dongen et al., 1985) an that GTP binding to the brain-enriched  $G_0$  protein ma<br>be modulated by GAP-43 (Strittmatter et al., 1990<br>Phosphorylation of GAP-43 appears to be correlated with<br>neur that GTP binding to the brain-enriched  $G_0$  protein may<br>be modulated by GAP-43 (Strittmatter et al., 1990).<br>Phosphorylation of GAP-43 appears to be correlated with<br>neurotransmitter release in rat hippocampal slices (Dekbe modulated by GAP-43 (Strittmatter et al., 1990).<br>Phosphorylation of GAP-43 appears to be correlated with<br>neurotransmitter release in rat hippocampal slices (Dek-<br>ker et al., 1989b), whereas introduction of antibodies<br>ag Phosphorylation of GAP-43 appears to be correlated neurotransmitter release in rat hippocampal slices (I<br>ker et al., 1989b), whereas introduction of antibo<br>against GAP-43 into permeabilized nerve terminals<br>decrease transmi urotransmitter release in rat hippocampal slices (Dek-<br> **A** r et al., 1989b), whereas introduction of antibodies<br>
ainst GAP-43 into permeabilized nerve terminals may<br>
crease transmitter release (Dekker et al., 1989a).<br>
A n ker et al., 1989b), whereas introduction of antibodies<br>against GAP-43 into permeabilized nerve terminals may<br>decrease transmitter release (Dekker et al., 1989a).<br>A number of studies have indicated that <sup>32</sup>P labeling<br>of G

against GAP-43 into permeabilized nerve terminals may<br>decrease transmitter release (Dekker et al., 1989a).<br>A number of studies have indicated that <sup>32</sup>P labeling<br>of GAP-43 during in vitro phosphorylation of membrane<br>fract decrease transmitter release (Dekker et al., 1989a).<br>A number of studies have indicated that <sup>32</sup>P labell<br>of GAP-43 during in vitro phosphorylation of membra<br>fractions with  $[\gamma^{32}P]ATP$  is increased in preparatio<br>from rat A number of studies have indicated that <sup>32</sup>P labeling<br>of GAP-43 during in vitro phosphorylation of membrane<br>fractions with  $[\gamma^{-32}P]ATP$  is increased in preparations<br>from rat hippocampus that had been subject to hippo-<br>ca of GAP-43 during in vitro phosphorylation of membrane<br>fractions with  $[\gamma^{-32}P]ATP$  is increased in preparations<br>from rat hippocampus that had been subject to hippo-<br>campal LTP (see section V.D) (Lovinger et al., 1985,<br>1986 fractions with  $[\gamma^{-32}P]ATP$  is increased in preparations<br>from rat hippocampus that had been subject to hippo-<br>campal LTP (see section V.D) (Lovinger et al., 1985,<br>1986; Routtenberg and Lovinger, 1985). This change in<br>the from rat hippocampus that had been subject to hippocampal LTP (see section V.D) (Lovinger et al., 1985, 1986; Routtenberg and Lovinger, 1985). This change in the in vitro phosphorylation of GAP-43 has been suggested to be campal LTP (see section V.D) (Lovinger et al., 1985, 1986; Routtenberg and Lovinger, 1985). This change in the in vitro phosphorylation of GAP-43 has been suggested to be related to the changes in synaptic function observe 1986; Routtenberg and Lovinger, 1985). This change in<br>the in vitro phosphorylation of GAP-43 has been sug-<br>gested to be related to the changes in synaptic function<br>observed during LTP (for examples, see Lovinger et al.,<br>19 the in vitro phosphorylation of GAP-43 has been sug-<br>gested to be related to the changes in synaptic function<br>observed during LTP (for examples, see Lovinger et al.,<br>1986). However, it is unclear whether this phenomenon<br>is observed during LTP (for examples, see Lovinger et al., 1986). However, it is unclear whether this phenomenon is caused by changes in the state of phosphorylation of GAP-43 in situ and/or changes in the activities of memobserved during LTP (for examples, see Lovinger et al., 1986). However, it is unclear whether this phenomenon is caused by changes in the state of phosphorylation of GAP-43 in situ and/or changes in the activities of membr 1986). However, it is unclear whether this phenomenos is caused by changes in the state of phosphorylation GAP-43 in situ and/or changes in the activities of menomenound protein kinase C (Akers et al., 1986) protein phosph is caused by changes in the state of phosphorylation GAP-43 in situ and/or changes in the activities of me<br>brane-bound protein kinase C (Akers et al., 1986)<br>protein phosphatases following LTP. The recent obs<br>vation that th GAP-43 in situ and/or changes in the activities of membrane-bound protein kinase C (Akers et al., 1986) or protein phosphatases following LTP. The recent observation that the MARCKS protein, which is not specifically enric

PROTEIN PHOSPHORY<br>also incorporates more <sup>32</sup>P during in vitro phosphory<br>tion following LTP (Nelson et al., 1989) would su PROTEIN PHOSPHORYLATION<br>also incorporates more <sup>32</sup>P during in vitro phosphoryla-<br>tion following LTP (Nelson et al., 1989) would suggest<br>that changes in protein kinase C activity may be respon-**EXECUTE PROTEIN PHOSPHORYLA**<br>also incorporates more <sup>32</sup>P during in vitro phosphory<br>tion following LTP (Nelson et al., 1989) would sugge<br>that changes in protein kinase C activity may be respo<br>sible. The functional importa also incorporates more <sup>32</sup>P during in vitro phosphoryla-<br>tion following LTP (Nelson et al., 1989) would suggest<br>that changes in protein kinase C activity may be respon-<br>sible. The functional importance of this phenomenon also incorporates more <sup>32</sup>P during in vitro phosphoryla-<br>tion following LTP (Nelson et al., 1989) would suggest<br>that changes in protein kinase C activity may be respon-<br>sible. The functional importance of this phenomenon **LTP).** Fible. The functional importance of this phenomenon is<br>not understood (see section V.D for further discussion of<br>LTP).<br>*B. Use of Nerve Terminal Phosphoproteins to Study*<br>*Presynaptic Receptors President Conducted (see sect*<br> *Presynaptic Receptors*<br> *Presynaptic Receptors*<br> *Presynaptic Receptors* 

CHEP SERVIE THE USE of Nerve Terminal Phosphoproteins to Study<br>
Esynaptic Receptors<br>
Use of the phosphoproteins described above has al-<br>
Wed examination of presynaptic receptors coupled to b B. Use of Nerve Terminal Phosphoproteins to Study<br>
Presynaptic Receptors<br>
Use of the phosphoproteins described above has al-<br>
lowed examination of presynaptic receptors coupled to bind<br>
distinct second messenger-regulated Distinct Second messenger-regulated above has<br>lowed examination of presynaptic receptors coupled<br>istinct second messenger-regulated protein phosphoralistinct second messenger-regulated protein phosphoralism The synapsis described above has allowed examination of presynaptic receptors coupled to histinct second messenger-regulated protein phosphor-<br>ylation systems. Because the synapsins are specifically to<br>localized in presyna Use of the phosphoproteins described above has allowed examination of presynaptic receptors coupled to distinct second messenger-regulated protein phosphor ylation systems. Because the synapsins are specifically localized lowed examination of presynaptic receptors coupled to distinct second messenger-regulated protein phosphor-<br>ylation systems. Because the synapsins are specifically<br>localized in presynaptic terminals, transmitter-induced<br>ph distinct second messenger-regulated protein phosphor-<br>
1988 ylation systems. Because the synapsins are specifically<br>
localized in presynaptic terminals, transmitter-induced<br>
inhosphorylation of these proteins in isolated n ylation systems. Because the synapsins are specifically localized in presynaptic terminals, transmitter-induced phosphorylation of these proteins in isolated nerve terminals or preparations containing intact nerve cells an localized in presynaptic terminals, transmitter-induced<br>phosphorylation of these proteins in isolated nerve ter-<br>minals or preparations containing intact nerve cells and<br>fibers can be used to characterize presynaptic recep minals or preparations containing intact nerve cells and  $1988$ ). Several receptors that are located in the cell<br>fibers can be used to characterize presynaptic receptors nucleus, and which are regulated by phosphorylation minals or preparations containing intact nerve cells and<br>fibers can be used to characterize presynaptic receptors<br>capable of activating cyclic AMP-dependent protein ki-<br>nase, CaM kinase I or CaM kinase II. This approach ha fibers can be used to characterize presynaptic receptors<br>capable of activating cyclic AMP-dependent protein ki-<br>nase, CaM kinase I or CaM kinase II. This approach has<br>been used to demonstrate presynaptic receptors for se-<br> capable of activating cyclic AMP-dependent protein ki-<br>mase, CaM kinase I or CaM kinase II. This approach has<br>been used to demonstrate presynaptic receptors for se-<br>rotonin on nerve fibers in the facial motor nucleus (Dol nase, CaM kinase I or CaM kinase II. This approach has<br>been used to demonstrate presynaptic receptors for se-<br>rotonin on nerve fibers in the facial motor nucleus (Dol-<br>phin and Greengard, 1981a,b),  $\beta$ -adrenergic recepto been used to demonstrate presynaptic receptors for se-<br>rotonin on nerve fibers in the facial motor nucleus (Dol-<br>phin and Greengard, 1981a,b),  $\beta$ -adrenergic receptors on and<br>a large number of nerve terminals in the neoc rotonin on nerve fibers in the facial motor nucleus (Diplin and Greengard, 1981a,b),  $\beta$ -adrenergic receptors a large number of nerve terminals in the neocort (Mobley and Greengard, 1985), dopamine D1 and leverotors on h phin and Greengard, 1981a,b),  $\beta$ -adrenergic receptors on and<br>a large number of nerve terminals in the neocortex dis-<br>(Mobley and Greengard, 1985), dopamine D1 and D2 meet<br>receptors on hypothalamopituitary fibers in the a large number of nerve terminals in the neocortex<br>(Mobley and Greengard, 1985), dopamine D1 and D2<br>receptors on hypothalamopituitary fibers in the neuro-<br>hypophysis (Tsou and Greengard, 1982; Treiman and<br>Greengard, 1985) (Mobley and Greengard, 1985), dopamine D1 and D2 metaphoric receptors on hypothalamopituitary fibers in the neuro-<br>hypophysis (Tsou and Greengard, 1982; Treiman and field<br>Greengard, 1985), and dopamine D1 receptors on ner receptors on hypothalamopituitary fibers in the neuro-<br>hypophysis (Tsou and Greengard, 1982; Treiman and<br>Greengard, 1985), and dopamine D1 receptors on nerve<br>terminals in the superior cervical ganglion (Nestler and<br>Greenga hypophysis (Tsou and Greengard, Greengard, 1985), and dopamine D1<br>terminals in the superior cervical ga<br>Greengard, 1980, 1982b), the neostri<br>stantia nigra (Walaas et al., 1989e).<br>The MARCKS protein appears to reengard, 1985), and dopamine D1 receptors on nerve<br>rminals in the superior cervical ganglion (Nestler and<br>reengard, 1980, 1982b), the neostriatum, and the sub-<br>antia nigra (Walaas et al., 1989e).<br>The MARCKS protein appear

terminals in the superior cervical ganglion (Nestler and Greengard, 1980, 1982b), the neostriatum, and the substantia nigra (Walaas et al., 1989e).<br>The MARCKS protein appears to be widely, but unevenly, distributed in nerv Greengard, 1980, 1982b), the neostriatum, and the substantia nigra (Walaas et al., 1989e).<br>The MARCKS protein appears to be widely, but unevenly, distributed in nerve cells and terminals (Ouimet et al., 1990). Examination stantia nigra (Walaas et al., 1989e).<br>The MARCKS protein appears to be widely, but un-<br>evenly, distributed in nerve cells and terminals (Ouimet<br>et al., 1990). Examination of isolated nerve terminals<br>prelabeled with [<sup>32</sup>P] The MARCKS protein appears to be widely, but uneversity, distributed in nerve cells and terminals (Ouimet et al., 1990). Examination of isolated nerve terminals to prelabeled with  $[^{32}P]$ orthophosphate (Wang et al., 198 evenly, distributed in nerve cells and terminals (Ouimet et al., 1990). Examination of isolated nerve terminals prelabeled with  $[^{32}P]$ orthophosphate (Wang et al., 1988) has shown that phosphorylation of this protein, w et al., 1990). Examination of isolated nerve terminals<br>prelabeled with  $[^{32}P]$ orthophosphate (Wang et al., 1988)<br>has shown that phosphorylation of this protein, when<br>studied in such preparations, can be used to demonstr prelabeled with  $[^{32}P]$ orthophosphate (Wang et al., 1988)<br>has shown that phosphorylation of this protein, when<br>studied in such preparations, can be used to demonstrate<br>the presence of presynaptic  $\alpha_1$  adrenergic or mu has shown that phosphorylation of this protein, when<br>studied in such preparations, can be used to demonstrate<br>the presence of presynaptic  $\alpha_1$  adrenergic or muscarinic<br>receptors linked to protein kinase C activation (Au studied in such preparations, can be used to demonstra<br>the presence of presynaptic  $\alpha_1$  adrenergic or muscarin<br>receptors linked to protein kinase C activation (Audigi<br>et al., 1988; J. K. T. Wang, S. M. P. Audigier, and<br> the presence of presynaptic  $\alpha_1$  adrenergic or muscarinic receptors linked to protein kinase C activation (Audigier et al., 1988; J. K. T. Wang, S. M. P. Audigier, and P. Greengard, unpublished observations). Given the receptors linked to protein kinase C activation (Audigier cet al., 1988; J. K. T. Wang, S. M. P. Audigier, and P. p. Greengard, unpublished observations). Given the exclusive presynaptic localization of GAP-43 (Gispen et et al., 1988; J. K. T. Wang, S. M. P. Audigier, and P. p.<br>Greengard, unpublished observations). Given the exclu-<br>sive presynaptic localization of GAP-43 (Gispen et al.,<br>1985), this phosphoprotein should also prove useful Greengard, unpublished observations). Given the exclusive presynaptic localization of GAP-43 (Gispen et al., 1985), this phosphoprotein should also prove useful for analysis of presynaptic receptors linked to protein kinas **V. Phosphoprotein should also prove useful for alysis of presynaptic receptors linked to protein kinase activation (for examples, see van Hooff et al., 1989).<br><b>V. Phosphoproteins and Postsynaptic Function**<br>It is now shund alysis of presynaptic receptors linked to protein kinase<br>activation (for examples, see van Hooff et al., 1989).<br>V. Phosphoproteins and Postsynaptic Function<br>It is now abundantly clear that most, if not all, neu-<br>transmitte

C activation (for examples, see van Hooff et al., 1989). <br> **V. Phosphoproteins and Postsynaptic Function**<br>
It is now abundantly clear that most, if not all, neu-<br>
rotransmitter receptors and ion channels are regulated<br>
by V. Phosphoproteins and Postsynaptic Function<br>It is now abundantly clear that most, if not all, neu-<br>rotransmitter receptors and ion channels are regulated<br>by phosphorylation. Because most studies of receptors<br>and ion chann V. FROSPROPTOCETTS and FOSESYRAPCE FURCTION<br>It is now abundantly clear that most, if not all, neurotransmitter receptors and ion channels are regulated<br>by phosphorylation. Because most studies of receptors<br>and ion channels It is now abundantly clear that most, if not all, neu-<br>rotransmitter receptors and ion channels are regulated<br>by phosphorylation. Because most studies of receptors<br>and ion channels have been carried out on neuronal<br>somata, rotransmitter receptors and ion channels are regulated row phosphorylation. Because most studies of receptors  $t$  and ion channels have been carried out on neuronal  $t$  somata, this topic is discussed in this section. How and ion channels have been carried out on neurons<br>somata, this topic is discussed in this section. Howeve<br>it should be kept in mind that the principles elucidate<br>by the study of cell body receptors and ion channels an<br>prob somata, this topic is discussed in this<br>it should be kept in mind that the pr<br>by the study of cell body receptors an<br>probably generally applicable to recep<br>nels on dendrites and axon terminals.

### *A. Regulation of Receptor Function*

Three general classes of plasma membrane receptors<br>have so far been defined in brain (table 7), all of which AND NEURONAL FUNCTION 319<br>
A. Regulation of Receptor Function<br>
Three general classes of plasma membrane receptors<br>
have so far been defined in brain (table 7), all of which<br>
appear to be associated with protein phosphoryla A. Regulation of Receptor Function<br>Three general classes of plasma membrane receptors<br>have so far been defined in brain (table 7), all of which<br>appear to be associated with protein phosphorylation<br>systems (Benovic and Lefk First degree and classes of plasma membrane receptors<br>have so far been defined in brain (table 7), all of which<br>appear to be associated with protein phosphorylation<br>systems (Benovic and Lefkowitz, 1987; Huganir and<br>Greenga Three general classes of plasma membrane receptors<br>have so far been defined in brain (table 7), all of which<br>appear to be associated with protein phosphorylation<br>systems (Benovic and Lefkowitz, 1987; Huganir and<br>Greengard, have so far been defined in brain (table 7), all of which<br>appear to be associated with protein phosphorylation<br>systems (Benovic and Lefkowitz, 1987; Huganir and<br>Greengard, 1987, 1990). One of these is represented by<br>those appear to be associated with protein phosphorylation<br>systems (Benovic and Lefkowitz, 1987; Huganir and<br>Greengard, 1987, 1990). One of these is represented by<br>those receptors that are directly coupled to and may be<br>an integ systems (Benovic and Lefkowitz, 1987; Huganir and Greengard, 1987, 1990). One of these is represented by those receptors that are directly coupled to and may be an integral part of an ion channel (Grenningloh et al., 1987; Greengard, 1987, 1990). One of these is represented<br>those receptors that are directly coupled to and may<br>an integral part of an ion channel (Grenningloh et a<br>1987; Schofield et al., 1987; Betz, 1990). Another class<br>represe those receptors that are directly coupled to and may be<br>an integral part of an ion channel (Grenningloh et al.,<br>1987; Schofield et al., 1987; Betz, 1990). Another class is<br>represented by receptors coupled to G-proteins (GT an integral part of an ion channel (Grenningloh et al., 1987; Schofield et al., 1987; Betz, 1990). Another class is represented by receptors coupled to G-proteins (GTP-binding proteins) (Gilman, 1987; Benovic and Lefkowitz 1987; Schofield et al., 1987; Betz, 1990). Another class is represented by receptors coupled to G-proteins (GTP binding proteins) (Gilman, 1987; Benovic and Lefkowitz 1987), and a third class is represented by those recept represented by receptors coupled to G-proteins (GTP-<br>binding proteins) (Gilman, 1987; Benovic and Lefkowitz,<br>1987), and a third class is represented by those receptors<br>that transduce information through activation of tyrobinding proteins) (Gilman, 1987; Benovic and Lefkowitz, 1987), and a third class is represented by those receptors that transduce information through activation of tyrosine-specific protein kinase activity, which often is 1987), and a third class is represented by those receptors<br>that transduce information through activation of tyro-<br>sine-specific protein kinase activity, which often is an<br>integral part of the receptor itself (Yarden and Ul that transduce information through activation of ty<br>sine-specific protein kinase activity, which often is<br>integral part of the receptor itself (Yarden and Ullri<br>1988). Several receptors that are located in the q<br>nucleus, a integral part of the receptor itself (Yarden and Ullrich.

**12. Several part of the receptor itself (Yarden and Ullrich,**<br> **881). Several receptors that are located in the cell**<br> **12. Ion channel-coupled receptors. Recent studies have**<br> **11. Ion channel-coupled receptors.** Recent 1988). Several receptors that are located in the cell<br>nucleus, and which are regulated by phosphorylation,<br>will also be mentioned.<br>*1. Ion channel-coupled receptors*. Recent studies have<br>demonstrated that some major ion ch nucleus, and which are regulated by phosphorylation<br>will also be mentioned.<br>1. Ion channel-coupled receptors. Recent studies have<br>demonstrated that some major ion channel-coupled receptors<br>(i.e., the GABA<sub>A</sub>, glycine, nico will also be mentioned.<br>
1. Ion channel-coupled receptors. Recent studies have<br>
demonstrated that some major ion channel-coupled re-<br>
ceptors (i.e., the GABA<sub>A</sub>, glycine, nicotinic acetylcholine,<br>
and, possibly, different and, possibly, different types of glutamate receptors) display considerable similarities in their structures and membrane topologies and appear to belong to the same demonstrated that some major ion channel-coupled receptors (i.e., the GABA<sub>A</sub>, glycine, nicotinic acetylcholine, and, possibly, different types of glutamate receptors) display considerable similarities in their structures ceptors (i.e., the GABA<sub>A</sub>, glycine, nicotinic acetylcholis<br>and, possibly, different types of glutamate receptor<br>display considerable similarities in their structures a<br>membrane topologies and appear to belong to the sar<br>g and, possibly, different types of glutamate receptors)<br>display considerable similarities in their structures and<br>membrane topologies and appear to belong to the same<br>gene superfamily of chemically gated ion channels (Schodisplay considerable similarities in their structures and<br>membrane topologies and appear to belong to the same<br>gene superfamily of chemically gated ion channels (Scho-<br>field et al., 1987; Grenningloh et al., 1987; Barnard membrane topologies and appear to belong to the same<br>gene superfamily of chemically gated ion channels (Scho-<br>field et al., 1987; Grenningloh et al., 1987; Barnard et al.,<br>1987; Betz, 1990). Although most, and possibly all gene superfamily of chemically gated ion channels (Scho-<br>field et al., 1987; Grenningloh et al., 1987; Barnard et al.,<br>1987; Betz, 1990). Although most, and possibly all, of<br>these receptors are regulated by phosphorylation field et al., 1987; Grenningloh et al., 1987; Barnard et al., 1987; Betz, 1990). Although most, and possibly all, of these receptors are regulated by phosphorylation (for reviews, see Huganir and Greengard, 1987, 1990), th these receptors are regulated by phosphorylation (for reviews, see Huganir and Greengard, 1987, 1990), the regulation of the nicotinic acetylcholine receptor and the GABA<sub>A</sub> receptor by phosphorylation has been most thor-o reviews, see Huganir and Greengard, 1987, 1990), the  $GABA_A$  receptor by phosphorylation has been most thorgulation of the nicotinic acetylcholine receptor and the ABA<sub>A</sub> receptor by phosphorylation has been most thor ghly studied. We will, therefore, restrict our discussion these receptor types.<br>The *nicotinic acetylcholine re* 

by phosphorylation. Because most studies of receptors that the nicotinic receptor can be phosphorylated on a<br>and ion channels have been carried out on neuronal total of seven sites. It appears that these phosphorylation<br>so  $GABA_A$  receptor by phosphorylation has been most thoroughly studied. We will, therefore, restrict our discussion<br>to these receptor types.<br>The *nicotinic acetylcholine receptor* from *Torpedo* elec-<br>tric organ has been stud oughly studied. We will, therefore, restrict our discussi<br>to these receptor types.<br>The *nicotinic acetylcholine receptor* from *Torpedo* ele<br>tric organ has been studied extensively (for review, s<br>Changeux et al., 1984). Th to these receptor types.<br>The *nicotinic acetylcholine receptor* from *Torpedo* electric organ has been studied extensively (for review, see Changeux et al., 1984). This receptor, which is a pentameric complex, consists of The *nicotinic acetylcholine receptor* from *Torpedo* electric organ has been studied extensively (for review, see Changeux et al., 1984). This receptor, which is a pentameric complex, consists of four types of subunits, tric organ has been studied extensively (for review, se Changeux et al., 1984). This receptor, which is a pentameric complex, consists of four types of subunits, terme  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ . Postsynaptic membranes fr Changeux et al., 1984). This receptor, which is a pent<br>meric complex, consists of four types of subunits, term<br> $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ . Postsynaptic membranes from *Torpe*<br>contain at least three protein kinases capable meric complex, consists of four types of subunits, termed  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ . Postsynaptic membranes from *Torpedo* contain at least three protein kinases capable of phosphorylating this receptor, i.e., cyclic AMP  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ . Postsynaptic membranes from *Torpedo*<br>contain at least three protein kinases capable of phos-<br>phorylating this receptor, i.e., cyclic AMP-dependent<br>protein kinase, protein kinase C, and an endo contain at least three protein kinases capable of phos-<br>phorylating this receptor, i.e., cyclic AMP-dependent<br>protein kinase, protein kinase C, and an endogenous<br>tyrosine-specific protein kinase immunologically related<br>to phorylating this receptor, i.e., cyclic AMP-dependent<br>protein kinase, protein kinase C, and an endogenous<br>tyrosine-specific protein kinase immunologically related<br>to pp60<sup>c-rrc</sup> (Huganir and Greengard, 1983; Huganir et<br>al protein kinase, protein kinase C, and an endogenous<br>tyrosine-specific protein kinase immunologically related<br>to pp60<sup>c-src</sup> (Huganir and Greengard, 1983; Huganir et<br>al., 1983, 1984; Safran et al., 1987). The cyclic AMP-<br>d tyrosine-specific protein kinase immunologically related<br>to pp60<sup>c-m</sup> (Huganir and Greengard, 1983; Huganir et<br>al., 1983, 1984; Safran et al., 1987). The cyclic AMP-<br>dependent protein kinase phosphorylates the  $\gamma$ - and to pp60<sup>c-src</sup> (Huganir and Greengard, 1983; Huganir et al., 1983, 1984; Safran et al., 1987). The cyclic AMP-<br>dependent protein kinase phosphorylates the  $\gamma$ - and  $\delta$ -<br>subunits, protein kinase C phosphorylates the  $\delta$ al., 1983, 1984; Safran et al., 1987). The cyclic AMP-<br>dependent protein kinase phosphorylates the  $\gamma$ - and  $\delta$ -<br>subunits, protein kinase C phosphorylates the  $\delta$ - and,<br>more slowly, the  $\alpha$ -subunits, and the protein t dependent protein kinase phosphorylates the  $\gamma$ - and  $\delta$ -<br>subunits, protein kinase C phosphorylates the  $\delta$ - and,<br>more slowly, the  $\alpha$ -subunits, and the protein tyrosine<br>kinase phosphorylates the  $\beta$ -,  $\gamma$ -, and  $\delta$ subunits, protein kinase C phosphorylates the  $\delta$ - and,<br>more slowly, the  $\alpha$ -subunits, and the protein tyrosine<br>kinase phosphorylates the  $\beta$ -,  $\gamma$ -, and  $\delta$ -subunits of this<br>receptor. These phosphorylation sites are more slowly, the  $\alpha$ -subunits, and the protein tyrosine<br>kinase phosphorylates the  $\beta$ -,  $\gamma$ -, and  $\delta$ -subunits of this<br>receptor. These phosphorylation sites are all distinct, so<br>that the nicotinic receptor can be phos kinase phosphorylates the  $\beta$ -,  $\gamma$ -, and  $\delta$ -subunits of this receptor. These phosphorylation sites are all distinct, so that the nicotinic receptor can be phosphorylated on a total of seven sites. It appears that the receptor. These phosphorylation sites are all distinct, so that the nicotinic receptor can be phosphorylated on<br>total of seven sites. It appears that these phosphorylatio<br>sites are all located in homologous regions in the majo<br>intracellular loop of the subunits and that multiple p total of seven sites. It appears that these phosphorylation<br>sites are all located in homologous regions in the major<br>intracellular loop of the subunits and that multiple phos-<br>phorylation sites within a loop are located in sites are all located in homologous regions in the mintracellular loop of the subunits and that multiple phorylation sites within a loop are located in close pimity to each other (for reviews, see Huganir, 1987; M<br>and Huga

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\* Summary of major types of transmitter receptors regulated by protein phosphorylation. Data compiled from: Huganir and Greengard (1990), **Summary of major types of transmit**<br>Benovic et al. (1988), Roeen (1987), Sor<br>others as in legend to Tables 1 and 2. Summary of major types of transmitter receptors regulated by protein phoroic et al. (1988), Rosen (1987), Song and Huang (1990). Abbreviations:<br>ners as in legend to Tables 1 and 2.<br>The functional consequences of phosphoryl phosphorylation. Data compiled from: Huganir and Greengard (1990), increases the rate of receptor desensitization, and stimulates the phosphorylation of the nicotinic acetyl-

numery of al. (1988), Rosen (1987), Song and Huang (1990). Abbreviations as in legend to Tables 1 and 2.<br>The functional consequences of phosphorylation of the nicotinic cholinergic receptor have been examined. Reconstitute others as in legend to Tables 1 and 2.<br>The functional consequences of phosphorylation of the<br>micotinic cholinergic receptor have been examined. Re-<br>constituted receptor that had been phosphorylated either<br>by the cyclic AMP The functional consequences of phosphorylation of the 19<br>nicotinic cholinergic receptor have been examined. Re-<br>constituted receptor that had been phosphorylated either che<br>by the cyclic AMP-dependent protein kinase or by The functional consequences of phosphorylation of the<br>nicotinic cholinergic receptor have been examined. Re-<br>constituted receptor that had been phosphorylated either<br>chy the cyclic AMP-dependent protein kinase or by the<br>en micotinic cholinergic receptor have been examined. Reconstituted receptor that had been phosphorylated either<br>by the cyclic AMP-dependent protein kinase or by the<br>endogenous protein tyrosine kinase was used, and it was<br>fou constituted receptor that had been phosphorylated either cheapthy the cyclic AMP-dependent protein kinase or by the AM<br>endogenous protein tyrosine kinase was used, and it was Mi<br>found that the phosphorylated receptor displ by the cyclic AMP-dependent protein kinase or by the endogenous protein tyrosine kinase was used, and it was found that the phosphorylated receptor displayed a severalfold increase in the rate of rapid desensitization, the endogenous protein tyrosine kinase was used, and it was<br>found that the phosphorylated receptor displayed a sev-<br>eralfold increase in the rate of rapid desensitization, the<br>process by which the receptor is inactivated in th found that the phosphorylated receptor displayed a severalfold increase in the rate of rapid desensitization, the process by which the receptor is inactivated in the presence of acetylcholine (Huganir et al., 1986; Hopfiel eralfold increase in the rate of rapid desensitization, the process by which the receptor is inactivated in the presence of acetylcholine (Huganir et al., 1986; Hopfield et al., 1988). Because similar desensitizations were process by which the receptor is inactivated in the presence of acetylcholine (Huganir et al., 1986; Hopfield et al., 1988). Because similar desensitizations were brought about by forskolin or phorbol esters in rat primary ence of acetylcholine (Huganir et al., 1986; Hopfield et al., 1988). Because similar desensitizations were brought about by forskolin or phorbol esters in rat primary myotube cultures (Middleton et al., 1986, 1988; Mulle e al., 1988). Because similar desensitizations were brought<br>about by forskolin or phorbol esters in rat primary my-<br>otube cultures (Middleton et al., 1986, 1988; Mulle et al.,<br>1988; Eusebi et al., 1985), it appears that pho about by forskolin or phorbol esters in rat primary my-<br>otube cultures (Middleton et al., 1986, 1988; Mulle et al.,<br>1988; Eusebi et al., 1985), it appears that phosphorylation<br>of the muscle-type receptor is involved in the otube cultures (Middleton et al., 1986, 1988; Mulle et al., 1988; Eusebi et al., 1985), it appears that phosphorylation of the muscle-type receptor is involved in the regulation of desensitization in situ (Steinbach and Ze 1988; Eusebi et al., 1985), it appears that phosphoryla<br>of the muscle-type receptor is involved in the regula<br>of desensitization in situ (Steinbach and Zempel, 1<br>Huganir and Greengard, 1987; 1990; Smith et al., 19<br>This pro of the muscle-type receptor is involved in the regulation<br>of desensitization in situ (Steinbach and Zempel, 1987;<br>Huganir and Greengard, 1987; 1990; Smith et al., 1989).<br>This probably also holds true for tyrosine kinase-m of desensitization in situ (Steinbach and Zempel, 198<br>Huganir and Greengard, 1987; 1990; Smith et al., 1989<br>This probably also holds true for tyrosine kinase-me<br>diated phosphorylation, because phosphorylation by th<br>latter Huganir and Greengard, 1987; 1990; Smith et al., 1989).<br>
This probably also holds true for tyrosine kinase-me-<br>
diated phosphorylation, because phosphorylation by the<br>
latter kinase appears to occur between the sites phos This probably also holds true for tyrosine kinase-me-<br>diated phosphorylation, because phosphorylation by the<br>latter kinase appears to occur between the sites phos-<br>phorylated by cyclic AMP-dependent protein kinase and<br>by diated phosphorylation, because phosphorylation by the<br>latter kinase appears to occur between the sites phos-<br>phorylated by cyclic AMP-dependent protein kinase and<br>by protein kinase C, at least on the  $\delta$ -subunit (Hugani latter kinase appears to occur between the sites phos-<br>phorylated by cyclic AMP-dependent protein kinase and<br>by protein kinase C, at least on the  $\delta$ -subunit (Huganii<br>and Greengard, 1990). In contrast, recent data indica matter anal act provided by cyclic AMP-dependent protein kinase and<br>by protein kinase C, at least on the  $\delta$ -subunit (Huganir<br>and Greengard, 1990). In contrast, recent data indicate<br>that cyclic AMP-dependent phosphorylat by protein kinase C, at least on the  $\delta$ -subunit (Huganir and Greengard, 1990). In contrast, recent data indicate that cyclic AMP-dependent phosphorylation of a neuronal acetylcholine receptor  $\alpha$ -type subunit increases and Greengard, 1990). In contrast, recent data indicat<br>that cyclic AMP-dependent phosphorylation of a neu<br>ronal acetylcholine receptor  $\alpha$ -type subunit increases the<br>response to ligand binding (Vijayaraghavan et al., 199 that cyclic AMP-dependent phosphorylation of a ne<br>ronal acetylcholine receptor  $\alpha$ -type subunit increases the<br>response to ligand binding (Vijayaraghavan et al., 1990<br>Hence, phosphorylation of distinct isoforms of the nic nal acetylcholine receptor  $\alpha$ -type subunit increassponse to ligand binding (Vijayaraghavan et al., ence, phosphorylation of distinct isoforms of the neurotrans of the neurotransmit-<br>Determination of the identities of th response to ligand binding (Vijayaraghavan et al., 1990)<br>Hence, phosphorylation of distinct isoforms of the nico-<br>tinic receptor may induce different types of responses.<br>Determination of the identities of the neurotransmit

Hence, phosphorylation of distinct isoforms of the nicotinic receptor may induce different types of responses.<br>Determination of the identities of the neurotransmitter(s) or hormone(s) responsible for the physiological regu tinic receptor may induce different types of responses.<br>Determination of the identities of the neurotransmit-<br>ter(s) or hormone(s) responsible for the physiological<br>regulation of the activity of the three protein kinases<br>t Determination of the identities of the neurotransmit<br>ter(s) or hormone(s) responsible for the physiologica<br>regulation of the activity of the three protein kinase<br>that phosphorylate the nicotinic acetylcholine recepto<br>is cu ter(s) or hormone(s) responsible for the physiological regulation of the activity of the three protein kinases<br>that phosphorylate the nicotinic acetylcholine receptor<br>is currently the subject of investigation in several la regulation of the activity of the three protein kinases<br>that phosphorylate the nicotinic acetylcholine receptor<br>is currently the subject of investigation in several labo-<br>ratories. In muscle cells, calcitonin gene-related that phosphorylate the nicotinic acetylcholine receptor<br>is currently the subject of investigation in several labo-<br>ratories. In muscle cells, calcitonin gene-related peptide,<br>a cotransmitter with acetylcholine in motor neu

bhosphorylation. Data complied from: Figure and Greengard (193 $\pi$ ) ons:  $\beta$ -ARK,  $\beta$ -adrenergic receptor kinase; insulin-R, insulin recept<br>1987), increases the rate of receptor desensitization, a<br>stimulates the phospho 1987), increases the rate of receptor desensitization, and<br>stimulates the phosphorylation of the nicotinic acetyl-<br>choline receptor on the same subunits as does cyclic<br>AMP-dependent protein kinase (Miles et al., 1987, 1989 1987), increases the rate of receptor desensitization, and<br>stimulates the phosphorylation of the nicotinic acetyl-<br>choline receptor on the same subunits as does cyclic<br>AMP-dependent protein kinase (Miles et al., 1987, 1989 1987), increases the rate of receptor desensitization, and<br>stimulates the phosphorylation of the nicotinic acetyl-<br>choline receptor on the same subunits as does cyclic<br>AMP-dependent protein kinase (Miles et al., 1987, 198 stimulates the phosphorylation of the nicotinic acetyl-<br>choline receptor on the same subunits as does cyclic<br>AMP-dependent protein kinase (Miles et al., 1987, 1989-<br>Mulle et al., 1988). Other evidence suggests that acetylcholine receptor on the same subunits as does cyclic<br>AMP-dependent protein kinase (Miles et al., 1987, 1989;<br>Mulle et al., 1988). Other evidence suggests that acetyl-<br>choline, by causing both Ca<sup>2+</sup> influx and diacylglycer AMP-dependent protein kinase (Miles et al., 1987, 1989;<br>Mulle et al., 1988). Other evidence suggests that acetyl-<br>choline, by causing both  $Ca^{2+}$  influx and diacylglycerol<br>formation through activation of muscarinic and p Mulle et al., 1988). Other evidence suggests that acetyl-<br>choline, by causing both Ca<sup>2+</sup> influx and diacylglycerol<br>formation through activation of muscarinic and possibly<br>nicotinic acetylcholine receptors, causes the acti choline, by causing both Ca<sup>2+</sup> influx and diacylglycerol formation through activation of muscarinic and possibly nicotinic acetylcholine receptors, causes the activation of protein kinase C and thereby the phosphorylation formation through activation of muscarinic and possibly<br>nicotinic acetylcholine receptors, causes the activation<br>of protein kinase C and thereby the phosphorylation of<br>the nicotinic acetylcholine receptor (Adamo et al., 19 micotinic acetylcholine receptors, causes the activation<br>of protein kinase C and thereby the phosphorylation of<br>the nicotinic acetylcholine receptor (Adamo et al., 1985;<br>Miles, Huganir, and Greengard, cited in Huganir and<br> of protein kinase C and thereby the phosphorylation of<br>the nicotinic acetylcholine receptor (Adamo et al., 1985;<br>Miles, Huganir, and Greengard, cited in Huganir and<br>Greengard, 1990). The nature of the first messenger<br>respo the nicotinic acetylcholine receptor (Adamo et al., 1985;<br>Miles, Huganir, and Greengard, cited in Huganir and<br>Greengard, 1990). The nature of the first messenger<br>responsible for the activation of the protein tyrosine<br>kinas Miles, Huganir, and Greengard, cited in Huganir and Greengard, 1990). The nature of the first messenger responsible for the activation of the protein tyrosine kinase that phosphorylates the nicotinic acetylcholine recepto reengard, 1990). The nature of the first messenger<br>sponsible for the activation of the protein tyrosine<br>nase that phosphorylates the nicotinic acetylcholine<br>ceptor has not yet been determined (Qu et al., 1990).<br>The  $GABA_A$  Signal transduction<br>
Down-regulation<br>
Down-regulation<br>
Down-regulation<br>
Down-regulation<br>
one:  $\beta$ -ARK,  $\beta$ -adrenergic receptor kinase; insulin-R, insulin receptor;<br>
1987), increases the rate of receptor desensitization,

responsible for the activation of the protein tyrosine<br>kinase that phosphorylates the nicotinic acetylcholine<br>receptor has not yet been determined (Qu et al., 1990).<br>The  $GABA_A$  receptor from rat brain consists of  $\alpha$ - and kinase that phosphorylates the nicotinic acetylcholine<br>receptor has not yet been determined (Qu et al., 1990).<br>The  $GABA_A$  receptor from rat brain consists of  $\alpha$ - and<br> $\beta$ -subunits, and molecular cloning has shown that se The  $GABA_A$  receptor from rat brain consists of  $\alpha$ - and  $\beta$ -subunits, and molecular cloning has shown that seven isoforms of these subunits exist (for review, see Ols and Towbin, 1990). This receptor also appears to orga  $\beta$ -subunits, and molecular cloning has shown that several<br>isoforms of these subunits exist (for review, see Olsen<br>and Towbin, 1990). This receptor also appears to be<br>organized in a pentameric structure, the  $\alpha$ - and  $\$ isoforms of these subunits exist (for review, see Olsen<br>and Towbin, 1990). This receptor also appears to be<br>organized in a pentameric structure, the  $\alpha$ - and  $\beta$ -sub-<br>units apparently having four transmembrane domains<br>a and Towbin, 1990). This receptor also appears to be organized in a pentameric structure, the  $\alpha$ - and  $\beta$ -sub-<br>units apparently having four transmembrane domains and displaying membrane topologies similar to those of<br>th organized in a pentameric structure, the  $\alpha$ - and  $\beta$ -sub-<br>units apparently having four transmembrane domains<br>and displaying membrane topologies similar to those of<br>the nicotinic acetylcholine receptor. Moreover, clones units apparently having four transmembrane domains<br>and displaying membrane topologies similar to those of<br>the nicotinic acetylcholine receptor. Moreover, clones for<br>additional  $\gamma$ - and  $\delta$ -subunits have also been report and displaying membrane topologies similar to those<br>the nicotinic acetylcholine receptor. Moreover, clones f<br>additional  $\gamma$ - and  $\delta$ -subunits have also been report<br>(Olsen and Towbin, 1990). There are predicted consens<br>s the nicotinic acetylcholine receptor. Moreover, clones for additional  $\gamma$ - and  $\delta$ -subunits have also been reported (Olsen and Towbin, 1990). There are predicted consensus sequences for phosphorylation by cyclic AMP-dep additional  $\gamma$ - and  $\delta$ -subunits have also been reported<br>(Olsen and Towbin, 1990). There are predicted consensus<br>sequences for phosphorylation by cyclic AMP-dependent<br>protein kinase and by protein kinase C in the  $\alpha$ - (Olsen and Towbin, 1990). There are predicted consensus<br>sequences for phosphorylation by cyclic AMP-dependent<br>protein kinase and by protein kinase C in the  $\alpha$ - and  $\beta$ -<br>subunits, and a  $\gamma$ -subunit clone has demonstrat sequences for phosphorylation by cyclic AMP-dependent<br>protein kinase and by protein kinase C in the  $\alpha$ - and  $\beta$ -<br>subunits, and a  $\gamma$ -subunit clone has demonstrated a<br>predicted consensus sequence for protein tyrosine k protein kinase and by protein kinase C in the  $\alpha$ - and  $\beta$ -<br>subunits, and a  $\gamma$ -subunit clone has demonstrated a<br>predicted consensus sequence for protein tyrosine ki-<br>nases (Olsen and Towbin, 1990). Studies of the puri subunits, and a  $\gamma$ -subunit clone has demonstrated a<br>predicted consensus sequence for protein tyrosine ki-<br>nases (Olsen and Towbin, 1990). Studies of the purified<br>GABA<sub>A</sub> receptor have shown that it is phosphorylated<br>whe predicted consensus sequence for protein tyrosine kinases (Olsen and Towbin, 1990). Studies of the purified GABA<sub>A</sub> receptor have shown that it is phosphorylated when incubated with either cyclic AMP-dependent protein kina nases (Olsen and Towbin, 1990). Studies of the pu<br>GABA<sub>A</sub> receptor have shown that it is phosphor<br>when incubated with either cyclic AMP-dependen<br>tein kinase (Kirkness et al., 1989), protein kin<br>(Browning et al., 1990), an  $GABA_A$  receptor have shown that it is phosphorylated when incubated with either cyclic AMP-dependent protein kinase (Kirkness et al., 1989), protein kinase C (Browning et al., 1990), and a second messenger-independent prot 1988).

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which constitutes a ligand-gated Cl<sup>-</sup> channel (Schofield PROTEIN PHOSPHORYLATION A<br>The functional properties of the GABA<sub>A</sub> receptor, twhich constitutes a ligand-gated Cl<sup>-</sup> channel (Schofield a<br>et al., 1987; Olsen and Towbin, 1990), are also regulated in PROTEIN PHOSPHORYLATION A<br>
The functional properties of the GABA<sub>A</sub> receptor, to<br>
which constitutes a ligand-gated Cl<sup>-</sup> channel (Schofield a<br>
et al., 1987; Olsen and Towbin, 1990), are also regulated in<br>
by phosphorylatio The functional properties of the  $GABA_A$  receptor, te<br>which constitutes a ligand-gated  $Cl^-$  channel (Schofield al<br>et al., 1987; Olsen and Towbin, 1990), are also regulated in<br>by phosphorylation (Stelzer et al., 1988). Activ The functional properties of the GABA<sub>A</sub> receptor, to<br>which constitutes a ligand-gated Cl<sup>-</sup> channel (Schofield al<br>et al., 1987; Olsen and Towbin, 1990), are also regulated in<br>by phosphorylation (Stelzer et al., 1988). Ac which constitutes a ligand-gated Cl<sup>-</sup> channel (Schofield<br>et al., 1987; Olsen and Towbin, 1990), are also regulated<br>by phosphorylation (Stelzer et al., 1988). Activation of<br>cyclic AMP-dependent protein kinase has been repo et al., 1987; Olsen and Towbin, 1990), are also regulated in the observation (Stelzer et al., 1988). Activation of cyclic AMP-dependent protein kinase has been reported to increase the rate of desensitization of the recept by phosphorylation (Stelzer et al., 1988). Activatio<br>cyclic AMP-dependent protein kinase has been repo<br>to increase the rate of desensitization of the recep<br>analogous to the observations made with the nico<br>acetylcholine rec cyclic AMP-dependent protein kinase has been reported tists to increase the rate of desensitization of the receptor, analogous to the observations made with the nicotinic to acetylcholine receptor (Tehrani et al., 1989; He to increase the rate of desensitization of the receptor,<br>analogous to the observations made with the nicotinic to<br>acetylcholine receptor (Tehrani et al., 1989; Heuschnei-A<br>der and Schwartz, 1989). Moreover, activation of p analogous to the observations made with the nicotinic tor<br>acetylcholine receptor (Tehrani et al., 1989; Heuschnei-AM<br>der and Schwartz, 1989). Moreover, activation of protein nov<br>kinase C by phorbol esters decreased the am acetylcholine receptor (Tehrani et al., 1989; Heuschnei-<br>der and Schwartz, 1989). Moreover, activation of protein<br>kinase C by phorbol esters decreased the amplitude of<br>the GABA<sub>A</sub> receptor current in oocytes expressing io der and Schwartz, 1989). Moreover, activation of previous kinase C by phorbol esters decreased the amplituthe GABA<sub>A</sub> receptor current in oocytes expressinchannels from total messenger RNA from chick fore (Sigel and Baur, channels from total messenger RNA from chick forebrain annels from total messenger RNA from chick forebrair<br>igel and Baur, 1988). Thus, both cyclic AMP-depend<br>t protein kinase and protein kinase C may regulate the<br>tivity of the GABA<sub>A</sub> receptor.<br>2. *G-protein-coupled receptors* 

(Sigel and Baur, 1988). Thus, both cyclic AMP-dependent protein kinase and protein kinase C may regulate the and activity of the GABA<sub>A</sub> receptor. dis<br>activity of the GABA<sub>A</sub> receptors. Recent evidence indi-<br>2. G-proteinent protein kinase and protein kinase C may regulate the activity of the GABA<sub>A</sub> receptor.<br>2. *G-protein-coupled receptors*. Recent evidence indicates that most or all G-protein-coupled receptors are single polypeptides t activity of the GABA<sub>A</sub> receptor.<br>
2. *G-protein-coupled receptors*. Recent evidence indicates that most or all G-protein-coupled receptors are<br>
single polypeptides that traverse the plasma membrane<br>
seven times (for exam 2. *G-protein-coupled receptors*. Recent evidence indicates that most or all G-protein-coupled receptors are single polypeptides that traverse the plasma membrane seven times (for examples, see Dohlman et al., 1987a,b; Hal cates that most or all G-protein-coupled receptors are<br>single polypeptides that traverse the plasma membrane<br>seven times (for examples, see Dohlman et al., 1987a,b;<br>Hall, 1987). These receptors, which include, inter alia,<br> single polypeptides that traverse the plasma membra<br>seven times (for examples, see Dohlman et al., 1987a<br>Hall, 1987). These receptors, which include, inter al<br>adrenergic receptors, dopamine receptors, muscarin<br>acetylcholin seven times (for examples, see Dohlman et al., 1987a,b;<br>Hall, 1987). These receptors, which include, inter alia,<br>adrenergic receptors, dopamine receptors, muscarinic<br>acetylcholine receptors, serotonin receptors, and tachy-Hall, 1987). These receptors, which include, inter alia<br>adrenergic receptors, dopamine receptors, muscarinia<br>acetylcholine receptors, serotonin receptors, and tachy<br>kinin receptors, do not themselves contain the machinery<br> adrenergic receptors, dopamine receptors, muscarinic<br>acetylcholine receptors, serotonin receptors, and tachy-<br>kinin receptors, do not themselves contain the machinery<br>for transduction of the signal across the membrane.<br>Ins acetylcholine receptors, serotonin receptors, and tachy-<br>kinin receptors, do not themselves contain the machinery<br>for transduction of the signal across the membrane.<br>Instead, these receptors interact with and activate varkinin receptors, do not themselves contain the machinery<br>for transduction of the signal across the membrane. courselns<br>discussions (G-proteins), which in turn can interact with add<br>and regulate enzymes such as adenylyl cyc for transduction of the signal across the membrane.<br>Instead, these receptors interact with and activate various membrane-associated guanine nucleotide-binding<br>proteins (G-proteins), which in turn can interact with<br>and regu Instead, these receptors interact with and activate var-<br>ious membrane-associated guanine nucleotide-binding<br>proteins (G-proteins), which in turn can interact with ad<br>and regulate enzymes such as adenylyl cyclase or phos-<br> proteins (G-proteins), which in turn can interact with a<br>and regulate enzymes such as adenylyl cyclase or phos-<br>pholipase C, or other types of effector systems such as<br>pion channels (Rodbell, 1980; Gilman, 1987). Although and regulate enzymes such as adenylyl cyclase or phospholipase C, or other types of effector systems such as<br>ion channels (Rodbell, 1980; Gilman, 1987). Although<br>most, and possibly all, of these receptors are regulated<br>by pholipase C, or other types of effector systems such as pose<br>ion channels (Rodbell, 1980; Gilman, 1987). Although (Ku<br>most, and possibly all, of these receptors are regulated Pau<br>by phosphorylation, the regulation of the ion channels (Rodbell, 1980; Gilman, 1987). Although (K<br>most, and possibly all, of these receptors are regulated Pa<br>by phosphorylation, the regulation of the  $\beta$ -adrenergic ph<br>receptor and the muscarinic acetylcholine re receptor and the muscarinic acetylcholine receptor by<br>phosphorylation has been most thoroughly studied. We<br>will, therefore, restrict most of our discussion to these<br>receptor types.<br>The  $\beta$ -adrenergic receptor, the protot ceptor and the muscarinic acetylcholine receptor losphorylation has been most thoroughly studied. V<br>II, therefore, restrict most of our discussion to the<br>ceptor types.<br>The  $\beta$ -*adrenergic receptor*, the prototype of this phosphorylation has been most thoroughly studied. Whill, therefore, restrict most of our discussion to the receptor types.<br>The  $\beta$ -*adrenergic receptor*, the prototype of this receptor class, can be phosphorylated by bot

will, therefore, restrict most of our discussion to these since<br>eptor types. The  $\beta$ -adrenergic receptor, the prototype of this recep-<br>tor class, can be phosphorylated by both cyclic AMP-<br>dependent protein kinase and by receptor types. The  $\beta$ -adrenergic receptor, the prototype of this receptor class, can be phosphorylated by both cyclic AMP-<br>dependent protein kinase and by protein kinase C, as well as by a newly discovered protein kina The  $\beta$ -adrenergic receptor, the prototype of this receptor class, can be phosphorylated by both cyclic AMP-<br>dependent protein kinase and by protein kinase C, as<br>well as by a newly discovered protein kinase specific for<br> tor class, can be phosphorylated by both cyclic AMP-<br>dependent protein kinase and by protein kinase C, as<br>well as by a newly discovered protein kinase specific for<br>the agonist-occupied receptor (for examples, see Benovic<br>a dependent protein kinase and by protein kinase C, as whell as by a newly discovered protein kinase specific for its the agonist-occupied receptor (for examples, see Benovic 198<br>and Lefkowitz, 1987; Benovic et al., 1985, 19 the agonist-occupied receptor (for examples, see Benovic 19<br>and Lefkowitz, 1987; Benovic et al., 1985, 1986b, 1987b, to<br>1988; Bouivier et al., 1987; Sibley et al., 1987). Such ne<br>phosphorylations appear to be intimately in and Lefkowitz, 1987; Benovic et al., 1985, 1986b, 1987b, 1988; Bouivier et al., 1987; Sibley et al., 1987). Such<br>phosphorylations appear to be intimately involved in the<br>coupling of the receptor to adenylyl cyclase and the 1988; Bouivier et al., 1987; Sibley et al., 1987). Suphosphorylations appear to be intimately involved in the coupling of the receptor to adenylyl cyclase and the desensitization of the receptor (Sibley et al., 1986; Let a phosphorylations appear to be intimately involved in coupling of the receptor to adenylyl cyclase and desensitization of the receptor (Sibley et al., 1986; kowitz et al., 1990; Hausdorf et al., 1990). Both hom gous and het desensitization of the receptor (Sibley et al., 1986; Lef-<br>kowitz et al., 1990; Hausdorf et al., 1990). Both homolo-<br>gous and heterologous desensitization, i.e., desensitiza-<br>tion induced by agonists either specific or non desensitization of the receptor (Sibley et al., 1986; Lef-<br>kowitz et al., 1990; Hausdorf et al., 1990). Both homolo-<br>gous and heterologous desensitization, i.e., desensitiza-<br>tion induced by agonists either specific or non kowitz et al., 1990; Hausdorf et al., 1990). Both homologous and heterologous desensitization, i.e., desensitization induced by agonists either specific or nonspecific, respectively, for that particular receptor, are known gous and heterologous desensitization, i.e., desensitiza-<br>tion induced by agonists either specific or nonspecific, where<br>spectively, for that particular receptor, are known to<br>phoccur with this receptor type (Benovic and tion induced by agonists either specific or nonspecific, respectively, for that particular receptor, are known to occur with this receptor type (Benovic and Lefkovitz, 1987). Evidence from studies of phosphorylation of th occur with this receptor type (Benovic and Lefkovitz, 1987). Evidence from studies of phosphorylation of the purified  $\beta$ -adrenergic receptor, as well as studies of intact cells, indicate that heterologous desensitizatio 1987). Evidence from studies of phosphorylation of the purified  $\beta$ -adrenergic receptor, as well as studies of intact<br>cells, indicate that heterologous desensitization may be<br>mediated, at least partly, by phosphorylation

PROTEIN PHOSPHORYLATION AND NEURONAL FUNCTION<br>The functional properties of the GABA, receptor, tein kinase; similarly, activators of protein kinase C can also induce desensitization of  $\beta$ -adrenergic receptors in AND NEURONAL FUNCTION 321<br>tein kinase; similarly, activators of protein kinase C can<br>also induce desensitization of  $\beta$ -adrenergic receptors in<br>intact cells, suggesting that phospholipase C-coupled re-AND NEURONAL FUNCTION 321<br>tein kinase; similarly, activators of protein kinase C can<br>also induce desensitization of  $\beta$ -adrenergic receptors in<br>intact cells, suggesting that phospholipase C-coupled re-<br>ceptors promote an tein kinase; similarly, activators of protein kinase C dalso induce desensitization of  $\beta$ -adrenergic receptors intact cells, suggesting that phospholipase C-coupled ceptors promote another form of heterologous desentiza tein kinase; similarly, activators of  $\beta$ -a<br>also induce desensitization of  $\beta$ -a<br>intact cells, suggesting that phosp<br>ceptors promote another form of<br>tization (Lefkowitz et al., 1990).<br>Homologous desensitization of t So induce desensitization of  $\beta$ -adrenergic receptors<br>tact cells, suggesting that phospholipase C-coupled reptors promote another form of heterologous desensition (Lefkowitz et al., 1990).<br>Homologous desensitization of t

the GABA<sub>A</sub> receptor current in oocytes expressing ion adrenergic receptor and has, therefore, been designated channels from total messenger RNA from chick forebrain  $\beta$ -adrenergic receptor kinase (Benovic et al., 1986b, intact cells, suggesting that phospholipase C-coupled receptors promote another form of heterologous desensitization (Lefkowitz et al., 1990).<br>Homologous desensitization of the  $\beta$ -adrenergic receptor has been found to o ceptors promote another form of heterologous desensi-<br>tization (Lefkowitz et al., 1990).<br>Homologous desensitization of the  $\beta$ -adrenergic recep-<br>tor has been found to occur in cell lines devoid of cyclic<br>AMP-dependent pr tization (Lefkowitz et al., 1990).<br>Homologous desensitization of the  $\beta$ -adrenergic receptor has been found to occur in cell lines devoid of cyclic<br>AMP-dependent protein kinase and appears to involve a<br>novel protein kina Homologous desensitization of the  $\beta$ -adrenergic receptor has been found to occur in cell lines devoid of cyclic AMP-dependent protein kinase and appears to involve a novel protein kinase. This enzyme, which has been pur AMP-dependent protein kinase and appears to involve a novel protein kinase. This enzyme, which has been pu-AMP-dependent protein kinase and appears to involve a<br>novel protein kinase. This enzyme, which has been pu-<br>rified from bovine brain, appears to be specific for the  $\beta$ -<br>adrenergic receptor and has, therefore, been desig movel protein kinase. This enzyme, which has been pu-<br>rified from bovine brain, appears to be specific for the  $\beta$ -<br>adrenergic receptor and has, therefore, been designated<br> $\beta$ -adrenergic receptor kinase (Benovic et al., rified from bovine brain, appears to be specific for the  $\beta$ -<br>adrenergic receptor and has, therefore, been designated<br> $\beta$ -adrenergic receptor kinase (Benovic et al., 1986b,<br>1987b). It is independent of any known second adrenergic receptor and has, therefore, been designated  $\beta$ -adrenergic receptor kinase (Benovic et al., 1986b, 1987b). It is independent of any known second messenger and phosphorylates the receptor on as many as nine di 1987b). It is independent of any known second messenger 1987b). It is independent of any known second messe<br>and phosphorylates the receptor on as many as<br>distinct phosphorylation sites but only when agon<br>bound to the receptor. This phosphorylation mechan<br>therefore, represents s tion, which is a highly effective mechanism for limiting desensitization to the homologous type.<br>Homologous desensitization of the  $\beta$ -adrenergic recepdistinct phosphorylation sites but only w<br>bound to the receptor. This phosphorylati<br>therefore, represents substrate-activated<br>tion, which is a highly effective mechania<br>desensitization to the homologous type.<br>Homologous d und to the receptor. This phosphorylation mechaniss<br>erefore, represents substrate-activated phosphoryl<br>on, which is a highly effective mechanism for limitii<br>sensitization to the homologous type.<br>Homologous desensitization therefore, represents substrate-activated phosphorylation, which is a highly effective mechanism for limitined desensitization to the homologous type.<br>Homologous desensitization of the  $\beta$ -adrenergic receptor is striking

ious membrane-associated guanine nucleotide-binding ent in photoreceptors, appears to be related to the  $\beta$ -<br>proteins (G-proteins), which in turn can interact with adrenergic receptor kinase (Kelleher and Johnson, 1990). by phosphorylation, the regulation of the  $\beta$ -adrenergic phosphorylate the  $\beta$ -adrenergic receptor in its agonist-<br>receptor and the muscarinic acetylcholine receptor by bound form; conversely, the  $\beta$ -adrenergic recept the agonist-occupied receptor (for examples, see Benovic 1986). This mechanism, which appears to be analogous and Lefkowitz, 1987; Benovic et al., 1985, 1986b, 1987b, to the one responsible for desensitization of the  $\beta$ tion, which is a highly effective mechanism for limiting<br>desensitization to the homologous type.<br>Homologous desensitization of the  $\beta$ -adrenergic recep-<br>tor is strikingly similar to the mechanism of light adap-<br>tion in t desensitization to the homologous type.<br>
Homologous desensitization of the  $\beta$ -adrenergic receptor is strikingly similar to the mechanism of light adaption in the retina. This latter mechanism involves the loss of the ab Homologous desensitization of the  $\beta$ -adrenergic receptor is strikingly similar to the mechanism of light adaption in the retina. This latter mechanism involves the loss of the ability of the visual pigment, rhodopsin, t tor is strikingly similar to the mechanism of light adaption in the retina. This latter mechanism involves th<br>loss of the ability of the visual pigment, rhodopsin, t<br>couple to and activate a G-protein termed transducii<br>(S tion in the retina. This latter mechanism involves the loss of the ability of the visual pigment, rhodopsin, to couple to and activate a G-protein termed transducin (Stryer, 1986). *Rhodopsin kinase*, a protein kinase pre loss of the ability of the visual pigment, rhodopsin, to couple to and activate a G-protein termed transducin (Stryer, 1986). *Rhodopsin kinase*, a protein kinase present in photoreceptors, appears to be related to the  $\$ couple to and activate a G-protein termed transdu (Stryer, 1986). *Rhodopsin kinase*, a protein kinase poent in photoreceptors, appears to be related to the adrenergic receptor kinase (Kelleher and Johnson, 1995). For exam (Stryer, 1986). *Rhodopsin kinase*, a protein kinase present in photoreceptors, appears to be related to the  $\beta$ -<br>adrenergic receptor kinase (Kelleher and Johnson, 1990).<br>For example, rhodopsin kinase phosphorylates ligh ent in photoreceptors, appears to be related to the  $\beta$ -<br>adrenergic receptor kinase (Kelleher and Johnson, 1990).<br>For example, rhodopsin kinase phosphorylates light-ex-<br>posed and bleached, but not unbleached, rhodopsin<br>( adrenergic receptor kinase (Kelleher and Johnson, 1990).<br>For example, rhodopsin kinase phosphorylates light-ex-<br>posed and bleached, but not unbleached, rhodopsin<br>(Kuhn, 1974; Shichi and Somers, 1978; Lee et al., 1981;<br>Pau For example, rhodopsin kinase phosphorylates light-<br>posed and bleached, but not unbleached, rhodop<br>(Kuhn, 1974; Shichi and Somers, 1978; Lee et al., 19<br>Paulsen and Bentrop, 1983). Rhodopsin kinase can a<br>phosphorylate the posed and bleached, but not unbleached, rhodopsin (Kuhn, 1974; Shichi and Somers, 1978; Lee et al., 1981; Paulsen and Bentrop, 1983). Rhodopsin kinase can also phosphorylate the  $\beta$ -adrenergic receptor in its agonist-bou Paulsen and Bentrop, 1983). Rhodopsin kinase can also Paulsen and Bentrop, 1983). Rhodopsin kinase can also<br>phosphorylate the  $\beta$ -adrenergic receptor in its agonist-<br>bound form; conversely, the  $\beta$ -adrenergic receptor kinase<br>can phosphorylate bleached, but not unbleached, phosphorylate the  $\beta$ -adrenergic receptor in its agonist-<br>bound form; conversely, the  $\beta$ -adrenergic receptor kinase<br>can phosphorylate bleached, but not unbleached, rhodop-<br>sin in vitro (Benovic et al., 1986a). Phosphor bound form; conversely, the  $\beta$ -adrenergic receptor kinase<br>can phosphorylate bleached, but not unbleached, rhodop-<br>sin in vitro (Benovic et al., 1986a). Phosphorylation of<br>rhodopsin by rhodopsin kinase attenuates the int can phosphorylate bleached, but not unbleached, rhodopsin in vitro (Benovic et al., 1986a). Phosphorylation of<br>rhodopsin by rhodopsin kinase attenuates the interaction<br>of rhodopsin with transducin, apparently through a<br>mec sin in vitro (Benovic et al., 1986a). Phosphorylation of<br>rhodopsin by rhodopsin kinase attenuates the interaction<br>of rhodopsin with transducin, apparently through a<br>mechanism involving a cytosolic protein termed arrestin,<br> rhodopsin by rhodopsin kinase attenuates the interaction<br>of rhodopsin with transducin, apparently through a<br>mechanism involving a cytosolic protein termed arrestin,<br>which binds to phosphorylated rhodopsin and prevents<br>its of rhodopsin with transducin, apparently through a<br>mechanism involving a cytosolic protein termed arrestin,<br>which binds to phosphorylated rhodopsin and prevents<br>its binding and interaction with transducin (Stryer,<br>1986). mechanism involving a cytosolic protein termed arrest<br>which binds to phosphorylated rhodopsin and prever<br>its binding and interaction with transducin (Stry<br>1986). This mechanism, which appears to be analogo<br>to the one resp which binds to phosphorylated rhodopsin and prevents<br>its binding and interaction with transducin (Stryer,<br>1986). This mechanism, which appears to be analogous<br>to the one responsible for desensitization of the  $\beta$ -adre-<br>n 1986). This mechanism, which appears to be analogous signal transduction. the one responsible for desensitization of the  $\beta$ -adre-rgic receptor (Benovic et al., 1987a,b; Lohse et al., 90), may be responsible for the termination of visual mal transduction.<br>The *muscarinic acetylcholine receptor* nergic receptor (Benovic et al., 1987a,b; Lohse et a 1990), may be responsible for the termination of vist<br>signal transduction.<br>The *muscarinic acetylcholine receptor* is also subject<br>regulation by phosphorylation (Burgoyn

occur with this receptor type (Benovic and Lefkovitz, been cloned and sequenced and have been found to be 1987). Evidence from studies of phosphorylation of the homologous to the  $\beta$ -adrenergic receptor in their amino pu 1990), may be responsible for the termination of visual<br>signal transduction.<br>The *muscarinic acetylcholine receptor* is also subject to<br>regulation by phosphorylation (Burgoyne, 1983). Differ-<br>ent subtypes of muscarinic rec signal transduction.<br>The *muscarinic acetylcholine receptor* is also subject t<br>regulation by phosphorylation (Burgoyne, 1983). Diffe<br>ent subtypes of muscarinic receptors, the activation w<br>hich can either inhibit adenylyl c The *muscarinic acetylcholine receptor* is also subject to regulation by phosphorylation (Burgoyne, 1983). Different subtypes of muscarinic receptors, the activation of which can either inhibit adenylyl cyclase, increase regulation by phosphorylation (Burgoyne, 1983). Different subtypes of muscarinic receptors, the activation of which can either inhibit adenylyl cyclase, increase phosphoinositide turnover, or activate  $K^+$  channels, have ent subtypes of muscarinic receptors, the activation of which can either inhibit adenylyl cyclase, increase phosphoinositide turnover, or activate  $K^+$  channels, have been cloned and sequenced and have been found to be h which can either inhibit adenylyl cyclase, increase p<br>phoinositide turnover, or activate K<sup>+</sup> channels, h<br>been cloned and sequenced and have been found to<br>homologous to the  $\beta$ -adrenergic receptor in their am<br>acid sequen phoinositide turnover, or activate  $K^+$  channels, have<br>been cloned and sequenced and have been found to be<br>homologous to the  $\beta$ -adrenergic receptor in their amino<br>acid sequences and topologies (for review, see Nathan-<br> been cloned and sequenced and have been found to<br>homologous to the  $\beta$ -adrenergic receptor in their ami<br>acid sequences and topologies (for review, see Natha<br>son, 1987). The  $\beta$ -adrenergic receptor kinase has recen<br>been homologous to the  $\beta$ -adrenergic receptor in their amino<br>acid sequences and topologies (for review, see Nathan-<br>son, 1987). The  $\beta$ -adrenergic receptor kinase has recently<br>been reported to phosphorylate the purified  $M_$ 

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<sup>322</sup> **WALAAS AND GREENGARD** ner (Kwatra at al., 1989). Moreover, treatment of chick waLAAS A<br>her (Kwatra et al., 1989). Moreover, treatment of chic<br>hearts with muscarinic agonists both increased the phos-<br>phorylation and decreased the affinity of the muscarin waLAAS AND<br>ner (Kwatra et al., 1989). Moreover, treatment of chick<br>hearts with muscarinic agonists both increased the phos-<br>phorylation and decreased the affinity of the muscarinic<br>receptor for agonist (Kwatra and Hosey, 1 receptor for agonists both increased the phos-<br>phorylation and decreased the affinity of the muscarinic phorylation and decreased the affinity of the muscarinic preceptor for agonist (Kwatra and Hosey, 1986; Kwatra vet al. ner (Kwatra et al., 1989). Moreover, treatment of chick<br>hearts with muscarinic agonists both increased the phos-<br>phorylation and decreased the affinity of the muscarinic<br>pleceptor for agonist (Kwatra and Hosey, 1986; Kwatr hearts with muscarinic agonists both increased the phos-<br>phorylation and decreased the affinity of the muscarinic place  $\epsilon$ <br>receptor for agonist (Kwatra and Hosey, 1986; Kwatra with a<br>et al., 1987; Ho et al., 1987). In ad phorylation and decreased the affinity of the muscarinic<br>receptor for agonist (Kwatra and Hosey, 1986; Kwatra<br>et al., 1987; Ho et al., 1987). In addition, both cyclic<br>AMP-dependent protein kinase and protein kinase C<br>have receptor for agonist (Kwatra and Hosey, 1986; Kwatra<br>et al., 1987; Ho et al., 1987). In addition, both cyclic<br>AMP-dependent protein kinase and protein kinase C<br>have been reported to phosphorylate purified muscarinic<br>recept et al., 1987; Ho et al., 1987). In addition, both cyclic AMP-dependent protein kinase and protein kinase C<br>have been reported to phosphorylate purified muscarinic<br>receptors (Rosenbaum et al., 1987; Uchiyama et al., 1990;<br>H AMP-dependent protein kinase and protein kinase C al., have been reported to phosphorylate purified muscarinic ana receptors (Rosenbaum et al., 1987; Uchiyama et al., 1990; tion Haga et al., 1990). These results, therefor have been reported to phosphorylate purified muscarinic<br>receptors (Rosenbaum et al., 1987; Uchiyama et al., 1990;<br>Haga et al., 1990). These results, therefore, indicate that<br>the muscarinic acetylcholine receptors are subj receptors (Rosenbaum et al., 1987; Uchiyama et al., 1990;<br>Haga et al., 1990). These results, therefore, indicate that<br>the muscarinic acetylcholine receptors are subject to<br>regulation by protein phosphorylation.  $\beta$ -Adren Haga et al., 1990). These results, therefore, indicate the muscarinic acetylcholine receptors are subject regulation by protein phosphorylation.  $\beta$ -Adrenergic ceptor kinase, or a similar protein kinase, may regulatiomol the muscarinic acetylcholine receptors are subject to regulation by protein phosphorylation.  $\beta$ -Adrenergic receptor kinase, or a similar protein kinase, may regulate homologous desensitization of the muscarinic acetylch regulation by protein phosphorylation.  $\beta$ -Adrenergic receptor kinase, or a similar protein kinase, may regulate<br>homologous desensitization of the muscarinic acetylcho-<br>line receptor in response to acetylcholine, whereas ceptor kinase, or a similar protein kinase, may regulate indi-<br>homologous desensitization of the muscarinic acetylcho-<br>line receptor in response to acetylcholine, whereas pro-<br>mertein kinase C and cyclic AMP-dependent prot homologous desensitization<br>line receptor in response to<br>tein kinase C and cyclic AM<br>may regulate heterologous c<br>other extracellular signals.<br>Other G-protein-coupled is receptor in response to acetylcholine, whereas prometin kinase C and cyclic AMP-dependent protein kinase lever<br>hay regulate heterologous desensitization in response to photor extracellular signals.<br>Other G-protein-coup tein kinase C and cyclic AMP-dependent protein kina<br>may regulate heterologous desensitization in response<br>other extracellular signals.<br>Other G-protein-coupled receptors are also subject<br>phosphorylation. For example, the

may regulate heterologous desensitization in response to<br>other extracellular signals.<br>Other G-protein-coupled receptors are also subject to<br>phosphorylation. For example, the  $\alpha_2$ -adrenergic recep-<br>tor, which is coupled other extracellular signals.<br>
Other G-protein-coupled receptors are also subject to<br>
phosphorylation. For example, the  $\alpha_2$ -adrenergic recep-<br>
tor, which is coupled to inhibition of adenylyl cyclase,<br>
can be phosphoryla Other G-protein-coupled receptors are also subject to at the phosphorylation. For example, the  $\alpha_2$ -adrenergic recep-<br>tor, which is coupled to inhibition of adenylyl cyclase, des<br>can be phosphorylated by the  $\beta$ -adrene phosphorylation. For example, the  $\alpha_2$ -adrenergic receptor, which is coupled to inhibition of adenylyl cyclase, dependent can be phosphorylated by the  $\beta$ -adrenergic receptor kilimase (Benovic et al., 1987c). This phos tor, which is coupled to inhibition of adenylyl cyclas<br>can be phosphorylated by the  $\beta$ -adrenergic receptor l<br>nase (Benovic et al., 1987c). This phosphorylation is al<br>agonist dependent and may be involved in the same ty<br> can be phosphorylated by the  $\beta$ -adrenergic receptor ki-<br>nase (Benovic et al., 1987c). This phosphorylation is also sue<br>agonist dependent and may be involved in the same type<br>of homologous desensitization as the  $\beta$ -adr nase (Benovic et al., 1987c). This phosphorylation is agonist dependent and may be involved in the same of homologous desensitization as the  $\beta$ -adrenergic retor. Similarly, the *dopamine D1 receptor*, recently class of agonist dependent and may be involved in the same type<br>of homologous desensitization as the  $\beta$ -adrenergic recep-<br>tor. Similarly, the *dopamine D1 receptor*, recently cloned<br>and expressed, belongs to the same class of Gof homologous desensitization as the  $\beta$ -adrenergic rece<br>tor. Similarly, the *dopamine D1 receptor*, recently clone<br>and expressed, belongs to the same class of G-protei<br>linked receptors and possesses potential phosphoryl tor. Similarly, the *dopamine D1 receptor*, recently cloned<br>and expressed, belongs to the same class of G-protein-<br>linked receptors and possesses potential phosphorylation<br>sites on intracellular domains, suggesting that t and expressed, belongs to the same class of G-protein-<br>linked receptors and possesses potential phosphorylation<br>sites on intracellular domains, suggesting that this recep-<br>tor type will be regulated by similar mechanisms ( linked receptors and possesses potential phosphorylation  $\mu$ <br>sites on intracellular domains, suggesting that this recep-<br>tor type will be regulated by similar mechanisms (Dearry let<br>al., 1990; Monsma et al., 1990; Sunaha sites on intracellular domains, suggesting that this receptor type will be regulated by similar mechanisms (Dearry lag et al., 1990; Monsma et al., 1990; Sunahara et al., 1990; AMZhou et al., 1990). Similar data have been Watson, **1991).**

tachykinin receptors (Yokota et al., 1989; Guard and Watson, 1991).<br>3. Tyrosine kinase-coupled receptors. One of the best studied receptors of this class is the *insulin receptor* (for reviews, see Rosen, 1987; Yarden and Watson, 1991).<br>
3. Tyrosine kinase-coupled receptors. One of the best<br>
studied receptors of this class is the insulin receptor (for<br>
reviews, see Rosen, 1987; Yarden and Ullrich, 1988).<br>
This receptor, which is enriched i 3. Tyrosine kinase-coupled receptors. One of the best<br>studied receptors of this class is the insulin receptor (for<br>reviews, see Rosen, 1987; Yarden and Ullrich, 1988). Pre<br>This receptor, which is enriched in brain (Rees-J studied receptors of this class is the *insulin receptor* (for reviews, see Rosen, 1987; Yarden and Ullrich, 1988).<br>This receptor, which is enriched in brain (Rees-Jones et al., 1984; Zahniser et al., 1984; Adamo et al., reviews, see Rosen, 1987; Yarden and Ullrich, 1988)<br>This receptor, which is enriched in brain (Rees-Jones et<br>al., 1984; Zahniser et al., 1984; Adamo et al., 1989), is<br>composed of  $\alpha$ -subunits, which are located extracell This receptor, which is enriched in brain (Rees-Jones et al., 1984; Zahniser et al., 1984; Adamo et al., 1989), is composed of  $\alpha$ -subunits, which are located extracellularly and contain the insulin-binding site, and  $\beta$ al., 1984; Zahniser et al., 1984; Adamo et al., 1989), is<br>composed of  $\alpha$ -subunits, which are located extracellularly<br>and contain the insulin-binding site, and  $\beta$ -subunits,<br>which are transmembrane proteins and presumab composed of  $\alpha$ -subunits, which are located extracellularly<br>and contain the insulin-binding site, and  $\beta$ -subunits,<br>which are transmembrane proteins and presumably con-<br>vey the insulin signal into the cells (Rosen, 1987 and contain the insulin-binding site, and  $\beta$ -subunits,<br>which are transmembrane proteins and presumably con-<br>vey the insulin signal into the cells (Rosen, 1987). The<br>COOH-terminal part of the  $\beta$ -subunit contains tyrosi which are transmembrane proteins and presumably convey the insulin signal into the cells (Rosen, 1987). The COOH-terminal part of the  $\beta$ -subunit contains tyrosine kinase activity and has extensive homology with other ty vey the insulin signal into the cells (Rosen, 1987). The<br>
COOH-terminal part of the  $\beta$ -subunit contains tyrosine<br>
kinase activity and has extensive homology with other<br>
tyrosine kinases (Rosen, 1987; Yarden and Ullrich, COOH-terminal part of the  $\beta$ -subunit contains tyrosine<br>kinase activity and has extensive homology with othe<br>tyrosine kinases (Rosen, 1987; Yarden and Ullrich, 1988)<br>Binding of insulin increases the tyrosine kinase activ kinase activity and has extensive homology with other<br>tyrosine kinases (Rosen, 1987; Yarden and Ullrich, 1988).<br>Binding of insulin increases the tyrosine kinase activity<br>of the receptor and is manifested by autophosphoryl tyrosine kinases (Rosen, 1987; Yarden and Ullrich, 1988).<br>
Binding of insulin increases the tyrosine kinase activity<br>
of the receptor and is manifested by autophosphorylation<br>
of the  $\beta$ -subunit on multiple tyrosine resi Binding of insulin increases the tyrosine kinase activity<br>of the receptor and is manifested by autophosphorylation<br>of the  $\beta$ -subunit on multiple tyrosine residues (Kasuga B. i<br>et al., 1982a,b). Extensive analysis has sh of the receptor and is manifested by autophosphorylation<br>of the  $\beta$ -subunit on multiple tyrosine residues (Kasuga  $R$ <br>et al., 1982a,b). Extensive analysis has shown that this<br>tyrosine kinase domain is obligatory for expr of the  $\beta$ -subunit on multiple tyrosine residues (Kasuga et al., 1982a,b). Extensive analysis has shown that this tyrosine kinase domain is obligatory for expression of a number of insulin effects in different cell types tyrosine kinase domain is obligatory for expression of a opening and closing of ion channels in the plasma mem-<br>number of insulin effects in different cell types (for brane. Many types of ionic currents are known to be<br>rev tyrosine kinase domain is obligatory for expression of<br>number of insulin effects in different cell types (f<br>reviews, see Rosen, 1987; Yarden and Ullrich, 1984<br>Agonist-induced activation of receptor tyrosine kinas<br>also appe number of insulin effects in different cell types (for reviews, see Rosen, 1987; Yarden and Ullrich, 1988).<br>Agonist-induced activation of receptor tyrosine kinases also appears to be part of the signal transduction mechani reviews, see Rosen, 1987; Yarden and Agonist-induced activation of receptor<br>also appears to be part of the signal tranism used by a variety of other growth<br>receptors (Yarden and Ullrich, 1988).

EENGARD<br>When analyzed in broken cell preparations, the insu<br>-induced phosphorylation of the insulin receptor take GREENGARD<br>When analyzed in broken cell preparations, the insu-<br>lin-induced phosphorylation of the insulin receptor takes<br>place exclusively on tyrosine residues and is associated GREENGARD<br>When analyzed in broken cell preparations, the insu-<br>lin-induced phosphorylation of the insulin receptor takes<br>place exclusively on tyrosine residues and is associated<br>with an increased protein tyrosine kinase ac When analyzed in broken cell preparations, the insu-<br>lin-induced phosphorylation of the insulin receptor takes<br>place exclusively on tyrosine residues and is associated<br>with an increased protein tyrosine kinase activity tha When analyzed in broken cell preparations, the insulin-induced phosphorylation of the insulin receptor takes place exclusively on tyrosine residues and is associated with an increased protein tyrosine kinase activity that lin-induced phosphorylation of the insulin receptor takes<br>place exclusively on tyrosine residues and is associated<br>with an increased protein tyrosine kinase activity that is<br>independent of insulin (Kasuga et al., 1982a,b; place exclusively on tyrosine residues and is assoc<br>with an increased protein tyrosine kinase activity tl<br>independent of insulin (Kasuga et al., 1982a,b; Ros<br>al., 1983; Cobb and Rosen, 1983). In contrast,<br>analyzed in intac with an increased protein tyrosine kinase activity that is<br>independent of insulin (Kasuga et al., 1982a,b; Rosen et<br>al., 1983; Cobb and Rosen, 1983). In contrast, when<br>analyzed in intact cells, insulin stimulates phosphory al., 1983; Cobb and Rosen, 1983). In contrast, when analyzed in intact cells, insulin stimulates phosphorylation of the insulin receptor on both serine and tyrosine residues (Kasuga et al., 1982b). The identities of the in al., 1983; Cobb and Rosen, 1983). In contrast, when<br>analyzed in intact cells, insulin stimulates phosphoryla-<br>tion of the insulin receptor on both serine and tyrosine<br>residues (Kasuga et al., 1982b). The identities of the<br> analyzed in intact cells, insulin stimulates phosphorylation of the insulin receptor on both serine and tyrosine residues (Kasuga et al., 1982b). The identities of the insulin-regulated protein kinases responsible for the tion of the insulin receptor on both serine and tyrosine<br>residues (Kasuga et al., 1982b). The identities of the<br>insulin-regulated protein kinases responsible for the<br>serine phosphorylation are not clear. However, evidence<br> residues (Kasuga et al., 1982b). The identities of the insulin-regulated protein kinases responsible for the receptor. However, evident indicates that both cyclic AMP-dependent protein kinas<br>and protein kinase C regulate t insulin-regulated protein kinases responsible for the<br>serine phosphorylation are not clear. However, evidence<br>indicates that both cyclic AMP-dependent protein kinase<br>and protein kinase C regulate the receptor. Thus, treatindicates that both cyclic AMP-dependent protein kinase<br>and protein kinase C regulate the receptor. Thus, treat-<br>ment of intact cells with agents that increase cyclic AMP<br>levels has been reported to increase serine and thr indicates that both cyclic AMP-dependent protein kinase<br>and protein kinase C regulate the receptor. Thus, treat-<br>ment of intact cells with agents that increase cyclic AMP<br>levels has been reported to increase serine and thr and protein kinase C regulate the receptor. Thus, treatment of intact cells with agents that increase cyclic AMP<br>levels has been reported to increase serine and threonine<br>phosphorylation of the receptor, presumably through ment of intact cells with agents that increase cyclic AMP<br>levels has been reported to increase serine and threonine<br>phosphorylation of the receptor, presumably through<br>indirect mechanisms (Stadtmauer and Rosen, 1986), and<br> levels has been reported to increase serine and threonine<br>phosphorylation of the receptor, presumably through<br>indirect mechanisms (Stadtmauer and Rosen, 1986), and<br>at the same time decrease the effect of insulin on tyrosin indirect mechanisms (Stadtmauer and Rosen, 1986), and<br>at the same time decrease the effect of insulin on tyrosine<br>phosphorylation, thereby effectively causing a functional<br>desensitization of the receptor (Tanti et al., 198 sumably through activation of protein kinase C, also at the same time decrease the effect of insulin on tyrosine<br>phosphorylation, thereby effectively causing a functional<br>desensitization of the receptor (Tanti et al., 1987). Sim-<br>ilarly, treatment of intact cells with phorbo phosphorylation, thereby effectively causing a functional<br>desensitization of the receptor (Tanti et al., 1987). Sim-<br>ilarly, treatment of intact cells with phorbol esters, pre-<br>sumably through activation of protein kinase desensitization of the receptor (Tanti et al., 1987). Similarly, treatment of intact cells with phorbol esters, presumably through activation of protein kinase C, also increases phosphorylation of the insulin receptor on s ilarly, treatment of intact cells with phorbol esters,<br>sumably through activation of protein kinase C,<br>increases phosphorylation of the insulin receptor<br>serine and threonine residues (Takayama et al., 19<br>and decreases the sumably through activation of protein kinase C, also<br>increases phosphorylation of the insulin receptor on<br>serine and threonine residues (Takayama et al., 1984)<br>and decreases the effect of insulin on tyrosine phosphor-<br>ylat increases phosphorylation of the insulin receptor on serine and threonine residues (Takayama et al., 1984) and decreases the effect of insulin on tyrosine phosphorylation. The insulin receptor can be phosphorylated by prot serine and threonine residues (Takayama et al., 1984)<br>and decreases the effect of insulin on tyrosine phosphor-<br>ylation. The insulin receptor can be phosphorylated by<br>protein kinase C in vitro, and this phosphorylation deand decreases the effect of insulin on tyrosine phosphor-<br>ylation. The insulin receptor can be phosphorylated by<br>protein kinase C in vitro, and this phosphorylation de-<br>creases the tyrosine kinase activity of the receptor ylation. The insulin receptor can be phosphorylated by<br>protein kinase C in vitro, and this phosphorylation de-<br>creases the tyrosine kinase activity of the receptor (Bol-<br>lag et al., 1986). Therefore, agents working through protein kinase C in vitro, and this phosphorylation de-<br>creases the tyrosine kinase activity of the receptor (Bol-<br>lag et al., 1986). Therefore, agents working through cyclic<br>AMP-dependent protein kinase or protein kinase eases the tyrosine kinase activity of the receptor (Boly et al., 1986). Therefore, agents working through cyclical MP-dependent protein kinase or protein kinase C may wn-regulate this type of receptor.<br>4. *Intracellular re* 

et al., 1990; Monsma et al., 1990; Sunahara et al., 1990;<br> **3. Tyrosine kinase-coupled receptors.** One of the best<br> **3. Tyrosine kinase-coupled receptors.** One of the best<br> **3. Tyrosine kinase-coupled receptors.** One of th tachykinin receptors (Yokota et al., 1989; Guard and<br>Watson, 1991).<br>3. Tyrosine kinase-coupled receptors. One of the best<br>studied receptors of this class is the *insulin receptor* (for<br>reviews, see Rosen, 1987; Yarden and lag et al., 1986). Therefore, agents working through cycl<br>AMP-dependent protein kinase or protein kinase C ma<br>down-regulate this type of receptor.<br>4. Intracellular receptors. Several hormones and reg<br>latory agents influenc latory agents influence cellular function through intradown-regulate this type of receptor.<br>4. Intracellular receptors. Several hormones and regulatory agents influence cellular function through intracellular receptors, which may be regulated by phosphorylation mechanisms. Thu 4. Intracellular receptors. Several hormones and regulatory agents influence cellular function through intracellular receptors, which may be regulated by phosphor-<br>ylation mechanisms. Thus, a superfamily of receptors pres latory agents influence cellular function through intracellular receptors, which may be regulated by phosphor-<br>ylation mechanisms. Thus, a superfamily of receptors<br>present in cell nuclei consists of receptors for steroids, cellular receptors, which may be regulated by phosphor-<br>ylation mechanisms. Thus, a superfamily of receptors<br>present in cell nuclei consists of receptors for steroids,<br>vitamin D<sub>3</sub>, thyroid hormones, or retinoic acid; thes ylation mechanisms. Thus, a superfamily of receptor<br>present in cell nuclei consists of receptors for steroic<br>vitamin D<sub>3</sub>, thyroid hormones, or retinoic acid; the<br>receptors transduce their signals into changes in prote<br>syn present in cell nuclei consists of receptors for steroids,<br>vitamin  $D_3$ , thyroid hormones, or retinoic acid; these<br>receptors transduce their signals into changes in protein<br>synthesis. Evidence has been presented that the vitamin  $D_3$ , thyroid hormones, or retinoic acid; these receptors transduce their signals into changes in protein synthesis. Evidence has been presented that these receptors are targets for phosphorylation (for examples, receptors transduce their signals into changes in protein<br>synthesis. Evidence has been presented that these recep-<br>tors are targets for phosphorylation (for examples, see<br>Weigel et al., 1981; Housley and Pratt, 1983; Singh synthesis. Evidence has been presented that these receptors are targets for phosphorylation (for examples, see Weigel et al., 1981; Housley and Pratt, 1983; Singh and Moudgil, 1985; Tienrungroj et al., 1987; Auricchio et a tors are targets for phosphorylation (for examples, see<br>Weigel et al., 1981; Housley and Pratt, 1983; Singh and<br>Moudgil, 1985; Tienrungroj et al., 1987; Auricchio et al.,<br>1988; Brown and DeLuca, 1990; Denner et al., 1990;<br> Weigel et al., 1981; Housley and Pratt, 1983; Singh and<br>Moudgil, 1985; Tienrungroj et al., 1987; Auricchio et al.,<br>1988; Brown and DeLuca, 1990; Denner et al., 1990;<br>Hoeck and Groner, 1990; Moudgil, 1990). Whether such<br>mod Moudgil, 1985; Tienrungroj et al., 1987; Auricchio et al., 1988; Brown and DeLuca, 1990; Denner et al., 1990;<br>Hoeck and Groner, 1990; Moudgil, 1990). Whether such<br>modifications of these receptor types take place in brain,<br> 1988; Brown and DeLuca, 1990; Denner<br>Hoeck and Groner, 1990; Moudgil, 1990). Imodifications of these receptor types take and whether such phosphorylations lead<br>neuronal function, remain to be examined.<br>R. Regulation of Ion Froeck and Croner, 1350, Moddy<br>modifications of these receptor t<br>and whether such phosphorylat<br>neuronal function, remain to be<br>*B. Regulation of Ion Channels*<br>The electrical behavior of ne The electrical behavior of neurons is shaped by the<br>The electrical behavior of neurons is shaped by the<br>The electrical behavior of neurons is shaped by the

opening and function, remain to be examined.<br>
B. Regulation of Ion Channels<br>
The electrical behavior of neurons is shaped by the plasma membrane. Many types of ionic currents are known to be<br>
brane. Many types of ionic cur B. Regulation of Ion Channels<br>The electrical behavior of neurons is shaped by the<br>opening and closing of ion channels in the plasma mem-<br>brane. Many types of ionic currents are known to be<br>modulated by second messenger sys B. Regulation of Ion Channels<br>The electrical behavior of neurons is shaped by the<br>opening and closing of ion channels in the plasma mem-<br>brane. Many types of ionic currents are known to be<br>modulated by second messenger sys The electrical behavior of neurons is shaped by the opening and closing of ion channels in the plasma membrane. Many types of ionic currents are known to be modulated by second messenger systems, and these regulation mecha opening and closing of ion channels in the plasma mem-<br>brane. Many types of ionic currents are known to be<br>modulated by second messenger systems, and these reg-<br>ulation mechanisms differ among distinct cell types (ta-<br>ble brane. Many types of ionic currents are known to modulated by second messenger systems, and these relation mechanisms differ among distinct cell types (ble 8) (for review, see Kaczmarek and Levitan, 198 Physiological studi modulated by second messenger systems, and these regulation mechanisms differ among distinct cell types (table 8) (for review, see Kaczmarek and Levitan, 1986).<br>Physiological studies, usually using intracellular recordings



TABLE 8

con-regulated cannot are channel properties. Data from intracellular injection experiments where activated protein phosphorylation systems have been found to regulate ion<br>
channel properties. Data compiled from Kaczmarek a CaM kinase II Photoreceptor (Hermissenda) CaM kinase II K<sup>+</sup> current inactivation  $\uparrow$ K<sup>+</sup> channel<br>
\* Summary of data from intracellular injection experiments where activated protein phosphorylation systems have been foun <sup>\*</sup> Summary of data from intracellular injection experiments where activated protein phosphorylation systems have<br>channel properties. Data compiled from Kaczmarek and Levitan (1986), Kaczmarek (1987, 1988), Paupardin-Trita of second properties. Data compiled from Kaczmarek and Levitan (1986)<br>al. (1986), Siegelbaum et al. (1982). Further details are given in text.<br>kinase; CCK, cholecystokinin; PKG, cyclic GMP-dependent protein ki<br>of second me Kaczmarek (1987, 1988), Paupardin-Tritsch et al. (1986a,b), Woody et breviations: PKI, protein inhibitor of cyclic AMP-dependent protein<br>e; others as in legend to Tables 1 and 3.<br>(Costa and Catterall, 1984a,b; Costa et al.

al. (1986), Siegelbaum et al. (1982). Further details are given in text. Abbr<br>kinase; CCK, cholecystokinin; PKG, cyclic GMP-dependent protein kinase;<br>of second messengers and/or protein kinases, and bio- (C<br>chemical invest kinase; CCK, cholecystokinin; PKG, cyclic GMP-dependent protein kinase<br>of second messengers and/or protein kinases, and bio-<br>chemical investigations of purified channel proteins as<br>a targets for protein kinases have shown of second messengers and/or protein kinases, and biochemical investigations of purified channel proteins at targets for protein kinases have shown that various type of ion channels, including Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Cl<sup>-</sup> of second messengers and/or protein kinases, and bio-<br>chemical investigations of purified channel proteins as<br>targets for protein kinases have shown that various types<br>of ion channels, including  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{$ chemical investigations of purified channel proteins as targets for protein kinases have shown that various types of ion channels, including Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Cl<sup>-</sup> channels, are regulated by protein phosphorylation targets for protein kinases have shown that various types Alof ion channels, including  $Na^+$ ,  $K^+$ ,  $Ca^{2+}$ , and  $Cl^-$  channels, are regulated by protein phosphorylation (for reinviews, see Rossie and Catterall, 1987a; Hu of ion channels, including Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Cl<sup>-</sup> channels, are regulated by protein phosphorylation (for r views, see Rossie and Catterall, 1987a; Huganir, 1986a, Levitan, 1985, 1988; Kaczmarek, 1987, 1988). In so nels, are regulated by protein phosphorylation (for views, see Rossie and Catterall, 1987a; Huganir, 1986a<br>Levitan, 1985, 1988; Kaczmarek, 1987, 1988). In son<br>cases, phosphorylation of the channel proteins the<br>selves has b views, see Rossie and Catterall, 1987a; Huganir, 1986a,b; m<br>Levitan, 1985, 1988; Kaczmarek, 1987, 1988). In some 19<br>cases, phosphorylation of the channel proteins them-<br>selves has been observed, whereas in other cases regu Levitan, 1985, 1988; Kaczmarek, 1987, 1988). In some 19 cases, phosphorylation of the channel proteins them-<br>selves has been observed, whereas in other cases regula-<br>protion of ion conductances appears to be mediated throu cases, phosphorylation of the channel proteins them-<br>selves has been observed, whereas in other cases regula-<br>proj<br>tion of ion conductances appears to be mediated through<br>phosphorylation of associated regulatory proteins. selves has been observed, whereas in other cases regulation of ion conductances appears to be mediated through phosphorylation of associated regulatory proteins. The phosphorylation of the channel complexes may alter ion c tion of ion conductances appears to be mediated through phosphorylation of associated regulatory proteins. The was<br>phosphorylation of the channel complexes may alter ion this<br>channel properties, leading to changes in the phosphorylation of associated regulatory proteins. The we<br>phosphorylation of the channel complexes may alter ion<br>channel properties, leading to changes in the electrical Ca<br>behavior of the cells (for examples, see Kaczmare phosphorylation of the channel complexes may alter<br>channel properties, leading to changes in the electr<br>behavior of the cells (for examples, see Kaczmarek<br>Levitan, 1986; Levitan, 1985, 1988). In other cases<br>exact physiolog channel properties, leading to changes in the electrical<br>behavior of the cells (for examples, see Kaczmarek and<br>Levitan, 1986; Levitan, 1985, 1988). In other cases the<br>exact physiological importance of ion channel phosphor behavior of the cells (for examples, see Kaczmarek and 2<br>Levitan, 1986; Levitan, 1985, 1988). In other cases the K<sup>+</sup><br>exact physiological importance of ion channel phosphor-<br>ertylation remains to be established (Costa and Levitan, 1986; Levitan, 1985, 1988). In other cases the exact physiological importance of ion channel phosphor-<br>ylation remains to be established (Costa and Catterall, 1984a,b; Rossie and Catterall, 1987a). In this section exact physiological importance of ion channel phosphor-<br>ylation remains to be established (Costa and Catterall,<br>1984a,b; Rossie and Catterall, 1987a). In this section we<br>will briefly describe some examples of phosphorylat ylation remains to be established (Costa and Catterall, 1984a,b; Rossie and Catterall, 1987a). In this section we will briefly describe some examples of phosphorylation mechanisms involving either voltage-dependent  $Na^+$ c 1984a,b; Rossie and Catterall, 1987a). In this section w<br>will briefly describe some examples of phosphorylation<br>mechanisms involving either voltage-dependent Na<br>channels, a number of  $K^+$  channels, or various  $Ca^2$ <br>chann will briefly describe some examples of phosphorylation<br>mechanisms involving either voltage-dependent  $Na^+$  tij<br>channels, a number of  $K^+$  channels, or various  $Ca^{2+}$  fo<br>channels. Ligand-gated ion channels such as the ni channels, a number of  $K^+$  channels, or various  $Ca^{2+}$ <br>channels. Ligand-gated ion channels such as the nico-<br>tinic acetylcholine receptor and  $GABA_A$  receptors have<br>been discussed in section V.A.1, and the epithelial Cl<sup>-</sup> channels, a number of  $K^+$  channels, or various  $Ca^{2+}$  for the channels. Ligand-gated ion channels such as the nico-<br>tinic acetylcholine receptor and  $GABA_A$  receptors have axon<br>been discussed in section V.A.1, and the ep channels. Ligand-gated ion channels such as the nico-<br>tinic acetylcholine receptor and  $GABA_A$  receptors have<br>been discussed in section V.A.1, and the epithelial Cl<sup>-</sup><br>in<br>channel defective in cystic fibrosis will be discuss been discussed in sect<br>channel defective in cy<br>section VI.B. Certain<br>conductances by distin<br>briefly in section II.<br>*1. Na<sup>+</sup> channels*. Tl annel defective in cystic fibrosis will be discussed in<br> *2. Na. Certain aspects of the regulation of ionic*<br> *nductances by distinct protein kinases were discussed*<br> *iefly in section II.*<br> *1. Na<sup>+</sup> channels. The volta* 

section VI.B. Certain aspects of the regulation of ionic<br>conductances by distinct protein kinases were discussed<br>briefly in section II.<br>1.  $Na^{+}$  channels. The voltage-sensitive  $Na^{+}$  channel<br>from rat brain, which has be conductances by distinct protein kinases were discussed in v<br>briefly in section II. the<br>1.  $Na^+$  channels. The voltage-sensitive  $Na^+$  channel wer<br>from rat brain, which has been extensively characterized 198<br>(Agnew, 1984; briefly in section II.<br>
1.  $Na^+$  channels. The voltage-sensitive  $Na^+$  channel<br>
from rat brain, which has been extensively characterized<br>
(Agnew, 1984; Barchi, 1984; Catterall, 1986), contains a<br>
major  $\alpha$ -subunit of app 1.  $Na^+$  channels. The voltage-sensitive  $Na^+$  channel word from rat brain, which has been extensively characterized 19 (Agnew, 1984; Barchi, 1984; Catterall, 1986), contains a Timajor  $\alpha$ -subunit of approximately 260 kD from rat brain, which has been extensively characterized 1985; 1<br>(Agnew, 1984; Barchi, 1984; Catterall, 1986), contains a Thus,<br>major  $\alpha$ -subunit of approximately 260 kDa. This subunit channe<br>has been found to be phospho

breviations: PKI, protein inhibitor of cyclic AMP-dependent protein<br>is; others as in legend to Tables 1 and 3.<br>(Costa and Catterall, 1984a,b; Costa et al., 1982; Rossie<br>and Catterall, 1987b, 1989). Phosphorylation by cycli e; others as in legend to Tables 1 and 3.<br>(Costa and Catterall, 1984a,b; Costa et al., 1982; Rossie<br>and Catterall, 1987b, 1989). Phosphorylation by cyclic<br>AMP-dependent protein kinase was found to occur in<br>reaction mixture (Costa and Catterall, 1984a,b; Costa et al., 1982; Rossie<br>and Catterall, 1987b, 1989). Phosphorylation by cyclic<br>AMP-dependent protein kinase was found to occur in<br>reaction mixtures containing purified components, in<br>intac and Catterall, 1987b, 1989). Phosphorylation by cyclic AMP-dependent protein kinase was found to occur in reaction mixtures containing purified components, in intact, isolated nerve terminal preparations, and in pri-mary c and Catterall, 1987b, 1989). Phosphorylation by cyclic AMP-dependent protein kinase was found to occur in reaction mixtures containing purified components, in intact, isolated nerve terminal preparations, and in primary cu AMP-dependent protein kinase was found to occur in reaction mixtures containing purified components, in intact, isolated nerve terminal preparations, and in primary cultures of rat brain neurons (Rossi and Catterall, 1987b mary cultures of rat brain neurons (Rossi and Catterall, 1987b, 1989). This suggests that physiological changes<br>in levels of cyclic AMP in nerve terminals regulate the<br>properties of this channel. However, a major effect of intact, isolated nerve terminal preparations, and in primary cultures of rat brain neurons (Rossi and Catterall, 1987b, 1989). This suggests that physiological changes in levels of cyclic AMP in nerve terminals regulate th mary cultures of rat brain neurons (Rossi and Catterall, 1987b, 1989). This suggests that physiological changes<br>in levels of cyclic AMP in nerve terminals regulate the<br>properties of this channel. However, a major effect of 1987b, 1989). This suggests that physiological changes<br>in levels of cyclic AMP in nerve terminals regulate the<br>properties of this channel. However, a major effect of<br>phosphorylation on the properties of these Na<sup>+</sup> channel in levels of cyclic AMP in nerve terminals regulate the properties of this channel. However, a major effect of phosphorylation on the properties of these Na<sup>+</sup> channels was not observed, and the physiological importance of properties of this channel. However, a major exphasion on the properties of these Na<sup>+</sup> cl<br>was not observed, and the physiological import<br>this phenomenon remains to be established (Coor<br>Catterall, 1984a,b; Rossie and Catt *2.* hostigation on the properties of these Na<sup>+</sup> channels<br>is not observed, and the physiological importance of<br>is phenomenon remains to be established (Costa and<br>interall, 1984a,b; Rossie and Catterall, 1987a).<br>2. *K*<sup>+</sup>

was not observed, and the physiological importance of this phenomenon remains to be established (Costa an Catterall, 1984a,b; Rossie and Catterall, 1987a).<br>
2. K<sup>+</sup> channels. Nerve cells express a great variety of the prop this phenomenon remains to be established (Costa and Catterall, 1984a,b; Rossie and Catterall, 1987a).<br>
2. K<sup>+</sup> channels. Nerve cells express a great variety of K<sup>+</sup> channels, which display a number of distinctive properti Catterall, 1984a,b; Rossie and Catterall, 1987a).<br>
2.  $K^+$  channels. Nerve cells express a great variety of  $K^+$  channels, which display a number of distinctive properties (for review, see Kaczmarek, 1988). The activity 2.  $K^+$  channels. Nerve cells<br>K<sup>+</sup> channels, which display a n<br>erties (for review, see Kaczman<br>several of these K<sup>+</sup> currents h<br>lated by protein phosphorylatic<br>The regulation of the voltag erties (for review, see Kaczmarek, 1988). The activity of several of these K<sup>+</sup> currents has been found to be regulated by protein phosphorylation.<br>The regulation of the voltage-dependent *delayed rec-*

been discussed in section V.A.1, and the epithelial  $Cl^-$  increases in both the amplitude and the duration of the channel defective in cystic fibrosis will be discussed in  $K^+$  currents activated by a large depolarization erties (for review, see Kaczmarek, 1988). The activity of several of these K<sup>+</sup> currents has been found to be regulated by protein phosphorylation.<br>The regulation of the voltage-dependent *delayed rec-*<br>tifier K<sup>+</sup> current several of these  $K^+$  currents has been found to be regulated by protein phosphorylation.<br>The regulation of the voltage-dependent *delayed rec-*<br>tifier  $K^+$  current, which in many instances is responsible<br>for the termin lated by protein phosphorylation.<br>
The regulation of the voltage-dependent *delayed rec-*<br> *tifier*  $K^+$  current, which in many instances is responsible<br>
for the termination of neuronal action potentials (Hille,<br>
1984), h The regulation of the voltage-dependent *delayed rec-*<br>tifier  $K^+$  current, which in many instances is responsible<br>for the termination of neuronal action potentials (Hille,<br>1984), has been studied in, for example, squid tifier  $K^+$  current, which in many instances is responsible<br>for the termination of neuronal action potentials (Hille,<br>1984), has been studied in, for example, squid giant<br>axons. Internal dialysis of these axons with ATP for the termination of neuronal action potentials (Hille, 1984), has been studied in, for example, squid giant axons. Internal dialysis of these axons with ATP led to increases in both the amplitude and the duration of the 1984), has been studied in, for example, squid giant<br>axons. Internal dialysis of these axons with ATP led to<br>increases in both the amplitude and the duration of the<br>K<sup>+</sup> currents activated by a large depolarization of the<br> axons. Internal dialysis of these axons with ATP led to<br>increases in both the amplitude and the duration of the<br>K<sup>+</sup> currents activated by a large depolarization of the<br>membrane. Similar changes were seen in perfused axons increases in both the amplitude and the duration of the K<sup>+</sup> currents activated by a large depolarization of the membrane. Similar changes were seen in perfused axons in which the cytoplasm had been extruded, if ATP and th K<sup>+</sup> currents activated by a large depolarization of the membrane. Similar changes were seen in perfused axons in which the cytoplasm had been extruded, if ATP and the C subunit of cyclic AMP-dependent protein kinase were membrane. Similar changes were seen in perfused axons<br>in which the cytoplasm had been extruded, if ATP and<br>the C subunit of cyclic AMP-dependent protein kinase<br>were added to the perfusing medium (Bezanilla et al.,<br>1985; Pe in which the cytoplasm had been extruded, if ATP and<br>the C subunit of cyclic AMP-dependent protein kinase<br>were added to the perfusing medium (Bezanilla et al.,<br>1985; Perozo et al., 1986; Perozo and Bezanilla, 1990).<br>Thus, the C subunit of cyclic AMP-dependent protein kinase<br>were added to the perfusing medium (Bezanilla et al.,<br>1985; Perozo et al., 1986; Perozo and Bezanilla, 1990).<br>Thus, cyclic AMP-catalyzed phosphorylation of the<br>channel i were added to the perfusing medium (Bezanilla et al. 1985; Perozo et al., 1986; Perozo and Bezanilla, 1990)<br>Thus, cyclic AMP-catalyzed phosphorylation of the channel itself or of an associated protein appears to be<br>importa CCK-regulated Ca<sup>1+</sup> current i<sub>n</sub> Ca<sup>1+</sup> channel<br>
In II K<sup>+</sup> crimes in *K*<sup>1</sup> channel<br>
in dipertian phosphorylation systems have been found to regulate ion<br>
mutations PKI, preside in and 3.<br>
University of  $\alpha$ , 1988), Papa

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<sup>324</sup> **WALAAS AND GREENGARD** channels that contribute to the repolarization phase of walaas<br>
channels that contribute to the repolarization phase<br>
action potentials have been termed *S channels* (Sieg<br>
baum et al., 1982). The closure of these channels **baum at all the values of the separature of the set al., 1982). The closure of these channels by**  $\frac{3}{2}$ .<br> **baum et al., 1982). The closure of these channels by**  $\frac{3}{2}$ .<br> **serotonin and by endogenous neuropeptides** channels that contribute to the repolarization phase of<br>action potentials have been termed S channels (Siegel-<br>baum et al., 1982). The closure of these channels by<br>serotonin and by endogenous neuropeptides enhances<br>action channels that contribute to the repolarization phase of baction potentials have been termed  $S$  channels (Siegel-<br>baum et al., 1982). The closure of these channels by<br>serotonin and by endogenous neuropeptides enhances (<br>a action potentials have been termed  $S$  channels (Siegel-baum et al., 1982). The closure of these channels by serotonin and by endogenous neuropeptides enhances action potentials and appears to be partly responsible for th serotonin and by endogenous neuropeptides enhances<br>action potentials and appears to be partly responsible for<br>the increased transmitter release that accompanies sen-<br>sitization of withdrawal reflexes by noxious stimuli<br>(Ka action potentials and appears to be partly responsible if<br>the increased transmitter release that accompanies se<br>sitization of withdrawal reflexes by noxious stime<br>(Kandel and Schwartz, 1982). Opening of Schannels h<br>been sh the increased transmitter release that accompanies sensitization of withdrawal reflexes by noxious stimuli (Kandel and Schwartz, 1982). Opening of S channels has been shown to be regulated by cyclic AMP-dependent protein k sitization of withdrawal reflexes by noxious stimuli dia<br>
(Kandel and Schwartz, 1982). Opening of S channels has<br>
been shown to be regulated by cyclic AMP-dependent bo<br>
protein kinase (Castellucci et al., 1980, 1982): appl (Kandel and Schwartz, 1982). Opening of S channels has centr<br>been shown to be regulated by cyclic AMP-dependent both<br>protein kinase (Castellucci et al., 1980, 1982): application 1986;<br>of the C subunit of this enzyme to th been shown to be regulated by cyclic AMP-dependent<br>protein kinase (Castellucci et al., 1980, 1982): application<br>of the C subunit of this enzyme to the cytoplasmic face<br>of membrane patches closes about one-third of the S<br>ch protein kinase (Castellucci et<br>of the C subunit of this enzy<br>of membrane patches close<br>channels monitored in the<br>1982; Shuster et al., 1985).<br>Other types of voltage-dep the C subunit of this enzyme to the cytoplasmic face<br>membrane patches closes about one-third of the S<br>annels monitored in the patches (Siegelbaum et al.,<br>82; Shuster et al., 1985).<br>Other types of voltage-dependent K<sup>+</sup> ch of membrane patches closes about one-third of the<br>channels monitored in the patches (Siegelbaum et<br>1982; Shuster et al., 1985).<br>Other types of voltage-dependent  $K^+$  channels app<br>to be subject to regulation by protein ph

channels monitored in the patches (Siegelbaum et al., Ca<br>1982; Shuster et al., 1985). of<br>Other types of voltage-dependent K<sup>+</sup> channels appear<br>to be subject to regulation by protein phosphorylation. pur<br>These include the t 1982; Shuster et al., 1985). of of the types of voltage-dependent  $K^+$  channels appear 1983 to be subject to regulation by protein phosphorylation. purifiese include the transient inactivating A current, the which amplit Other types of voltage-dependent  $K^+$  channels appear<br>to be subject to regulation by protein phosphorylation.<br>These include the transient inactivating  $A$  current, the<br>amplitude of which has been reported to be decreased to be subject to regulation by protein phosphorylation.<br>These include the transient inactivating A current, the<br>amplitude of which has been reported to be decreased by<br>the intracellular application of various protein kinas These include the transient inactivating *A current*, the whamplitude of which has been reported to be decreased by su<br>the intracellular application of various protein kinases chin photoreceptors of *Hermissenda* (Alkon et amplitude of which has been reported to be decreased by<br>the intracellular application of various protein kinase<br>in photoreceptors of *Hermissenda* (Alkon et al., 1983<br>Neary and Alkon, 1983; Sakakibara et al., 1986; Farley<br> in photoreceptors of *Hermissenda* (Alkon et al., 1983; Neary and Alkon, 1983; Sakakibara et al., 1986; Farley and Auerbach, 1986), and the  $M$  current, which in bull-<br>frog sympathetic neurons has been found to be dimin-<br> Brown, 1984). d Auerbach, 1986), and the *M current*, which in but op sympathetic neurons has been found to be dimined by activators of protein kinase C (Adams a cown, 1984).<br>Multiple types of Ca<sup>2+</sup>-activated K<sup>+</sup> currents, inclug the

frog sympathetic neurons has been found to be dimin-<br>ished by activators of protein kinase C (Adams an<br>Brown, 1984).<br>Multiple types of  $Ca^{2+}$ -activated K<sup>+</sup> currents, including the K<sup>+</sup> current responsible for the prolon ished by activators of protein kinase C (Adams and Jong Brown, 1984). O<br>Brown, 1984). O<br>Multiple types of Ca<sup>2+</sup>-activated K<sup>+</sup> currents, includ-<br>hig the K<sup>+</sup> current responsible for the prolonged after-<br>hyperpolarization Brown, 1984). (Multiple types of  $Ca^{2+}$ -activated  $K^+$  currents, including the  $K^+$  current responsible for the prolonged afterenties in pitchly perpolarization that follows action potential bursts in pitchly many neur Multiple types of  $Ca^{2+}$ -activated  $K^+$  currents, includ-<br>ing the  $K^+$  current responsible for the prolonged after-<br>hyperpolarization that follows action potential bursts in pitt<br>many neurons (Pennefather et al., 1985) ing the K<sup>+</sup> current responsible for the prolonged after hyperpolarization that follows action potential bursts many neurons (Pennefather et al., 1985), appear to regulated by protein phosphorylation. Both positive an nega hyperpolarization that follows action potential bursts in pionary neurons (Pennefather et al., 1985), appear to be more regulated by protein phosphorylation. Both positive and dependent protein kinase and by protein kinase many neurons (Pennefather et al., 1985), appear to be margulated by protein phosphorylation. Both positive and de negative modulation of such channels by cyclic AMP-W dependent protein kinase and by protein kinase C have w regulated by protein phosphorylation. Both positive and<br>negative modulation of such channels by cyclic AMP-<br>dependent protein kinase and by protein kinase C have<br>been reported (for review, see Kaczmarek, 1988). One<br>example negative modulation of such channels by cyclic AMP-<br>dependent protein kinase and by protein kinase C have<br>been reported (for review, see Kaczmarek, 1988). One<br>example of such regulation has been found in intact<br>*Helix* neu dependent protein kinase and by protein kinase C ha<br>been reported (for review, see Kaczmarek, 1988). O<br>example of such regulation has been found in inta<br>*Helix* neurons (De Peyer et al., 1982; Ewald et al., 1984<br>Intracellu been reported (for review, see Kaczmarek, 1988). One kexample of such regulation has been found in intact with *Helix* neurons (De Peyer et al., 1982; Ewald et al., 1985). Intracellular application of the C subunit of cyc example of such regulation has been found in intact w<br>Helix neurons (De Peyer et al., 1982; Ewald et al., 1985). re<br>Intracellular application of the C subunit of cyclic AMP-<br>of dependent protein kinase into these neurons *Helix* neurons (De Peyer et al., 1982; Ewald et al., 1985)<br>Intracellular application of the C subunit of cyclic AMP<br>dependent protein kinase into these neurons increased<br>the amplitude of the Ca<sup>2+</sup>-activated K<sup>+</sup> current Intracellular application of the C subunit of cyclic AMP-<br>dependent protein kinase into these neurons increased<br>the amplitude of the  $Ca^{2+}$ -activated  $K^+$  current that was<br>recorded during depolarization. When membrane f dependent protein kinase into these neurons increased<br>the amplitude of the Ca<sup>2+</sup>-activated K<sup>+</sup> current that was<br>recorded during depolarization. When membrane frac-<br>tions from *Helix* were reconstituted into phospholipid the amplitude of the Ca<sup>2+</sup>-activated K<sup>+</sup> current that w<br>recorded during depolarization. When membrane fra<br>tions from *Helix* were reconstituted into phospholip<br>bilayers, single Ca<sup>2+</sup>-activated K<sup>+</sup> channels were d<br>tect tions from *Helix* were reconstituted into phospholipid<br>bilayers, single  $Ca^{2+}$ -activated  $K^+$  channels were de-<br>tected. Application of the C subunit of cyclic AMP-<br>dependent protein kinase in the presence of ATP pro-<br>d bilayers, single Ca<sup>2+</sup>-activated K<sup>+</sup> channels were de-<br>tected. Application of the C subunit of cyclic AMP-<br>polarization, in contrast to the brief opening responses<br>dependent protein kinase in the presence of ATP pro-<br>du bilayers, single  $Ca^{2+}$ -activated  $K^+$  channels were dected. Application of the C subunit of cyclic AMP-<br>dependent protein kinase in the presence of ATP pro-<br>duced a dramatic increase in the probability of opening ki<br>of tected. Application of the C subunit of cyclic AMI dependent protein kinase in the presence of ATP produced a dramatic increase in the probability of openin of the channels (Ewald et al., 1985). The results wer consistent dependent protein kinase in the presence of ATP pro-<br>duced a dramatic increase in the probability of opening kind<br>of the channels (Ewald et al., 1985). The results were com<br>consistent with the hypothesis that this type of duced a dra<br>of the chan<br>consistent v<br>phorylation<br>Ca<sup>2+</sup> ions.<br>In the rhy the channels (Ewald et al., 1985). The results we maistent with the hypothesis that this type of phorylation of the channel increased its sensitivity  $a^{2+}$  ions.<br>In the rhythmically bursting neuron R15 of the abdomlar g

consistent with the hypothesis that this type of phos-<br>phorylation of the channel increased its sensitivity to<br>Ca<sup>2+</sup> ions.<br>In the rhythmically bursting neuron R15 of the abdom-<br>inal ganglion of *Aplysia*, serotonin increa phorylation of the channel increased its sensitivity to  $Ca^{2+}$  ions.<br>
In the rhythmically bursting neuron R15 of the abdominal ganglion of *Aplysia*, serotonin increased cyclic AMP the levels and thereby enhanced the ampl Ca<sup>2+</sup> ions.<br>
In the rhythmically bursting neuron R15 of the abdom-<br>
inal ganglion of *Aplysia*, serotonin increased cyclic AMP<br>
levels and thereby enhanced the amplitude of an *inwardly*<br> *actifying K*<sup>+</sup> current (Benson In the rhythmically bursting neuron R15 of the abdominal ganglion of *Aplysia*, serotonin increased cyclic AMP levels and thereby enhanced the amplitude of an *inwardly* rectifying  $K^+$  current (Benson and Levitan, 1983) inal ganglion of *Aplysia*, serotonin increased cyclic AMP the levels and thereby enhanced the amplitude of an *inwardly* an *rectifying*  $K^+$  current (Benson and Levitan, 1983). This (E effect, which leads to an enhance levels and thereby enhanced the amplitude of an *inwardly* rectifying  $K^+$  current (Benson and Levitan, 1983). This effect, which leads to an enhancement of the interburst hyperpolarization and is caused by an increase i rectifying  $K^+$  current (Benson and Levitan, 1983). This (Eckert and Chad, 1984; Chad and Eckert, 1986; Kalman effect, which leads to an enhancement of the interburst et al., 1988; Armstrong, 1989). This phenomenon, whic

BREENGARD<br>be blocked by the protein inhibitor of this enzyme (Ad-<br>ams and Levitan, 1982; Lemos et al., 1985). EREENGARD<br>be blocked by the protein inhibitor of this er<br>ams and Levitan, 1982; Lemos et al., 1985).<br>3.  $Ca^{2+}$  channels. Multiple types of voltage

action potentials and appears to be partly responsible for eration and also serve to couple cell surface electrical<br>the increased transmitter release that accompanies sen-<br>sitization of withdrawal reflexes by noxious stim Neary and Alkon, 1983; Sakakibara et al., 1986; Farley several protein kinases in vitro (for examples, see Curtis and Auerbach, 1986), and the *M current*, which in bull- and Catterall, 1985; Hosey et al., 1986; Imagawa et *3. EENGARD*<br>*3. Ca<sup>2+</sup> channels. Multiple types of <i>voltage-dependent*<br>*3. Ca<sup>2+</sup> channels. Multiple types of <i>voltage-depende*<br> $a^{2+}$  channels, which participate in action potential general be blocked by the protein inhibitor of this enzyme (Adams and Levitan, 1982; Lemos et al., 1985).<br>
3.  $Ca^{2+}$  channels. Multiple types of *voltage-dependent*<br>  $Ca^{2+}$  channels, which participate in action potential generat be blocked by the protein inhibitor of this enzyme (Ad-<br>ams and Levitan, 1982; Lemos et al., 1985).<br>3.  $Ca^{2+}$  channels. Multiple types of *voltage-dependent*<br> $Ca^{2+}$  channels, which participate in action potential gen-<br>e ams and Levitan, 1982; Lemos et al., 1985).<br>  $3. Ca^{2+}$  channels. Multiple types of *voltage-dependent*<br>  $Ca^{2+}$  channels, which participate in action potential generation and also serve to couple cell surface electrical<br> 3.  $Ca^{2+}$  channels. Multiple types of voltage-dependent  $Ca^{2+}$  channels, which participate in action potential generation and also serve to couple cell surface electrical signals to intracellular physiological responses  $Ca^{2+}$  channels, which participate in action potential generation and also serve to couple cell surface electrical signals to intracellular physiological responses by mediating voltage-dependent increases in the cytosoli eration and also serve to couple cell surface electrical<br>signals to intracellular physiological responses by me-<br>diating voltage-dependent increases in the cytosolic con-<br>centration of  $Ca^{2+}$  (Catterall et al., 1988), ar signals to intracellular physiological responses by me-<br>diating voltage-dependent increases in the cytosolic con-<br>centration of Ca<sup>2+</sup> (Catterall et al., 1988), are present in<br>both vertebrate and invertebrate neurons (Tsie diating voltage-dependent increases in the cytosolic co<br>centration of Ca<sup>2+</sup> (Catterall et al., 1988), are present<br>both vertebrate and invertebrate neurons (Tsien, 198<br>1986; Tsien et al., 1988; Hess, 1990). Studies of hea<br> centration of  $Ca^{2+}$  (Catterall et al., 1988), are present in<br>both vertebrate and invertebrate neurons (Tsien, 1983,<br>1986; Tsien et al., 1988; Hess, 1990). Studies of heart<br>cells showed that activation of cyclic AMP-depe both vertebrate and invertebrate neurons (Tsien, 1983, 1986; Tsien et al., 1988; Hess, 1990). Studies of heart cells showed that activation of cyclic AMP-dependent protein kinase mediated increases in the probability of Ca 1986; Tsien et al., 1988; Hess, 1990). Studies of heart cells showed that activation of cyclic AMP-dependent protein kinase mediated increases in the probability of  $Ca^{2+}$  channel opening and also increases in the number cells showed that activation of cyclic AMP-dependent<br>protein kinase mediated increases in the probability of<br>Ca<sup>2+</sup> channel opening and also increases in the number<br>of channels available for opening (Osterrieder et al.,<br>19 protein kinase mediated increases in the probability o  $Ca^{2+}$  channel opening and also increases in the numbe of channels available for opening (Osterrieder et al. 1982). The  $Ca^{2+}$  channel in heart appears similar to t  $Ca^{2+}$  channel opening and also increases in the number of channels available for opening (Osterrieder et al. 1982). The  $Ca^{2+}$  channel in heart appears similar to tha purified from skeletal muscle T-tubule membranes wh of channels available for opening (Osterrieder et al., 1982). The Ca<sup>2+</sup> channel in heart appears similar to that purified from skeletal muscle T-tubule membranes, which is identified by its ability to bind dihydropyridin 1982). The Ca<sup>2+</sup> channel in heart appears similar to that purified from skeletal muscle T-tubule membranes, which is identified by its ability to bind dihydropyridines such as nimodipine and nifedipine. This purified Ca<sup></sup> purified from skeletal muscle T-tubule membranes,<br>which is identified by its ability to bind dihydropyridines<br>such as nimodipine and nifedipine. This purified  $Ca^{2+}$ <br>channel, termed the L channel (Nowycky et al., 1985),<br> which is identified by its ability to bind dihydropyridines<br>such as nimodipine and nifedipine. This purified Ca<sup>2+</sup><br>channel, termed the L channel (Nowycky et al., 1985),<br>has been found to be subject to phosphorylation by<br>s such as nimodipine and nifedipine. This purified Ca<sup>2+</sup><br>channel, termed the L channel (Nowycky et al., 1985),<br>has been found to be subject to phosphorylation by<br>several protein kinases in vitro (for examples, see Curtis<br>an channel, termed the L channel (Nowycky et al., 1985),<br>has been found to be subject to phosphorylation by<br>several protein kinases in vitro (for examples, see Curtis<br>and Catterall, 1985; Hosey et al., 1986; Imagawa et al.,<br>1 has been found to be subject to phosphore<br>several protein kinases in vitro (for examples<br>and Catterall, 1985; Hosey et al., 1986; Imag<br>1987; Hosey and Lazdunski, 1988; Tsien et al<br>Jongh et al., 1989; Röhrkasten et al., 199 veral protein kinases in vitro (for examples, see Curt<br>d Catterall, 1985; Hosey et al., 1986; Imagawa et a<br>87; Hosey and Lazdunski, 1988; Tsien et al., 1988; I<br>ngh et al., 1989; Röhrkasten et al., 1990).<br>Other studies have

and Catterall, 1985; Hosey et al., 1986; Imagawa et al., 1987; Hosey and Lazdunski, 1988; Tsien et al., 1988; De<br>Jongh et al., 1989; Röhrkasten et al., 1990).<br>Other studies have indicated that similar Ca<sup>2+</sup> chan-<br>nels in 1987; Hosey and Lazdunski, 1988; Tsien et al., 1988; De<br>Jongh et al., 1989; Röhrkasten et al., 1990).<br>Other studies have indicated that similar  $Ca^{2+}$  chan-<br>nels in invertebrate neurons (Kostyuk, 1984; Doroshenko<br>et al., Jongh et al., 1989; Röhrkasten et al., 1990).<br>
Other studies have indicated that similar Ca<sup>2+</sup> chan-<br>
nels in invertebrate neurons (Kostyuk, 1984; Doroshenko<br>
et al., 1984; Eckert et al., 1986) and in the mammalian<br>
pitui nels in invertebrate neurons (Kostyuk, 1984; Doroshenko<br>et al., 1984; Eckert et al., 1986) and in the mammalian<br>pituitary cell line  $GH_3$  (Armstrong and Eckert, 1987)<br>may maintain their responsiveness through cyclic AMP-<br> nels in invertebrate neurons (Kostyuk, 1984; Doroshenko<br>et al., 1984; Eckert et al., 1986) and in the mammalian<br>pituitary cell line GH<sub>3</sub> (Armstrong and Eckert, 1987)<br>may maintain their responsiveness through cyclic AMP-<br>d et al., 1984; Eckert et al., 1986) and in the mammalian<br>pituitary cell line GH<sub>3</sub> (Armstrong and Eckert, 1987)<br>may maintain their responsiveness through cyclic AMP-<br>dependent protein phosphorylation (Armstrong, 1989).<br>When pituitary cell line GH<sub>3</sub> (Armstrong and Eckert, 1987)<br>may maintain their responsiveness through cyclic AMP-<br>dependent protein phosphorylation (Armstrong, 1989).<br>When excised patches from GH<sub>3</sub> cells were incubated<br>with t may maintain their responsiveness through cyclic AMP-<br>dependent protein phosphorylation (Armstrong, 1989).<br>When excised patches from  $GH_3$  cells were incubated<br>with the C subunit of cyclic AMP-dependent protein<br>kinase tog dependent protein phosphorylation (Armstrong, 1989).<br>When excised patches from  $GH_3$  cells were incubated<br>with the C subunit of cyclic AMP-dependent protein<br>kinase together with ATP, the L-type  $Ca^{2+}$  channels<br>were found When excised patches from  $GH_3$  cells were incubated<br>with the C subunit of cyclic AMP-dependent protein<br>kinase together with ATP, the L-type  $Ca^{2+}$  channels<br>were found to open normally, and they rapidly stopped<br>respondin with the C subunit of cyclic AMP-dependent pro<br>kinase together with ATP, the L-type Ca<sup>2+</sup> char<br>were found to open normally, and they rapidly stop<br>responding to membrane depolarization in the abs<br>of reagents that could sup kinase together with ATP, the L-type  $Ca^{2+}$  channels<br>were found to open normally, and they rapidly stopped<br>responding to membrane depolarization in the absence<br>of reagents that could support such protein phosphoryl<br>ation were found to open normally, and they rapidly stopped<br>responding to membrane depolarization in the absence<br>of reagents that could support such protein phosphoryl-<br>ation (Armstrong and Eckert, 1985). Other studies indi-<br>ca responding to membrane depolarization in the absence<br>of reagents that could support such protein phosphoryl-<br>ation (Armstrong and Eckert, 1985). Other studies indi-<br>cated that similar voltage-dependent  $Ca^{2+}$  channels fr of reagents that could support such protein phosphorylation (Armstrong and Eckert, 1985). Other studies indicated that similar voltage-dependent Ca<sup>2+</sup> channels from pituitary GH<sub>3</sub> cells were also sensitive to addition of ation (Armstrong and Eckert, 1985). Other studies indicated that similar voltage-dependent  $Ca^{2+}$  channels from pituitary  $GH_3$  cells were also sensitive to addition of CaM kinase II, the latter enzyme inducing very long cated that similar voltage-dependent  $Ca^{2+}$  channels from pituitary  $GH_3$  cells were also sensitive to addition of CaM kinase II, the latter enzyme inducing very long opening times of the individual channels following de CaM kinase II, the latter enzyme inducing very long CaM kinase II, the latter enzyme inducing very long<br>opening times of the individual channels following de-<br>polarization, in contrast to the brief opening responses<br>seen in the presence of cyclic AMP-dependent protein<br>kina opening times of the individual channels following de-<br>polarization, in contrast to the brief opening responses<br>seen in the presence of cyclic AMP-dependent protein<br>kinase in these preparations (Armstrong et al., 1987). I polarization, in contrast to the brief opening responses<br>seen in the presence of cyclic AMP-dependent protein<br>kinase in these preparations (Armstrong et al., 1987). In<br>contrast, Ca<sup>2+</sup> channels from GH<sub>3</sub> cells were inhibi en in the presence of cyclic AMP-dependent protein<br>nase in these preparations (Armstrong et al., 1987). In<br>ntrast, Ca<sup>2+</sup> channels from GH<sub>3</sub> cells were inhibited by<br>otein kinase C activators (Marchetti and Brown, 1988).<br>

kinase in these preparations (Armstrong et al., 1987). In contrast,  $Ca^{2+}$  channels from  $GH_3$  cells were inhibited by protein kinase C activators (Marchetti and Brown, 1988). The dihydropyridine-binding L-type  $Ca^{2+}$  c protein kinase C activators (Marchetti and Brown, 1988).<br>The dihydropyridine-binding L-type Ca<sup>2+</sup> channels are<br>known to be rapidly inactivated by the Ca<sup>2+</sup> ions which<br>enter through the channels during depolarization,<br>th protein kinase C activators (Marchetti and Brown, 1988).<br>The dihydropyridine-binding L-type Ca<sup>2+</sup> channels are<br>known to be rapidly inactivated by the Ca<sup>2+</sup> ions which<br>enter through the channels during depolarization,<br>th The dihydropyridine-binding L-type Ca<sup>2+</sup> channels are<br>known to be rapidly inactivated by the Ca<sup>2+</sup> ions which<br>enter through the channels during depolarization,<br>thereby reducing the opening frequency of the channels<br>and known to be rapidly inactivated by the  $Ca^{2+}$  ions which<br>enter through the channels during depolarization,<br>thereby reducing the opening frequency of the channels<br>and reducing the accumulation of intracellular  $Ca^{2+}$ <br>(Ec enter through the channels during depolarization,<br>thereby reducing the opening frequency of the channels<br>and reducing the accumulation of intracellular  $Ca^{2+}$ <br>(Eckert and Chad, 1984; Chad and Eckert, 1986; Kalman<br>et al., thereby reducing the opening frequency of the channes<br>and reducing the accumulation of intracellular Ca<br>(Eckert and Chad, 1984; Chad and Eckert, 1986; Kalm-<br>et al., 1988; Armstrong, 1989). This phenomenon, whi<br>can be preve and reducing the accumulation of intracellular  $Ca^2$ <br>(Eckert and Chad, 1984; Chad and Eckert, 1986; Kalman<br>et al., 1988; Armstrong, 1989). This phenomenon, which<br>can be prevented by agents that promote cyclic AMP<br>dependen (Eckert and Chad, 1984; Chad and Eckert, 1986; Kalman<br>et al., 1988; Armstrong, 1989). This phenomenon, which<br>can be prevented by agents that promote cyclic AMP-<br>dependent protein phosphorylation (Armstrong and Eck-<br>ert, 19



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1 or -2A have also been reported to inactivate such  $Ca^{2+}$  plots channels (Hescheler et al., 1987). <br>
Another type of voltage-dependent  $Ca^{2+}$  channel is in found in the bag cell neurons of *Aplysia*. Exposure of repres channels (Hescheler et al., 1987).<br>
Another type of voltage-dependent  $Ca^{2+}$  channel<br>
found in the bag cell neurons of *Aplysia*. Exposure<br>
these cells to phorbol esters or intracellular injection<br>
protein kinase C was f Another type of voltage-dependent  $Ca^{2+}$  channel is in found in the bag cell neurons of *Aplysia*. Exposure of rethese cells to phorbol esters or intracellular injection of st protein kinase C was found to enhance the vo found in the bag cell neurons of *Aplysia*. Exposure of these cells to phorbol esters or intracellular injection of protein kinase C was found to enhance the voltage-sensitive  $Ca^{2+}$  current mostly responsible for the in these cells to phorbol esters or intracellular injection of protein kinase C was found to enhance the voltage-<br>sensitive  $Ca^{2+}$  current mostly responsible for the inward<br>current, without affecting voltage-dependent K<sup>+</sup> protein kinase C was found to enhance the voltage-<br>sensitive Ca<sup>2+</sup> current mostly responsible for the inward<br>current, without affecting voltage-dependent K<sup>+</sup> currents<br>(DeRiemer et al., 1985). Further analysis indicated sensitive Ca<sup>2+</sup> current mostly responsible for the inward current, without affecting voltage-dependent  $K^+$  curren (DeRiemer et al., 1985). Further analysis indicated that this increase was due to an apparent recruitmen current, without affecting voltage-dependent  $K^+$  currents<br>(DeRiemer et al., 1985). Further analysis indicated that<br>this increase was due to an apparent recruitment of<br>previously inactive  $Ca^{2+}$  channels in the neuronal this increase was due to an apparent recruitment of previously inactive  $Ca^{2+}$  channels in the neuronal membrane et brane (Strong et al., 1987; Kaczmarek, 1987). In contrast, phactivation of cyclic AMP-dependent protein previously inactive  $Ca^{2+}$  channels in the neuronal membrane (Strong et al., 1987; Kaczmarek, 1987). In contrast, activation of cyclic AMP-dependent protein kinase caused decreases in at least three  $K^+$  currents in the brane (Strong et al., 1987; H<br>activation of cyclic AMI<br>caused decreases in at les<br>same neurons without affee<br>(Kaczmarek et al., 1980).<br>Neurotransmitter-induce tivation of cyclic AMP-dependent protein kinase<br>used decreases in at least three  $K^+$  currents in the<br>me neurons without affecting the inward  $Ca^{2+}$  current<br>faczmarek et al., 1980).<br>Neurotransmitter-induced regulation o

caused decreases in at least three  $K^+$  currents in the<br>same neurons without affecting the inward  $Ca^{2+}$  current st<br>(Kaczmarek et al., 1980).<br>Neurotransmitter-induced regulation of  $Ca^{2+}$  channels so<br>mediated by protei same neurons without affecting the inward  $Ca^{2+}$  current<br>
(Kaczmarek et al., 1980).<br>
Neurotransmitter-induced regulation of  $Ca^{2+}$  channels<br>
mediated by protein phosphorylation also occurs in *Helix*<br>
neurons. In these (Kaczmarek et al., 1980).<br>
Neurotransmitter-induced regulation of  $Ca^{2+}$  channels<br>
mediated by protein phosphorylation also occurs in *Helix*<br>
peurons. In these snails, serotonin induced an increase<br>
of  $Ca^{2+}$  currents Neurotransmitter-induced regulation of  $Ca^{2+}$  channel mediated by protein phosphorylation also occurs in  $He$  neurons. In these snails, serotonin induced an increase of  $Ca^{2+}$  currents in a set of ventral neurons, with t mediated by protein phosphorylation also occurs in  $Helix$  pen<br>neurons. In these snails, serotonin induced an increase cre<br>of  $Ca^{2+}$  currents in a set of ventral neurons, with this bra<br>effect apparently being mediated throu of  $Ca^{2+}$  currents in a set of ventral neurons, with effect apparently being mediated through cyclic GM<br>dependent protein kinase, because the effect could<br>mimicked by intracellular injection of cyclic GMP o<br>an inhibitor effect apparently being mediated through cyclic GMP-<br>dependent protein kinase, because the effect could be<br>mimicked by intracellular injection of cyclic GMP or of<br>an inhibitor of cyclic GMP phosphodiesterase (Paupar-<br>din-T dependent protein kinase, because the effect could be<br>mimicked by intracellular injection of cyclic GMP or of<br>an inhibitor of cyclic GMP phosphodiesterase (Paupar-<br>din-Tritsch et al., 1986a,b). Further evidence for protei mimicked by intracellular injection of cyclic GMP or of<br>an inhibitor of cyclic GMP phosphodiesterase (Paupar-<br>din-Tritsch et al., 1986a,b). Further evidence for protein<br>phosphorylation being involved was obtained when it<br>w an inhibitor of cyclic GMP phosphodiesterase (Paupar-<br>din-Tritsch et al., 1986a,b). Further evidence for protein<br>phosphorylation being involved was obtained when it<br>was found that the effect of serotonin was potentiated<br>b din-Tritsch et al., 1986a,b). Further evidence for protein<br>phosphorylation being involved was obtained when it<br>was found that the effect of serotonin was potentiated<br>by injection of activated cyclic GMP-dependent protein<br> phosphorylation being involved was obtained when it<br>was found that the effect of serotonin was potentiated<br>by injection of activated cyclic GMP-dependent protein<br>kinase (Paupardin-Tritsch et al., 1986b). These data<br>indicat was found that the effect of serotonin was potentiat<br>by injection of activated cyclic GMP-dependent prote<br>kinase (Paupardin-Tritsch et al., 1986b). These da<br>indicate that serotonin in these cells causes an increa<br>in cyclic by injection of activated cyclic GMP-dependent protein<br>kinase (Paupardin-Tritsch et al., 1986b). These data<br>indicate that serotonin in these cells causes an increase<br>in cyclic GMP levels, thereby activating cyclic GMP-<br>dep kinase (Paupardin-Tritsch et al., 1986b). These data<br>indicate that serotonin in these cells causes an increase<br>in cyclic GMP levels, thereby activating cyclic GMP-<br>dependent protein kinase and inducing phosphorylation<br>of indicate that serotonin in these cells causes an incre<br>in cyclic GMP levels, thereby activating cyclic GM<br>dependent protein kinase and inducing phosphorylat<br>of the Ca<sup>2+</sup> channel or some associated protein, which<br>turn mod zation. pendent protein kinase and inducing phosphorylation<br>the Ca<sup>2+</sup> channel or some associated protein, which in<br>rn modulates the response of the channel to depolari-<br>tion.<br>In other *Helix* neurons, cholecystokinin, a widely di turn modulates the response of the channel to depolarization.<br>In other *Helix* neurons, cholecystokinin, a widely dis-

turn modulates the response of the channel to depolarization.<br>
In other *Helix* neurons, cholecystokinin, a widely distributed neuropeptide, appeared to modulate  $Ca^{2+}$  currents through protein kinase C (Hammond et al., zation.<br>
In other *Helix* neurons, cholecystokinin, a widely dis-<br>
tributed neuropeptide, appeared to modulate  $Ca^{2+}$  cur-<br>
rents through protein kinase C (Hammond et al., 1987).<br>
Extracellular application of sulfated ch In other *Helix* neurons, cholecystokinin, a widely dis-<br>tributed neuropeptide, appeared to modulate  $Ca^{2+}$  cur-<br>rents through protein kinase C (Hammond et al., 1987).<br>Extracellular application of sulfated cholecystokini In view neutral heating, encorrection and the Ca<sup>2+</sup> currents through protein kinase C (Hammond et al., 1987).<br>
Extracellular application of sulfated cholecystokinin occurrents through protein kinase C (Hammond et al., 19 of the  $Ca^{2+}$  current in these cells. Moreover, intracellular injections of low concentrations of protein kinase C, dependent action potential and decreased the amplitude tapeptide or activators of protein kinase C, or intracel-<br>lular injection of protein kinase C, shortened the  $Ca^{2+}$ -<br>dependent action potential and decreased the amplitude<br>of the  $Ca^{2+}$  current in these cells. Moreover, lular injection of protein kinase C, shortened the  $Ca^{2+}$ -<br>dependent action potential and decreased the amplitude<br>of the  $Ca^{2+}$  current in these cells. Moreover, intracellular<br>injections of low concentrations of protein dependent action potential and decreased the amplitude<br>of the  $Ca^{2+}$  current in these cells. Moreover, intracellular<br>injections of low concentrations of protein kinase C,<br>which by themselves were ineffective, enhanced th of the Ca<sup>2+</sup> current in these cells. Moreover, intracellular injections of low concentrations of protein kinase C, which by themselves were ineffective, enhanced the effectiveness of low concentrations of cholecystokinin injections of low concentrations of protein kinase C,<br>which by themselves were ineffective, enhanced the ef-<br>fectiveness of low concentrations of cholecystokinin oc-<br>tapeptide on the  $Ca^{2+}$  current (Hammond et al., 1987) which by themselves were ineffective, enhanced the effectiveness of low concentrations of cholecystokinin octapeptide on the  $Ca^{2+}$  current (Hammond et al., 1987).<br>Similar results have been obtained in chick dorsal root fectiveness of low concentrations of cholecystokinin oc-<br>tapeptide on the  $Ca^{2+}$  current (Hammond et al., 1987).<br>Similar results have been obtained in chick dorsal root<br>ganglion cells with noradrenaline and activators of tapeptide on the  $Ca^{2+}$  current (Hammond et al., 198<br>Similar results have been obtained in chick dorsal reganglion cells with noradrenaline and activators of p<br>tein kinase C, agents that shortened the duration<br>action pot Similar results have been obtained in chick dorsal<br>ganglion cells with noradrenaline and activators of<br>tein kinase C, agents that shortened the duratio<br>action potentials and decreased the amplitude of volt<br>dependent Ca<sup>2+</sup> nglion cells with noradrenaline and activators of prin kinase C, agents that shortened the duration is<br>tion potentials and decreased the amplitude of voltage<br>pendent Ca<sup>2+</sup> current (Rane and Dunlap, 1986).<br>IP<sub>3</sub>-dependent

(DeRiemer et al., 1985). Further analysis indicated that pone et al., 1988b) and found to be identical with the<br>this increase was due to an apparent recruitment of previously described Purkinje cell proteins P-400 (Mallet of  $Ca^{2+}$  currents in a set of ventral neurons, with this brane vesicles (Supattapone et al., 1988a). Such<br>effect apparently being mediated through cyclic GMP-<br>dependent protein kinase, because the effect could be releas AND NEURONAL FUNCTION 325<br>cellularly (Berridge, 1984, 1987), also appear to be regu-<br>lated by phosphorylation. As described in section II.A.1, AND NEURONAL FUNCTION 325<br>cellularly (Berridge, 1984, 1987), also appear to be regu-<br>lated by phosphorylation. As described in section II.A.1,<br>IP<sub>3</sub> is generated by receptor-regulated breakdown of AND NEURONAL FUNCTION 325<br>
1955<br>
1939 cellularly (Berridge, 1984, 1987), also appear to be regulated by phosphorylation. As described in section II.A.1,<br>
1P<sub>3</sub> is generated by receptor-regulated breakdown of<br>
phosphatidyli cellularly (Berridge, 1984, 1987), also appear to be regulated by phosphorylation. As described in section II.A.1,  $IP_3$  is generated by receptor-regulated breakdown of phosphatidylinositol bisphosphate and is believed to cellularly (Berridge, 1984, 1987), also appear to be regulated by phosphorylation. As described in section II.A.1,  $IP_3$  is generated by receptor-regulated breakdown of phosphatidylinositol bisphosphate and is believed to lated by phosphorylation. As described in section II.A.1,  $IP_3$  is generated by receptor-regulated breakdown of phosphatidylinositol bisphosphate and is believed to regulate intracellular  $Ca^{2+}$  levels by releasing  $Ca^{2+$ phosphatidylinositol bisphosphate and is believed to regulate intracellular  $Ca^{2+}$  levels by releasing  $Ca^{2+}$  from intracellular stores in the endoplasmic reticulum (for a recent review, see Berridge and Irvine, 1989). ulate intracellular  $Ca^{2+}$  levels by releasing  $Ca^{2+}$  from intracellular stores in the endoplasmic reticulum (for a recent review, see Berridge and Irvine, 1989). Recent studies have shown that Purkinje cells in the cer ulate intracellular Ca<sup>2+</sup> levels by releasing Ca<sup>2+</sup> fro<br>intracellular stores in the endoplasmic reticulum (for<br>recent review, see Berridge and Irvine, 1989). Rece<br>studies have shown that Purkinje cells in the cerebellu<br> intracellular stores in the endoplasmic reticulum (for a recent review, see Berridge and Irvine, 1989). Recent studies have shown that Purkinje cells in the cerebellum contain uniquely high levels of an intracellular  $IP_3$ studies have shown that Purkinje cells in the cerebellum<br>contain uniquely high levels of an intracellular  $IP_3$  recep-<br>tor (Worley et al., 1989; Mignery et al., 1989). This<br>protein has been purified from the cerebellum (S previously described Purkinje cell proteins P-400 (Mallet contain uniquely high levels of an intracellular  $IP_3$  receptor (Worley et al., 1989; Mignery et al., 1989). This protein has been purified from the cerebellum (Supattapone et al., 1988b) and found to be identical with th tor (Worley et al., 1989; Mignery et al., 1989). The protein has been purified from the cerebellum (Supattipone et al., 1988b) and found to be identical with the previously described Purkinje cell proteins P-400 (Malli et protein has been purified from the cerebellum (Supa<br>pone et al., 1988b) and found to be identical with<br>previously described Purkinje cell proteins P-400 (Ma<br>et al., 1976) and PCPP-260, a protein efficiently pl<br>phorylated i pone et al., 1988b) and found to be identical with the previously described Purkinje cell proteins P-400 (Mallet et al., 1976) and PCPP-260, a protein efficiently phosphorylated in cerebellar membranes by cyclic AMP-depend previously described Purkinje cell proteins P-400 (Mall<br>et al., 1976) and PCPP-260, a protein efficiently pho<br>phorylated in cerebellar membranes by cyclic AMP-c<br>pendent protein kinase (Walaas et al., 1983b, 1986<br>Weeks et a et al., 1976) and PCPP-260, a protein efficiently phos-<br>phorylated in cerebellar membranes by cyclic AMP-de-<br>pendent protein kinase (Walaas et al., 1983b, 1986b;<br>Weeks et al., 1988; Yamamoto et al., 1989). When recon-<br>sti phorylated in cerebellar membranes by cyclic AMP-de<br>pendent protein kinase (Walaas et al., 1983b, 1986b<br>Weeks et al., 1988; Yamamoto et al., 1989). When recon<br>stituted into liposomes, this protein induced both IP<br>binding pendent protein kinase (Walaas et al., 1983b, 198<br>Weeks et al., 1988; Yamamoto et al., 1989). When rec<br>stituted into liposomes, this protein induced both<br>binding and IP<sub>3</sub>-sensitive Ca<sup>2+</sup> transport in these li<br>somes (Ferr Weeks et al., 1988; Yamamoto et al., 1989). When reconstituted into liposomes, this protein induced both  $IP_3$  binding and  $IP_3$ -sensitive  $Ca^{2+}$  transport in these liposomes (Ferris et al., 1989). Moreover, cyclic AMP-d stituted into liposomes, this protein induced both II<br>binding and IP<sub>3</sub>-sensitive Ca<sup>2+</sup> transport in these lip<br>somes (Ferris et al., 1989). Moreover, cyclic AMP-d<br>pendent phosphorylation of the protein appeared to d<br>crea binding and IP<sub>3</sub>-sensitive Ca<sup>2+</sup> transport in these liposomes (Ferris et al., 1989). Moreover, cyclic AMP-dependent phosphorylation of the protein appeared to decrease the capacity for Ca<sup>2+</sup> release from cerebellar mem somes (Ferris et al., 1989). Moreover, cyclic AMP-de-<br>pendent phosphorylation of the protein appeared to de-<br>crease the capacity for  $Ca^{2+}$  release from cerebellar mem-<br>brane vesicles (Supattapone et al., 1988a). Such<br>ph pendent phosphorylation of the protein appeared to  $c$  crease the capacity for  $Ca^{2+}$  release from cerebellar meer brane vesicles (Supattapone et al., 1988a). Suphosphorylation-induced decreases in  $IP_3$ -regulated  $Ca$  re crease the capacity for  $Ca^{2+}$  release from cerebellar mem-<br>brane vesicles (Supattapone et al., 1988a). Such<br>phosphorylation-induced decreases in IP<sub>3</sub>-regulated  $Ca^{2+}$ <br>release from intracellular stores may constitute a brane vesicles (Supattapone et al., 1988a). Such phosphorylation-induced decreases in  $IP_3$ -regulated Ca<sup>r</sup> release from intracellular stores may constitute a mole-<br>ular mechanism whereby receptors acting through cycle AM phosphorylation-induced decreases in  $IP_3$ -regulated Ca<sup>2+</sup><br>release from intracellular stores may constitute a molec-<br>ular mechanism whereby receptors acting through cyclic<br>AMP (e.g.,  $\beta$ -adrenergic receptors) modulate t release from intracellular stores may constitute a molecular mechanism whereby receptors acting through cyclic AMP (e.g.,  $\beta$ -adrenergic receptors) modulate the physiological responses to those neurotransmitter receptors ar mechanism whereby receptors acting through cyclic<br>MP (e.g.,  $\beta$ -adrenergic receptors) modulate the phys-<br>ogical responses to those neurotransmitter receptors<br>at induce IP<sub>3</sub> generation and intracellular Ca<sup>2+</sup> release

AMP (e.g.,  $\beta$ -adrenergic receptors) modulate the physiological responses to those neurotransmitter receptors that induce IP<sub>3</sub> generation and intracellular Ca<sup>2+</sup> release.<br>Interestingly, examination of the primary struc iological responses to those neurotransmitter receptors<br>that induce  $IP_3$  generation and intracellular  $Ca^{2+}$  release.<br>Interestingly, examination of the primary structure of<br>the  $IP_3$  receptor protein, deduced from the n that induce IP<sub>3</sub> generation and intracellular Ca<sup>2+</sup> relea<br>Interestingly, examination of the primary structure<br>the IP<sub>3</sub> receptor protein, deduced from the nucleot<br>sequence of cloned complementary DNA, has indicat<br>that t Interestingly, examination of the primary structure<br>the  $IP_3$  receptor protein, deduced from the nucleotic<br>sequence of cloned complementary DNA, has indicate<br>that the protein is homologous to the so-called "ryan<br>dine rece the IP<sub>3</sub> receptor protein, deduced from the nucleotide sequence of cloned complementary DNA, has indicated that the protein is homologous to the so-called "ryano-<br>dine receptor" protein present in striated muscle sarco-<br> sequence of cloned complementary DNA, has indicated<br>that the protein is homologous to the so-called "ryano-<br>dine receptor" protein present in striated muscle sarco-<br>plasmic reticulum (Furuichi et al., 1989; Mignery et al., that the protein is homologous to the so-called "ryano-<br>dine receptor" protein present in striated muscle sarco-<br>plasmic reticulum (Furuichi et al., 1989; Mignery et al.,<br>1989, 1990). However, the latter protein, which is dine receptor" protein present in striated muscle sarco-<br>plasmic reticulum (Furuichi et al., 1989; Mignery et al.,<br>1989, 1990). However, the latter protein, which is re-<br>sponsible for that release of Ca<sup>2+</sup> from the sarcop plasmic reticulum (Furuichi et al., 1989; Mignery et a 1989, 1990). However, the latter protein, which is r sponsible for that release of  $Ca^{2+}$  from the sarcoplasm reticulum which initiates muscular contraction an which 1989, 1990). However, the latter protein, which is responsible for that release of  $Ca^{2+}$  from the sarcoplasmic reticulum which initiates muscular contraction and which is activated following sarcolemma depolarization, d sponsible for that release of  $Ca^{2+}$  from the sarcoplasmic<br>reticulum which initiates muscular contraction and<br>which is activated following sarcolemma depolarization,<br>does not share sequence homology with the IP<sub>3</sub> recept reticulum which initiates muscular contraction and<br>which is activated following sarcolemma depolarization,<br>does not share sequence homology with the IP<sub>3</sub> receptor<br>in those domains that contain possible phosphorylation<br>si which is activated following sarcolemma depolarization,<br>does not share sequence homology with the IP<sub>3</sub> receptor<br>in those domains that contain possible phosphorylation<br>sites for cyclic AMP-dependent protein kinase (Furuic does not share sequence homology with the IP<sub>3</sub> recept<br>in those domains that contain possible phosphorylati<br>sites for cyclic AMP-dependent protein kinase (Furuic<br>et al., 1989). The ryanodine receptor Ca<sup>2+</sup> channel<br>striat sites for cyclic AMP-dependent protein kinase (Furuichi striated muscle may thus be subject to regulatory mech-

## *Pathways*

The major may change of the IP<sub>3</sub> receptor.<br>
Regulation of Interactions of Neurotransmitter<br>
uthways<br>
One of the major roles played by protein phosph<br>
ion pathways in the nervous system is the media C. Regulation of Interactions of Neurotransmitter<br>Pathways<br>One of the major roles played by protein phosphoryl-<br>ation pathways in the nervous system is the mediation<br>of receptor-receptor interactions. The interaction of th C. Regulation of Interactions of Neurotransmitter<br>Pathways<br>One of the major roles played by protein phosphoryl-<br>ation pathways in the nervous system is the mediation<br>of receptor-receptor interactions. The interaction of th Pathways<br>One of the major roles played by protein phosphoryl<br>ation pathways in the nervous system is the mediation<br>of receptor-receptor interactions. The interaction of th<br>calcitonin gene-related peptide-receptor with the One of the major roles played by protein phosphorylation pathways in the nervous system is the mediation of receptor-receptor interactions. The interaction of the calcitonin gene-related peptide-receptor with the nicotinic ation pathways in the nervous system is the mediation<br>of receptor-receptor interactions. The interaction of the<br>calcitonin gene-related peptide-receptor with the nico-<br>tinic acetylcholine receptor, mediated through cyclic<br> of receptor-receptor interactions. The interaction of the calcitonin gene-related peptide-receptor with the nicotinic acetylcholine receptor, mediated through cyclic AMP-dependent protein kinase (see section V.A.1.), is an calcitonin gene-related peptide-receptor with the nice tinic acetylcholine receptor, mediated through cycl AMP-dependent protein kinase (see section V.A.1.), an example of such an interaction mediated by protein phosphoryl tinic acetylcholine receptor, mediated through cyclic AMP-dependent protein kinase (see section V.A.1.), is an example of such an interaction mediated by protein phosphorylation. A novel type of receptor-receptor interacti 326 **WALAAS AND GREENGARD**<br>protein phosphorylation pathway is the dopamine-glu-<br>tamate interaction that occurs in the medium-sized spiny has demons WALAAS AND GRI<br>protein phosphorylation pathway is the dopamine-glu-<br>tamate interaction that occurs in the medium-sized spiny ha<br>neurons of the neostriatum. It is generally accepted that of WALAAS AND<br>protein phosphorylation pathway is the dopamine-glu-<br>tamate interaction that occurs in the medium-sized spiny<br>neurons of the neostriatum. It is generally accepted that<br>dopamine, the neurotransmitter released fro protein phosphorylation pathway is the dopamine-glumate interaction that occurs in the medium-sized spin neurons of the neostriatum. It is generally accepted the dopamine, the neurotransmitter released from the nigrostriat protein phosphorylation pathway is the dopamine-glu-<br>tamate interaction that occurs in the medium-sized spiny<br>neurons of the neostriatum. It is generally accepted that<br>dopamine, the neurotransmitter released from the nigro tamate interaction that occurs in the medium-sized spiny has<br>neurons of the neostriatum. It is generally accepted that of<br>dopamine, the neurotransmitter released from the nigro-<br>tionstriatal neurons (for examples, see Moor neurons of the neostriatum. It is generally accepted that of dopamine, the neurotransmitter released from the nigro-<br>striatal neurons (for examples, see Moore and Bloom, si<br>1978), reduces the excitability of the medium-siz dopamine, the neurotransmitter released from the nigro-<br>striatal neurons (for examples, see Moore and Bloom,<br>1978), reduces the excitability of the medium-sized spiny<br>neurons to glutamate, the neurotransmitter released<br>fro striatal neurons (for examples, see Moore and Bloom, s<br>1978), reduces the excitability of the medium-sized spiny<br>neurons to glutamate, the neurotransmitter released<br>from the corticostriatal fibers (Calabresi et al., 1987; 1978), reduces the excitability of the medium-sized spiny manurons to glutamate, the neurotransmitter released str.<br>from the corticostriatal fibers (Calabresi et al., 1987; laa<br>Chiodo and Berger, 1986). Recent studies have neurons to glutamate, the neurotransmitter released strain from the corticostriatal fibers (Calabresi et al., 1987; last Chiodo and Berger, 1986). Recent studies have elucidated mis a protein phosphorylation pathway that a from the corticostriatal fibers (Calabresi et al., 19.<br>Chiodo and Berger, 1986). Recent studies have elucidat<br>a protein phosphorylation pathway that appears to<br>involved in this inhibitory process. Before describing t<br>detai Chiodo and Berger, 1986). Recent studie<br>a protein phosphorylation pathway th<br>involved in this inhibitory process. Befor<br>details of this pathway, a brief discussi<br>zation of the basal ganglia is warranted<br>The importance of b protein phosphorylation pathway that appears to be<br>volved in this inhibitory process. Before describing the<br>tails of this pathway, a brief discussion of the organi-<br>tion of the basal ganglia is warranted.<br>The importance of

involved in this inhibitory process. Before describing the details of this pathway, a brief discussion of the organization of the basal ganglia is warranted. The importance of basal ganglion neurons, particularly in the ni details of this pathway, a brief discussion of the organization of the basal ganglia is warranted. The importance of basal ganglion neurons, particularly in the nigrostriatal and striatonigral fiber tracts, in the by funct zation of the basal ganglia is warranted.<br>The importance of basal ganglion neurons, particularly<br>the nigrostriatal and striatonigral fiber tracts, in the<br>function and dysfunction of the mammalian brain, is<br>well documented The importance of basal ganglion neurons, particularly<br>the nigrostriatal and striatonigral fiber tracts, in the<br>function and dysfunction of the mammalian brain, is<br>well documented (Yahr, 1976; Divac and Oberg, 1979;<br>McKenz the nigrostriatal and striatonigral fiber tracts, in the function and dysfunction of the mammalian brain, is well documented (Yahr, 1976; Divac and Oberg, 1979; McKenzie et al., 1984; Goldman-Rakic and Selemon, 1990). Thes function and dysfunction of the mammalian brain, is (We<br>well documented (Yahr, 1976; Divac and Oberg, 1979; Hen<br>McKenzie et al., 1984; Goldman-Rakic and Selemon, cent<br>1990). These regions, which make up most of the so-<br>cal well documented (Yahr, 1976; Divac and Oberg, 1979;<br>McKenzie et al., 1984; Goldman-Rakic and Selemon,<br>1990). These regions, which make up most of the so-<br>called "extrapyramidal motor system," are organized in<br>distinct, int McKenzie et al., 1984; Goldman-Rakic and Selen<br>1990). These regions, which make up most of the<br>called "extrapyramidal motor system," are organize<br>distinct, interconnected nuclei that funnel informa<br>through the system in a 1990). These regions, which make up most of the so-<br>called "extrapyramidal motor system," are organized in vati<br>distinct, interconnected nuclei that funnel information Clare<br>through the system in a well-defined manner (Gol called "extrapyramidal motor system," are organized in distinct, interconnected nuclei that funnel information<br>through the system in a well-defined manner (Goldman-Rakic and Selemon, 1990). The neostriatum, which in<br>the ro distinct, interconnected nuclei that funnel information<br>through the system in a well-defined manner (Goldman-<br>Rakic and Selemon, 1990). The neostriatum, which in<br>the rodent consists of the caudatoputamen, the nucleus<br>accum through the system in a well-defined manner (Goldman-Rakic and Selemon, 1990). The neostriatum, which in the rodent consists of the caudatoputamen, the nucleus accumbens, and parts of the olfactory tubercle, receives major Rakic and Selemon, 1990). The neostriatum, which in ing<br>the rodent consists of the caudatoputamen, the nucleus wit<br>accumbens, and parts of the olfactory tubercle, receives Boy<br>major, excitatory inputs from different parts accumbens, and parts of the olfactory tubercle, receives<br>major, excitatory inputs from different parts of the cer-<br>ebral cortex (Graybiel and Ragsdale, 1983; Nauta and<br>Domesick, 1984). Evidence suggests that these input<br>fi accumbens, and parts of the olfactory tubercle, receives<br>major, excitatory inputs from different parts of the cer-<br>ebral cortex (Graybiel and Ragsdale, 1983; Nauta and<br>Domesick, 1984). Evidence suggests that these input<br>fi major, excitatory inputs from different parts of the cer-<br>ebral cortex (Graybiel and Ragsdale, 1983; Nauta and<br>Domesick, 1984). Evidence suggests that these input<br>fibers are predominantly glutamatergic (Fonnum et al.,<br>1981 ebral cortex (Graybiel and Ragsdale, 1983; Nauta and conduction processick, 1984). Evidence suggests that these input celessions are predominantly glutamatergic (Fonnum et al., 19. 1981). Following activation of the cortic Domesick, 1984). Evidence suggests that these in<br>fibers are predominantly glutamatergic (Fonnum et<br>1981). Following activation of the corticostriatal s<br>apses and information processing in the neostriatum,<br>nerve impulses ar fibers are predominantly glutamatergic (Fonnum et al<br>1981). Following activation of the corticostriatal syr<br>apses and information processing in the neostriatum, th<br>nerve impulses are funneled out through the predom<br>nantly 1981). Following activation of the corticostriatal syn<br>apses and information processing in the neostriatum, th<br>nerve impulses are funneled out through the predomi<br>nantly inhibitory, GABAergic and/or peptidergic path<br>ways w apses and information processing in the neostriatum, the<br>nerve impulses are funneled out through the predomi-<br>nantly inhibitory, GABAergic and/or peptidergic path-<br>ways which terminate in the globus pallidus, the ento-<br>ped nerve impulses are funneled out through the nantly inhibitory, GABAergic and/or peptiways which terminate in the globus pallidupeduncular nucleus, and the pars reticulate stantia nigra (Fonnum and Walaas, 1979). Major func

the neostriatum. The efficacy of the glutamatergic transpeduncular nucleus, and the pars reticulata of the su<br>stantia nigra (Fonnum and Walaas, 1979).<br>Major functional interactions in this neuronal syste<br>appear to take place at the corticostriatal synapses<br>the neostriatum. The stantia nigra (Fonnum and Walaas, 1979).<br>Major functional interactions in this neuronal system<br>appear to take place at the corticostriatal synapses in<br>the neostriatum. The efficacy of the glutamatergic trans-<br>mission in th Major functional interactions in this neuronal system<br>appear to take place at the corticostriatal synapses in<br>the neostriatum. The efficacy of the glutamatergic trans-<br>mission in the axodendritic synapses found on the denappear to take place at the corticostriatal synapses in<br>the neostriatum. The efficacy of the glutamatergic trans-<br>mission in the axodendritic synapses found on the den-<br>dritic spines of the medium-sized spiny striatal neur the neostriatum. The efficacy of the glutamatergic trans-<br>mission in the axodendritic synapses found on the den-<br>dritic spines of the medium-sized spiny striatal neurons<br>appears to be under control of dopaminergic fibers t mission in the axodendritic synapses found on the dendritic spines of the medium-sized spiny striatal neurons appears to be under control of dopaminergic fibers terminating on the spine necks, dendritic shafts, and somata dritic spines of the medium-sized spiny striatal neurons<br>appears to be under control of dopaminergic fibers ter-<br>minating on the spine necks, dendritic shafts, and somata<br>of the medium-sized spiny neurons (Freund et al., 1 appears to be under control of dopaminergic fibers ter-<br>minating on the spine necks, dendritic shafts, and somata<br>of the medium-sized spiny neurons (Freund et al., 1984).<br>In this synapse, dopamine, through cyclic AMP, indu minating on the spine necks, dendritic shafts, and somata<br>of the medium-sized spiny neurons (Freund et al., 1984).<br>In this synapse, dopamine, through cyclic AMP, induces<br>a rapid decrease in responsiveness to glutamate or g of the medium-sized spiny neurons (Freund et al., 1984). and this synapse, dopamine, through cyclic AMP, induces (1 a rapid decrease in responsiveness to glutamate or glu-<br>a rapid decrease in responsiveness to glutamate or In this synapse, dopamine, through cyclic AMP, induces (He<br>a rapid decrease in responsiveness to glutamate or glu-<br>tamate analogs (Woodruff et al., 1976; Bernardi et al., erat<br>1984; Calabresi et al., 1987). It, therefore, a rapid decrease in responsiveness to glutamate or glutamate analogs (Woodruff et al., 1976; Bernardi et al. 1984; Calabresi et al., 1987). It, therefore, appears oparticular importance that the dopamine D1 receptor, is a tamate analogs (Woodruff et al., 1976; Bernardi et al., 1984; Calabresi et al., 1987). It, therefore, appears of particular importance that the dopamine D1 receptor, in addition to  $\beta$ - adrenergic receptors, serotonin an 1984; Calabresi et al., 1987). It, therefore, appears of particular importance that the dopamine D1 receptor, in addition to  $\beta$ - adrenergic receptors, serotonin and adenosine receptors, and receptors for vasoactive inte particular importance that the dopamine D1 receptor, in addition to  $\beta$ - adrenergic receptors, serotonin and adenosine receptors, and receptors for vasoactive intestinal polypeptide, regulate the levels of cyclic AMP in addition to  $\beta$ - adrenergic receptors, serotonin and adenosine receptors, and receptors for vasoactive intestinal<br>polypeptide, regulate the levels of cyclic AMP in various<br>basal ganglion regions (Kebabian et al., 1972; F osine receptors, and receptors for vasoactive intestinal polypeptide, regulate the levels of cyclic AMP in various basal ganglion regions (Kebabian et al., 1972; Forn et al., 1974; Kebabian and Calne, 1979; Borghi et al., polypeptide, regulate the levels of cyclic AMP i<br>basal ganglion regions (Kebabian et al., 1972; F<br>1974; Kebabian and Calne, 1979; Borghi et a<br>Quik et al., 1978; Prémont et al., 1977, 1983; M<br>et al., 1978; Stoof and Kebabia

EENGARD<br>Examination of rat, monkey, and human basal ganglia<br>s demonstrated that these regions express a number FREENGARD<br>Examination of rat, monkey, and human basal ganglia<br>has demonstrated that these regions express a number<br>of phosphoproteins that may be involved in the regula-GREENGARD<br>Examination of rat, monkey, and human basal gang<br>has demonstrated that these regions express a numi<br>of phosphoproteins that may be involved in the regu<br>tion of neuronal excitability by dopamine. The mediu Examination of rat, monkey, and human basal ganges a num<br>has demonstrated that these regions express a num<br>of phosphoproteins that may be involved in the region<br>tion of neuronal excitability by dopamine. The mediu<br>sized sp Examination of rat, monkey, and human basal ganglia<br>has demonstrated that these regions express a number<br>of phosphoproteins that may be involved in the regula-<br>tion of neuronal excitability by dopamine. The medium-<br>sized s has demonstrated that these regions express a number of phosphoproteins that may be involved in the regulation of neuronal excitability by dopamine. The medium-<br>sized spiny striatofugal neurons, in particular, contain<br>many of phosphoproteins that may be involved in the regulation of neuronal excitability by dopamine. The medium-<br>sized spiny striatofugal neurons, in particular, contain<br>many phosphoproteins that appear to be specific sub-<br>stra tion of neuronal excitability by dopamine. The medium<br>sized spiny striatofugal neurons, in particular, contai<br>many phosphoproteins that appear to be specific sul<br>strates for cyclic AMP-dependent protein kinase (Wi<br>laas et sized spiny striatofugal neurons, in particular, contain many phosphoproteins that appear to be specific substrates for cyclic AMP-dependent protein kinase (Walass et al., 1983b,c, 1989a; Ouimet et al., 1984b; Hemmings et many phosphoproteins that appear to be specific substrates for cyclic AMP-dependent protein kinase (Walass et al., 1983b,c, 1989a; Ouimet et al., 1984b; Hemmings et al., 1987c). At the present time, *DARPP*-32 is the best strates for cyclic AMP-dependent protein kinase (Wa-<br>laas et al., 1983b,c, 1989a; Ouimet et al., 1984b; Hem-<br>mings et al., 1987c). At the present time, *DARPP-32* is<br>the best characterized of these proteins. Extensive evilaas et al., 1983b,c, 1989a; Ouimet et al., 1984b; He mings et al., 1987c). At the present time, *DARPP-32* the best characterized of these proteins. Extensive e dence indicates that this protein, which was describinergic mings et al., 1987c). At the present time, *DARPP-32* is<br>the best characterized of these proteins. Extensive evi-<br>dence indicates that this protein, which was described<br>briefly in section III, is involved in dopaminergic n the best characterized of these proteins. Extensive evidence indicates that this protein, which was described<br>briefly in section III, is involved in dopaminergic neuro-<br>transmission in the basal ganglia. DARPP-32 is enrich dence indicates that this protein, which was described<br>briefly in section III, is involved in dopaminergic neuro-<br>transmission in the basal ganglia. DARPP-32 is enriched<br>in those basal ganglion areas that are densely inne briefly in section III, is involved in dopaminergic neuro-<br>transmission in the basal ganglia. DARPP-32 is enriched<br>in those basal ganglion areas that are densely innervated<br>by the mesotelencephalic dopaminergic fiber syste transmission in the basal ganglia. DARPP-32 is enriched<br>in those basal ganglion areas that are densely innervated<br>by the mesotelencephalic dopaminergic fiber system<br>(Walaas and Greengard, 1984; Ouimet et al., 1984b<br>Hemming in those basal ganglion areas that are densely innervated<br>by the mesotelencephalic dopaminergic fiber system<br>(Walaas and Greengard, 1984; Ouimet et al., 1984b;<br>Hemmings and Greengard, 1986) and is specifically con-<br>centrat by the mesotelencephalic dopaminergic fiber system<br>(Walaas and Greengard, 1984; Ouimet et al., 1984b)<br>Hemmings and Greengard, 1986) and is specifically con-<br>centrated in those dopaminoceptive cells that have D1<br>dopamine re (Walaas and Greengard, 1984; Ouimet et al., 1984b;<br>Hemmings and Greengard, 1986) and is specifically concentrated in those dopaminoceptive cells that have D1<br>dopamine receptors (dopamine receptors linked to acti-<br>vation of Hemmings and Greengard, 1986) and is specifically concentrated in those dopaminoceptive cells that have D1 dopamine receptors (dopamine receptors linked to activation of adenylyl cyclase (Kebabian and Calne, 1979; Clark an centrated in those dopaminoceptive cells that helpomine receptors (dopamine receptors linked vation of adenylyl cyclase (Kebabian and Caln Clark and White, 1987)). Moreover, anatomical have shown that the distribution of D dopamine receptors (dopamine receptors linked to activation of adenylyl cyclase (Kebabian and Calne, 1979; Clark and White, 1987)). Moreover, anatomical studies have shown that the distribution of DARPP-32-containing neuro vation of adenylyl cyclase (Kebabian and Calne, 1979;<br>Clark and White, 1987)). Moreover, anatomical studies<br>have shown that the distribution of DARPP-32-contain-<br>ing neurons throughout the brain is in good agreement<br>with t Clark and White, 1987)). Moreover, anatomical studies<br>have shown that the distribution of DARPP-32-contain-<br>ing neurons throughout the brain is in good agreement<br>with the distribution of the D1 receptor (Aiso et al., 1987; have shown that the distribution of DARPP-32-contain-<br>ing neurons throughout the brain is in good agreement<br>with the distribution of the D1 receptor (Aiso et al., 1987;<br>Boyson et al., 1986). Recent studies have also shown ing neurons throughout the brain is in good agreement<br>with the distribution of the D1 receptor (Aiso et al., 1987;<br>Boyson et al., 1986). Recent studies have also shown that<br>DARPP-32 is present in certain peripheral cells t with the distribution of the D1 receptor (Aiso et al., 1987)<br>Boyson et al., 1986). Recent studies have also shown that<br>DARPP-32 is present in certain peripheral cells that<br>contain dopamine D1 receptors, including parathyro Boyson et al., 1986). Recent studies have also shown that<br>DARPP-32 is present in certain peripheral cells that<br>contain dopamine D1 receptors, including parathyroid<br>cells (Brown et al., 1977; Hemmings and Greengard,<br>1986), DARPP-32 is present in certain peripheral cells that<br>contain dopamine D1 receptors, including parathyroid<br>cells (Brown et al., 1977; Hemmings and Greengard,<br>1986), brown adipocytes (Meister et al., 1989). This dis-<br>tributi contain dopamine D1 receptors, including parathyroid<br>cells (Brown et al., 1977; Hemmings and Greengard,<br>1986), brown adipocytes (Meister et al., 1988), and cer-<br>tain renal tubular cells (Meister et al., 1989). This dis-<br>tr cells (Brown et al., 1977; Hemmings and Greengard 1986), brown adipocytes (Meister et al., 1988), and certain renal tubular cells (Meister et al., 1989). This distribution pattern suggests that DARPP-32 is involved in the 1986), brown adipocytes (Meister et al., 1988), and certain renal tubular cells (Meister et al., 1989). This distribution pattern suggests that DARPP-32 is involved in the actions of dopamine in these cells, and experiment in renal tubular cells (Meister et al., 1989). This dis-<br>bution pattern suggests that DARPP-32 is involved in<br>e actions of dopamine in these cells, and experimental<br>idence has been obtained that supports this hypothesis.<br>U

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nantly inhibitory, GABAergic and/or peptidergic path-<br>widence has been obtained that supports this hypothesis.<br>ways which terminate in the globus pallidus, the ento-<br>peduncular nucleus, and the pars reticulata of the sub-<br> tribution pattern suggests that DARPP-32 is involved in<br>the actions of dopamine in these cells, and experimental<br>evidence has been obtained that supports this hypothesis.<br>Under basal conditions, DARPP-32 is phosphorylated<br> the actions of dopamine in these cells, and experimental<br>evidence has been obtained that supports this hypothesis.<br>Under basal conditions, DARPP-32 is phosphorylated<br>in intact cells predominantly on a serine residue which<br> evidence has been obtained that supports this hypothesis.<br>
Under basal conditions, DARPP-32 is phosphorylated<br>
in intact cells predominantly on a serine residue which<br>
is a substrate for casein kinase II in vitro and in si Under basal conditions, DARPP-32 is phosphorylated<br>in intact cells predominantly on a serine residue which<br>is a substrate for casein kinase II in vitro and in situ<br>(Girault et al., 1989a, 1990). When dopamine, cyclic<br>AMP a in intact cells predominantly on a serine residue which<br>is a substrate for casein kinase II in vitro and in situ<br>(Girault et al., 1989a, 1990). When dopamine, cyclic<br>AMP analogs, or activators of adenylyl cyclase are added is a substrate for casein kinase II in vitro and in situ<br>(Girault et al., 1989a, 1990). When dopamine, cyclic<br>AMP analogs, or activators of adenylyl cyclase are added<br>to preparations containing these cells, DARPP-32 be-<br>co (Girault et al., 1989a, 1990). When dopamine, cyclic AMP analogs, or activators of adenylyl cyclase are added to preparations containing these cells, DARPP-32 becomes phosphorylated (Walaas et al., 1983a; Halpain et al., 1 AMP analogs, or activators of adenylyl cyclase are added<br>to preparations containing these cells, DARPP-32 be-<br>comes phosphorylated (Walaas et al., 1983a; Halpain et<br>al., 1990; Lewis et al., 1990), and this phosphorylation<br> to preparations containing these cells, DARPP-32 b comes phosphorylated (Walaas et al., 1983a; Halpain al., 1990; Lewis et al., 1990), and this phosphorylatic takes place on that threonine residue (Thr-34) which an excelle comes phosphorylated (Walaas et al., 1983a; Halpain et al., 1990; Lewis et al., 1990), and this phosphorylation takes place on that threonine residue (Thr-34) which is an excellent substrate for both cyclic AMP-dependent a al., 1990; Lewis et al., 1990), and this phosphorylation takes place on that threonine residue (Thr-34) which is an excellent substrate for both cyclic AMP-dependent and cyclic GMP-dependent protein kinases in vitro (Hemmi takes place on that threonine residue (Thr-34) which<br>an excellent substrate for both cyclic AMP-depender<br>and cyclic GMP-dependent protein kinases in vitt<br>(Hemmings et al., 1984b). Phosphorylation of purific<br>DARPP-32 by cas an excellent substrate for both cyclic AMP-depen<br>and cyclic GMP-dependent protein kinases in<br>(Hemmings et al., 1984b). Phosphorylation of pur<br>DARPP-32 by casein kinase II on serine residues a<br>erates the cyclic AMP-regulate and cyclic GMP-dependent protein kinases in<br>(Hemmings et al., 1984b). Phosphorylation of pul<br>DARPP-32 by casein kinase II on serine residues a<br>erates the cyclic AMP-regulated threonine phosph<br>ation; conversely, cyclic AMP-(Hemmings et al., 1984b). Phosphorylation of purified DARPP-32 by casein kinase II on serine residues accelerates the cyclic AMP-regulated threonine phosphorylation; conversely, cyclic AMP-stimulated phosphorylation of Thr DARPP-32 by casein kinase II on serine residues accel<br>erates the cyclic AMP-regulated threonine phosphoryl<br>ation; conversely, cyclic AMP-stimulated phosphoryla<br>tion of Thr-34 in vitro prevents dephosphorylation o<br>the phosp erates the cyclic AMP-regulated threonine phosphorylation; conversely, cyclic AMP-stimulated phosphorylation of Thr-34 in vitro prevents dephosphorylation of the phosphoserine residue. Thus, there is a bidirectional positi ation; conversely, cyclic AMP-stimulated phosphorylation of Thr-34 in vitro prevents dephosphorylation of the phosphoserine residue. Thus, there is a bidirectional positive feedback between the two phosphorylation systems, tion of Thr-34 in vitro prevents dephosphorylation of<br>the phosphoserine residue. Thus, there is a bidirectional<br>positive feedback between the two phosphorylation sys-<br>tems, with casein kinase II apparently increasing cycli the phosphoserine residue. Thus, there is a bidirectional positive feedback between the two phosphorylation systems, with casein kinase II apparently increasing cyclic AMP-regulated DARPP-32 phosphorylation and vice versa positive feedback between the two phosphorylation sys-<br>tems, with casein kinase II apparently increasing cyclic<br>AMP-regulated DARPP-32 phosphorylation and vice<br>versa (Girault et al., 1989a). If, as seems possible, casein<br>k

**REVIEW** PHARMACOLOGICAL PROTEIN PHOSPHORYLATION AT PROTEIN PHOSPHORYLATION<br>phosphorylation systems would provide an example of None class of receptor/receptor interaction, in this case PROTEIN PHOSPHORYLATION AN<br>phosphorylation systems would provide an example of Nl<br>one class of receptor/receptor interaction, in this case pa<br>between the dopamine receptor and the receptor for this ac **PROTEIN PHOSPHORYLATION A**<br>phosphorylation systems would provide an example of N<br>one class of receptor/receptor interaction, in this case<br>between the dopamine receptor and the receptor for this a<br>unknown neurotransmitter. phosphorylation system<br>one class of receptor/re<br>between the dopamine re<br>unknown neurotransmit<br>Biochemical studies h osphorylation systems would provide an example<br>e class of receptor/receptor interaction, in this c<br>tween the dopamine receptor and the receptor for in<br>known neurotransmitter.<br>Biochemical studies have demonstrated that DARI

one class of receptor/receptor interaction, in this case<br>between the dopamine receptor and the receptor for this<br>aunknown neurotransmitter.<br>Biochemical studies have demonstrated that DARPP-<br> $\frac{1}{2}$  may achieve its effect between the dopamine receptor and the receptor for this actual<br>unknown neurotransmitter. See<br>Biochemical studies have demonstrated that DARPP-<br>22 may achieve its effects through inhibition of protein fer<br>phosphatase-1 (see unknown neurotransmitter. see<br>Biochemical studies have demonstrated that DARPP-<br>32 may achieve its effects through inhibition of protein<br>ferphosphatase-1 (see section III). Characterization of the<br>primary structure of the Biochemical studies have demonstrated that DARI<br>32 may achieve its effects through inhibition of protophosphatase-1 (see section III). Characterization of<br>primary structure of the protein showed that Thr-34,<br>amino acid res 32 may achieve its effects through inhibition of protein felphosphatase-1 (see section III). Characterization of the obprimary structure of the protein showed that Thr-34, the the amino acid residue phosphorylated by cycl phosphatase-1 (see section III). Characterization of the primary structure of the protein showed that Thr-34, the amino acid residue phosphorylated by cyclic AMP-dependent protein kinase, is located in a domain highly simi primary structure of the protein showed that Thr-34, the amino acid residue phosphorylated by cyclic AMP-dependent protein kinase, is located in a domain highly similar to a comparable domain in protein phosphatase inhibit amino acid residue phosphorylated by cyclic AMP-c<br>pendent protein kinase, is located in a domain high<br>similar to a comparable domain in protein phosphata<br>inhibitor-1 (Williams et al., 1986; Aitken et al., 198<br>Moreover, as pendent protein kinase, is located in a domain high<br>similar to a comparable domain in protein phosphatas<br>inhibitor-1 (Williams et al., 1986; Aitken et al., 1982<br>Moreover, as observed with protein phosphatase inhib<br>tor-1, D similar to a comparable domain in protein phosphata<br>inhibitor-1 (Williams et al., 1986; Aitken et al., 1982<br>Moreover, as observed with protein phosphatase inhit<br>tor-1, DARPP-32 is a potent inhibitor of protein pho<br>phataseinhibitor-1 (Williams et al., 1986; Aitken et al., 1982).  $\tau$ <br>Moreover, as observed with protein phosphatase inhibitor-1, DARPP-32 is a potent inhibitor of protein phos-<br>phatase-1 only when it is phosphorylated on this t Moreover, as observed with protein phosphatase inhibitor-1, DARPP-32 is a potent inhibitor of protein phos-<br>phatase-1 only when it is phosphorylated on this threo-<br>inne residue (Hemmings et al., 1984a). Therefore, it d<br>wou tor-1, DARPP-32 is a potent inhibitor of protein phos-<br>phatase-1 only when it is phosphorylated on this threo-<br>nine residue (Hemmings et al., 1984a). Therefore, it de<br>would appear that DARPP-32 is involved in mediating He phatase-1 only when it is phosphorylated on this threo-<br>nine residue (Hemmings et al., 1984a). Therefore, it de<br>would appear that DARPP-32 is involved in mediating H<br>or modulating transsynaptic effects of dopamine acting a mine residue (Hemmings et al., 1984a). Therefore, it dwould appear that DARPP-32 is involved in mediating F<br>or modulating transsynaptic effects of dopamine acting a<br>on D1 receptors by regulating the activity of protein<br>pho would appear that DARPP-32 is involved in mediating <sup>F</sup><br>or modulating transsynaptic effects of dopamine acting a<br>on D1 receptors by regulating the activity of protein<br>phosphatase-1. In this way, dopamine would indirectly<br>r or modulating transs<br>
on D1 receptors by<br>
phosphatase-1. In the<br>
regulate the state of<br>
protein phosphatase<br>
DARPP-32 phosp D1 receptors by regulating the activity of protein cosphatase-1. In this way, dopamine would indirectly gulate the state of phosphorylation of substrates fo otein phosphatase-1.<br>DARPP-32 phosphorylation provides a positive

phosphatase-1. In this way, dopamine would indirectly<br>regulate the state of phosphorylation of substrates for<br>protein phosphatase-1.<br>DARPP-32 phosphorylation provides a positive feed-<br>back mechanism for those phosphoprotei regulate the state of phosphorylation of substrates<br>protein phosphatase-1.<br>DARPP-32 phosphorylation provides a positive fo<br>back mechanism for those phosphoproteins that are s<br>strates for protein phosphatase-1 and that are protein phosphatase-1.<br>
DARPP-32 phosphorylation provides a positive feed-<br>
back mechanism for those phosphoproteins that are sub-<br>
strates for protein phosphatase-1 and that are phosphor-<br>
ylated by the dopamine D1-recept DARPP-32 phosphorylation provides a positive fee<br>back mechanism for those phosphoproteins that are strates for protein phosphatase-1 and that are phosph<br>ylated by the dopamine D1-receptor/cyclic AMP/cyc<br>AMP-dependent prote back mechanism for those phosphoproteins that are substrates for protein phosphatase-1 and that are phosphor-<br>ylated by the dopamine D1-receptor/cyclic AMP/cyclic<br>AMP-dependent protein kinase pathway. This mecha-<br>nism woul ylated by the dopamine D1-receptor/cyclic AMP/cyclic malian brain, further analysis of the characteristics of<br>AMP-dependent protein kinase pathway. This mecha-<br>nism would potentiate the dopamine-induced functional<br>respons AMP-dependent protein kinase pathway. This mechanism would potentiate the dopamine-induced functional response(s) in which that particular phosphoprotein was involved. (Such a positive feedback mechanism appears to have b AMP-dependent protein kinase pathway. This mechanism would potentiate the dopamine-induced functional response(s) in which that particular phosphoprotein was involved. (Such a positive feedback mechanism appears to have b mism would potentiate the dopamine-induced functional  $D$ . If response(s) in which that particular phosphoprotein was<br>involved. (Such a positive feedback mechanism appears for to have been used by dopamine in the regulati response(s) in which that particular phosphoprotein was<br>involved. (Such a positive feedback mechanism appears<br>to have been used by dopamine in the regulation of Na<sup>+</sup>,<br> $K^+$ -ATPase activity in renal tubule cells, as discu involved. (Such a positive feedback mechanism appears<br>to have been used by dopamine in the regulation of Na<sup>+</sup>,<br> $K^+$ -ATPase activity in renal tubule cells, as discussed in<br>section VI. D). DARPP-32 may also be involved in to have been used by dopamine in the regulation of Na<br>K<sup>+</sup>-ATPase activity in renal tubule cells, as discussed<br>section VI. D). DARPP-32 may also be involved in t<br>interaction between dopamine and other first messenge<br>that a K<sup>+</sup>-ATPase activity in renal tubule cells, as discussed in section VI. D). DARPP-32 may also be involved in thinteraction between dopamine and other first messenger that act through protein kinases other than cyclic AMP d section VI. D). DARPP-32 may also be involved in the interaction between dopamine and other first messengers that act through protein kinases other than cyclic AMP-dependent protein kinase. In this class of interaction, ph that act through protein kinases other than cyclic AMP-<br>dependent protein kinase. In this class of interaction,<br>phospho-DARPP-32 formed in the presence of dopamine<br>might prevent the dephosphorylation of substrate prodependent protein kinase. In this class of interaction-<br>phospho-DARPP-32 formed in the presence of dopa<br>might prevent the dephosphorylation of substrate<br>teins phosphorylated by these other protein kinases<br>increased phospho phospho-DARPP-32 formed in the presence of dopamine been<br>might prevent the dephosphorylation of substrate pro-<br>teins phosphorylated by these other protein kinases. The<br>increased phosphorylation and decreased dephosphoryl-<br> might prevent the dephosphorylation of substrate pro-<br>teins phosphorylated by these other protein kinases. The<br>increased phosphorylation and decreased dephosphoryl-<br>ation of these substrate proteins would be reflected in<br> increased phosphorylation and decreased dephosphorylation of these substrate proteins would be reflected in synergistic physiological actions of dopamine and these other neurotransmitters.<br>Another class of receptor-recepto ation of these substrate proteins would be reflected in<br>synergistic physiological actions of dopamine and these<br>other neurotransmitters.<br>Another class of receptor-receptor interaction, me-<br>diated through regulation of DARP

synergistic physiological actions of dopamine and these<br>other neurotransmitters.<br>Another class of receptor-receptor interaction, me-<br>diated through regulation of DARPP-32 phosphoryla-<br>tion, has also been elucidated. As ind diated through regulation of DARPP-32 phosphoryla-<br>tion, has also been elucidated. As indicated in section<br>III.A, glutamate and dopamine appear to exert antago-<br>characteristics of the postsynaptic response have reother neurotransmitters.<br>
Another class of receptor-receptor interaction, n<br>
diated through regulation of DARPP-32 phosphory<br>
tion, has also been elucidated. As indicated in sect<br>
III.A, glutamate and dopamine appear to ex Another class of receptor-receptor interaction, idiated through regulation of DARPP-32 phosphormetion, has also been elucidated. As indicated in section, all III.A, glutamate and dopamine appear to exert ants mistic effect diated through regulation of DARPP-32 phosphorylation, has also been elucidated. As indicated in section III.A, glutamate and dopamine appear to exert antagonistic effects on the state of phosphorylation of DARPP-32. Depho tion, has also been elucidated. As indicated in section cheapting in the state of phosphorylation of DARPP-<br>nistic effects on the state of phosphorylation of DARPP-<br>32. Dephosphorylation of Thr-34 on DARPP-32 is cata-<br>lyz III.A, glutamate and dopamine appear to exert antagonistic effects on the state of phosphorylation of DARPP-32. Dephosphorylation of Thr-34 on DARPP-32 is catalyzed in vitro most efficiently by phosphatase-2B, the Ca<sup>2+</sup>/c mistic effects on the state of phosphorylation of DARPP-<br>32. Dephosphorylation of Thr-34 on DARPP-32 is cata-<br>lyzed in vitro most efficiently by phosphatase-2B, the<br>Ca<sup>2+</sup>/calmodulin-dependent phosphatase specifically en-<br> 32. Dephosphorylation of Thr-34 on DARPP-32 is cata-<br>lyzed in vitro most efficiently by phosphatase-2B, the<br>Ca<sup>2+</sup>/calmodulin-dependent phosphatase specifically en-<br>piched in some of the cells in which DARPP-32 is located lyzed in vitro most efficiently by phosphatase-2B, the c<br>Ca<sup>2+</sup>/calmodulin-dependent phosphatase specifically en-<br>riched in some of the cells in which DARPP-32 is located u<br>(Goto et al., 1986; Ouimet et al., 1984b). Activa  $Ca^{2+}/cal$ ndmodulin-dependent phosphatase specifically enriched in some of the cells in which DARPP-32 is located use (Goto et al., 1986; Ouimet et al., 1984b). Activation of by the NMDA type of glutamate receptor in striat riched in some of the cells in which DARPP-32 is located<br>
(Goto et al., 1986; Ouimet et al., 1984b). Activation of by<br>
the NMDA type of glutamate receptor in striatal slices<br>
the versed the cyclic AMP-stimulated phosphoryl

<sup>327</sup> PROTEIN PHOSPHORYLATION AND NEURONAL FUNCTION<br>-phosphorylation systems would provide an example of NMDA-induced dephosphorylation of DARPP-32 (Halpain et al., 1990). Because the NMDA receptor, when activated, will allow  $Ca^{2+}$  influx into cells (for examples, and NEURONAL FUNCTION 327<br>
NMDA-induced dephosphorylation of DARPP-32 (Hal-<br>
pain et al., 1990). Because the NMDA receptor, when<br>
activated, will allow Ca<sup>2+</sup> influx into cells (for examples,<br>
see Dingledine, 1983), and be NMDA-induced dephosphorylation of DARPP-32 (Hal-<br>pain et al., 1990). Because the NMDA receptor, when<br>activated, will allow Ca<sup>2+</sup> influx into cells (for examples,<br>see Dingledine, 1983), and because dephosphorylation of<br>pho NMDA-induced dephosphorylation of DARPP-32 (Hal-<br>pain et al., 1990). Because the NMDA receptor, when<br>activated, will allow Ca<sup>2+</sup> influx into cells (for examples,<br>see Dingledine, 1983), and because dephosphorylation of<br>pho pain et al., 1990). Because the NMDA receptor, when<br>activated, will allow Ca<sup>2+</sup> influx into cells (for examples,<br>see Dingledine, 1983), and because dephosphorylation of<br>phosphoserine residues on DARPP-32, which are pre-<br>f activated, will allow  $Ca^{2+}$  influx into cells (for examples,<br>see Dingledine, 1983), and because dephosphorylation of<br>phosphoserine residues on DARPP-32, which are pre-<br>ferred substrates for phosphatases-1 and -2A, was n see Dingledine, 1983), and because dephosphorylation of phosphoserine residues on DARPP-32, which are preferred substrates for phosphatases-1 and -2A, was not observed, it was suggested that this effect was mediated throu phosphoserine residues on DARPP-32, which are pre-<br>ferred substrates for phosphatases-1 and -2A, was not<br>observed, it was suggested that this effect was mediated<br>through phosphatase-2B activation by Ca<sup>2+</sup> (Halpain et<br>al., ferred substrates for phosphatases-1 and -2A, was not observed, it was suggested that this effect was mediated through phosphatase-2B activation by  $Ca^{2+}$  (Halpain et al., 1990). Thus, the antagonistic effects of dopamin observed, it was suggested that this effect was me<br>through phosphatase-2B activation by  $Ca^{2+}$  (Halp<br>al., 1990). Thus, the antagonistic effects of dop<br>and glutamate on the excitability of striatal neuro<br>reflected in anta al., 1990). Thus, the antagonistic effects of dopamine<br>and glutamate on the excitability of striatal neurons are<br>reflected in antagonistic effects of these neurotransmit-<br>ters on the state of phosphorylation of DARPP-32.<br>I , 1990). Thus, the antagonistic effects of dopam<br>d glutamate on the excitability of striatal neurons<br>flected in antagonistic effects of these neurotransm<br>is on the state of phosphorylation of DARPP-32.<br>In addition to DARPP

and glutamate on the excitability of striatal neurons are<br>reflected in antagonistic effects of these neurotransmit-<br>ters on the state of phosphorylation of DARPP-32.<br>In addition to DARPP-32, a number of other phospho-<br>prot reflected in antagonistic effects of these neurotransm<br>ters on the state of phosphorylation of DARPP-32.<br>In addition to DARPP-32, a number of other phosph<br>proteins have been discovered that are enriched in t<br>basal ganglia ters on the state of phosphorylation of DARPP-32.<br>In addition to DARPP-32, a number of other phospho-<br>proteins have been discovered that are enriched in the<br>basal ganglia and that are substrates for cyclic AMP-<br>dependent p In addition to DARPP-32, a number of other phosphoproteins have been discovered that are enriched in the basal ganglia and that are substrates for cyclic AMP-<br>dependent protein kinase (Walaas et al., 1983c, 1989a;<br>Hemmings proteins have been discovered that are enriched in the basal ganglia and that are substrates for cyclic AMP-<br>dependent protein kinase (Walaas et al., 1983c, 1989a;<br>Hemmings et al., 1989). Most or all of these proteins<br>appe basal ganglia and that are substrates for cyclic AMP-<br>dependent protein kinase (Walaas et al., 1983c, 1989a;<br>Hemmings et al., 1989). Most or all of these proteins<br>appear to be localized to neurons that contain dopamine<br>rec dependent protein kinase (Walaas et al., 1983c, 1989a;<br>Hemmings et al., 1989). Most or all of these proteins<br>appear to be localized to neurons that contain dopamine<br>receptors, and they would, therefore, be expected to be<br>i Hemmings et al., 1989). Most or all of these prote<br>appear to be localized to neurons that contain dopam<br>receptors, and they would, therefore, be expected to<br>involved in the regulation of neuronal functions media<br>by dopamin appear to be localized to neurons that contain dopamine<br>receptors, and they would, therefore, be expected to be<br>involved in the regulation of neuronal functions mediated<br>by dopamine. Hypo- and hyperfunction of the dopami-<br> receptors, and they would, therefore, be expected to be<br>involved in the regulation of neuronal functions mediated<br>by dopamine. Hypo- and hyperfunction of the dopami-<br>nergic system are associated with motor dysfunctions<br>and involved in the regulation of neuronal functions mediated<br>by dopamine. Hypo- and hyperfunction of the dopami-<br>nergic system are associated with motor dysfunctions<br>and pathological behavior, respectively (for examples,<br>see by dopamine. Hypo- and hyperfunction of the dopam<br>nergic system are associated with motor dysfunction<br>and pathological behavior, respectively (for example<br>see Snyder, 1976; Creese and Snyder, 1978). Given the<br>importance of nergic system are associated with motor dysfunctions<br>and pathological behavior, respectively (for examples,<br>see Snyder, 1976; Creese and Snyder, 1978). Given the<br>importance of dopaminergic neurotransmission in mam-<br>malian and pathological behavior, respectivel<br>see Snyder, 1976; Creese and Snyder,<br>importance of dopaminergic neurotrans<br>malian brain, further analysis of the<br>these proteins will be of great interest.<br>D. Regulation of Long-Term P Exercing and *D.* **P. 1999** *D.* **Choose** and *D.* **Regulation of Long-** Term *Regulation of Long-Term Potentiation*<br>*D. Regulation of Long-Term Potentiation*<br>*LTP* is a phenomenon that has been use Alian brain, further analysis of the characteristics of<br>ese proteins will be of great interest.<br>Regulation of Long-Term Potentiation<br>LTP is a phenomenon that has been used as a model<br>r the early stages of memory formation

dependent protein kinase. In this class of interaction, place in many areas of the CNS, but most studies have<br>phospho-DARPP-32 formed in the presence of dopamine<br>might prevent the dephosphorylation of substrate pro-<br>teins for these proteins will be of great interest.<br>
D. Regulation of Long-Term Potentiation<br>
LTP is a phenomenon that has been used as a model<br>
for the early stages of memory formation and learning<br>
and that has attracted great D. Regulation of Long-Term Potentiation<br>
LTP is a phenomenon that has been used as a mo<br>
for the early stages of memory formation and learn<br>
and that has attracted great attention. In this pheno<br>
enon, brief tetanic stimul D. Regulation of Long-Term Potentiation<br>
LTP is a phenomenon that has been used as a model<br>
for the early stages of memory formation and learning<br>
and that has attracted great attention. In this phenom-<br>
enon, brief tetani LTP is a phenomenon that has been used as a model<br>for the early stages of memory formation and learning<br>and that has attracted great attention. In this phenom-<br>enon, brief tetanic stimulation of afferent fibers results<br>in and that has attracted great attention. In this phenom-<br>enon, brief tetanic stimulation of afferent fibers results<br>in a long-lasting increase in synaptic strength or efficacy,<br>as first observed in the dentate gyrus of the formation (Bliss and Lømo, 1973). LTP appears to take enon, brief tetanic stimulation of afferent fibers results<br>in a long-lasting increase in synaptic strength or efficacy,<br>as first observed in the dentate gyrus of the hippocampal<br>formation (Bliss and Lømo, 1973). LTP appear in a long-lasting increase in synaptic strength or efficacy,<br>as first observed in the dentate gyrus of the hippocampal<br>formation (Bliss and Lømo, 1973). LTP appears to take<br>place in many areas of the CNS, but most studies as first observed in the dentate gyrus of the hippocampal<br>formation (Bliss and Lømo, 1973). LTP appears to take<br>place in many areas of the CNS, but most studies have<br>been performed in the hippocampus, where strong evi-<br>den formation (Bliss and Lømo, 1973). LTP appears to take place in many areas of the CNS, but most studies have been performed in the hippocampus, where strong evidence has been obtained for the involvement of protein phosphor place in many areas of the CNS, but most studies have<br>been performed in the hippocampus, where strong evi-<br>dence has been obtained for the involvement of protein<br>phosphorylation (for reviews, see Malenka et al., 1989b;<br>Nic been performed in the hippocampus, where strong even<br>dence has been obtained for the involvement of prote<br>phosphorylation (for reviews, see Malenka et al., 1989<br>Nicoll et al., 1988). LTP appears to be composed of<br>number of dence has been obtained for the involvement of protein<br>phosphorylation (for reviews, see Malenka et al., 1989b;<br>Nicoll et al., 1988). LTP appears to be composed of a<br>number of different phenomena (for examples, see Swan-<br>s phosphorylation (for reviews, see Malenka et al., 1989b;<br>Nicoll et al., 1988). LTP appears to be composed of a<br>number of different phenomena (for examples, see Swan-<br>son et al., 1982; Zalutsky and Nicoll, 1990), one of whi Nicoll et al., 1988). LTP appears to be composed of a<br>number of different phenomena (for examples, see Swan-<br>son et al., 1982; Zalutsky and Nicoll, 1990), one of which<br>consists of increased release of transmitter from the<br> number of different phenomena (for examples, see Swanson et al., 1982; Zalutsky and Nicoll, 1990), one of which<br>consists of increased release of transmitter from the<br>afferent fibers involved (Dolphin et al., 1982; Feasey e consists of increased release of transmitter from the afferent fibers involved (Dolphin et al., 1982; Feasey et al., 1986; Bliss et al., 1986). Another mechanism includes changes in the postsynaptic cells. Several importan consists of increased release of transmitter from the afferent fibers involved (Dolphin et al., 1982; Feasey et al., 1986; Bliss et al., 1986). Another mechanism includes changes in the postsynaptic cells. Several importan afferent fibers involved (Dolphin et al., 1982; Feasey et al., 1986; Bliss et al., 1986). Another mechanism includes changes in the postsynaptic cells. Several important characteristics of the postsynaptic response have re al., 1986; Bliss et al., 1986). Another mechanism includes<br>changes in the postsynaptic cells. Several important<br>characteristics of the postsynaptic response have re-<br>cently been elucidated. First, LTP is dependent on de-<br>p changes in the postsynaptic cells. Several important<br>characteristics of the postsynaptic response have re-<br>cently been elucidated. First, LTP is dependent on de-<br>polarization of the postsynaptic membrane and on in-<br>creases characteristics of the postsynaptic response have recently been elucidated. First, LTP is dependent on depolarization of the postsynaptic membrane and on increases in  $Ca^{2+}$  levels in the postsynaptic cell. In the pyrami cently been elucidated. First, LTP is dependent on de-<br>polarization of the postsynaptic membrane and on in-<br>creases in Ca<sup>2+</sup> levels in the postsynaptic cell. In the<br>pyramidal cells in the CA1 region, these effects are<br>usu polarization of the postsynaptic membrane and on in-<br>creases in Ca<sup>2+</sup> levels in the postsynaptic cell. In the<br>pyramidal cells in the CA1 region, these effects are<br>usually achieved by glutamate, the transmitter released<br>by creases in  $Ca^{2+}$  levels in the postsynaptic cell. In<br>pyramidal cells in the CA1 region, these effects<br>usually achieved by glutamate, the transmitter relea<br>by the afferent fibers in CA1 (most of which derive f<br>the CA3 re pyramidal cells in the CA1 region, these effects are usually achieved by glutamate, the transmitter released by the afferent fibers in CA1 (most of which derive from the CA3 region of the ipsi- and contralateral hippocampu pus), binding to two classes of glutamate receptors (Cot-

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328 **WALAAS AND**<br>sible for normal excitatory postsynaptic potentials ap-<br>pears to be the so-called  $\alpha$ -amino-3-hydroxy-5-methyl-328<br>sible for normal excitatory postsynaptic pot<br>pears to be the so-called  $\alpha$ -amino-3-hydroxy<br>4-isoxazole propionic acid-selective glutamat 4-isoxazole propionic acid-selective glutamate receptor,<br>whereas to be the so-called  $\alpha$ -amino-3-hydroxy-5-methyl-<br>4-isoxazole propionic acid-selective glutamate receptor,<br>whereas the NMDA-type of glutamate receptor is e sible for normal excitatory postsynaptic potentials a<br>pears to be the so-called  $\alpha$ -amino-3-hydroxy-5-methy<br>4-isoxazole propionic acid-selective glutamate receptor<br>whereas the NMDA-type of glutamate receptor is esse<br>tial sible for normal excitatory postsynaptic potentials appears to be the so-called  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-selective glutamate receptor, whereas the NMDA-type of glutamate receptor is essenti pears to be the so-called  $\alpha$ -amino-3-hydroxy-5-met<br>4-isoxazole propionic acid-selective glutamate recept<br>whereas the NMDA-type of glutamate receptor is es<br>tial for LTP (for examples, see Collingridge, 1985).<br>tensive stu 4-isoxazole propionic acid-selective glutamate receptor<br>whereas the NMDA-type of glutamate receptor is ess<br>tial for LTP (for examples, see Collingridge, 1985).<br>tensive studies have indicated that, following glutama<br>induce whereas the NMDA-type of glutamate receptor is essential for LTP (for examples, see Collingridge, 1985). Extensive studies have indicated that, following glutamate-induced membrane depolarization through the  $\alpha$ -amino-3tial for LTP (for examples, see Collingridge, 1985). Ex-<br>tensive studies have indicated that, following glutamate-<br>induced membrane depolarization through the  $\alpha$ -amino-<br>3-hydroxy-5-methyl-4-isoxazole propionic acid-sele tensive studies have indicated that, following glutamate-<br>induced membrane depolarization through the  $\alpha$ -amino-<br>3-hydroxy-5-methyl-4-isoxazole propionic acid-selective de-<br>glutamate receptor, activation of the NMDA rece induced membrane depolarization through the  $\alpha$ -amino-<br>3-hydroxy-5-methyl-4-isoxazole propionic acid-selective<br>glutamate receptor, activation of the NMDA receptor<br>allows not only Na<sup>+</sup> but also Ca<sup>2+</sup> to flow into the<br>po 3-hydroxy-5-methyl-4-isoxazole propionic acid-selective glutamate receptor, activation of the NMDA receptor allows not only Na<sup>+</sup> but also  $Ca^{2+}$  to flow into the postsynaptic cells (for examples, see Dingledine, 1983). glutamate receptor, activat<br>allows not only Na<sup>+</sup> but<br>postsynaptic cells (for exan<br>This Ca<sup>2+</sup> influx is crucial fo<br>see Malenka et al., 1989b).<br> $Ca^{2+}$ -sensitive enzymes tl lows not only Na<sup>+</sup> but also  $Ca^{2+}$  to flow into the enstsynaptic cells (for examples, see Dingledine, 1983). of his  $Ca^{2+}$  influx is crucial for LTP to develop (for review,  $A^{2+}$  emailive enzymes that might be involv

postsynaptic cells (for examples, see Dingledine, 1983). of<br>This Ca<sup>2+</sup> influx is crucial for LTP to develop (for review,<br>see Malenka et al., 1989b).  $Ca^{2+}$ -sensitive enzymes that might be involved in the th<br>development This Ca<sup>2+</sup> influx is crucial for LTP to develop (for review,<br>see Malenka et al., 1989b).  $\text{ma}^2$ <br>Ca<sup>2+</sup>-sensitive enzymes that might be involved in the<br>development and persistence of LTP include protein C<sub>6</sub><br>kinases, p see Malenka et al., 1989b).<br>
Ca<sup>2+</sup>-sensitive enzymes that might be involved in the<br>
development and persistence of LTP include protein<br>
kinases, protein phosphatases, and/or proteases. The<br>
results of experiments in which development and persistence of LTP include protein CaM kinase II (Jefferson and Schulman, 1988), is capa-<br>kinases, protein phosphatases, and/or proteases. The ble of blocking LTP only if it is present during the<br>results o development and persistence of LTP include protein<br>kinases, protein phosphatases, and/or proteases. The<br>results of experiments in which relatively nonspecific<br>protein kinase inhibitors such as H-7 have been injected<br>into p kinases, protein phosphatases, and/or proteases. The<br>results of experiments in which relatively nonspecific in<br>protein kinase inhibitors such as H-7 have been injected the possible displays into pyramidal cells, leading t results of experiments in which relatively nonspecific incorportion kinase inhibitors such as H-7 have been injected the into pyramidal cells, leading to a blockade of LTP (Mal-<br>enka et al., 1989b), are consistent with th protein kinase inhibitors such as H-7 have been injected the into pyramidal cells, leading to a blockade of LTP (Mal-<br>enka et al., 1989b), are consistent with the possible revivolvement of  $Ca^{2+}$ -dependent protein kinase into pyramidal cells, leading to a blockade of LTP (Malenka et al., 1989b), are consistent with the possible involvement of  $Ca^{2+}$ -dependent protein kinases in the process. Both CaM kinase II and protein kinase C are hig process. Both CaM kinase II and protein kinase C are highly enriched in the hippocampus (Walaas et al., 1983b,c), and the possible involvement of these enzymes in the generation of LTP has been the subject of analysis. Con

highly enriched in the hippocampus (Walaas et al., 1983b,c), and the possible involvement of these enzymes in the generation of LTP has been the subject of analysis. Considerable evidence implicates protein kinase C in the 1983b,c), and the possible involvement of these enzymes<br>in the generation of LTP has been the subject of analysis. The<br>Considerable evidence implicates protein kinase C in<br>the process of LTP. Increases in inositol phospho in the generation of LTP has been the subject of analysis.<br>Considerable evidence implicates protein kinase C in<br>the process of LTP. Increases in inositol phospholipid<br>turnover have been associated with LTP, and protein<br>kin Considerable evidence implicates protein kinase C in<br>the process of LTP. Increases in inositol phospholipid<br>turnover have been associated with LTP, and protein<br>kinase C becomes translocated to particulate fractions,<br>and p the process of LTP. Increases in inositol phospholipid<br>turnover have been associated with LTP, and protein<br>kinase C becomes translocated to particulate fractions,<br>and presumably activated, when LTP is induced in the<br>perfor turnover have been associated with LTP, and protein<br>kinase C becomes translocated to particulate fractions,<br>and presumably activated, when LTP is induced in the<br>perforant path-granule cell synapse in the dentate gyrus<br>(Ake kinase C becomes translocated to particulate fractions,<br>and presumably activated, when LTP is induced in the<br>perforant path-granule cell synapse in the dentate gyrus<br>(Akers et al., 1986). Furthermore, phorbol esters and<br>ot and presumably activated, when LTP is induced in the perforant path-granule cell synapse in the dentate gyre (Akers et al., 1986). Furthermore, phorbol esters are other activators of protein kinase C (Linden et al., 1981) perforant path-granule cell synapse in the dentate gyrus (Akers et al., 1986). Furthermore, phorbol esters and other activators of protein kinase C (Linden et al., 1986, 1987) induce increases in synaptic transmission some (Akers et al., 1986). Furthermore, phorbol esters as other activators of protein kinase C (Linden et al., 1987) induce increases in synaptic transmission som what similarly to LTP (Malenka et al., 1986), where extracellula other activators of protein kinase C (Linden et al., 1986, 1987) induce increases in synaptic transmission somewhat similarly to LTP (Malenka et al., 1986), whereas extracellular application of putative, but not very speci 1987) induce increases in synaptic transmission some<br>what similarly to LTP (Malenka et al., 1986), wherea<br>extracellular application of putative, but not very specifically (for examples, see Jefferson and Schulman, 1988)<br>pr what similarly to LTP (Malenka et al., 1986), whereas<br>extracellular application of putative, but not very specifically (for examples, see Jefferson and Schulman, 1988), involved<br>protein kinase C inhibitors such as sphingos extracellular application of putative, but not very specifically (for examples, see Jefferson and Schulman, 1988),<br>protein kinase C inhibitors such as sphingosine, poly-<br>myxin B, or H-7 blocks several components of LTP<br>(Lo ically (for examples, see Jefferson and Schulman, 1988),<br>protein kinase C inhibitors such as sphingosine, poly-<br>myxin B, or H-7 blocks several components of LTP<br>(Lovinger et al., 1987; Reymann et al., 1988; Malinow et<br>al., protein kinase C inhibitors such as sphingosine, poly-<br>myxin B, or H-7 blocks several components of LTP<br>(Lovinger et al., 1987; Reymann et al., 1988; Malinow et<br>induced ware induced ware was it determined whether the chang myxin B, or H-7 blocks several components of LT (Lovinger et al., 1987; Reymann et al., 1988; Malinow et al., 1989; Colley et al., 1990). In none of these studies was it determined whether the changes induced were located (Lovinger et al., 1987; Reymann et al., 1988; Malinow et al., 1989; Colley et al., 1990). In none of these studies was it determined whether the changes induced were located presynaptically, postsynaptically, or both. How al., 1989; Colley et al., 1990). In none of these studies under the changes induced were subcated presynaptically, postsynaptically, or both. However, evidence suggesting a postsynaptic localization slopes from studies in was it determined whether the changes induced were<br>located presynaptically, postsynaptically, or both. How-<br>ever, evidence suggesting a postsynaptic localization<br>comes from studies in which intracellular injection of<br>puri located presynaptically, postsynaptically, or both. However, evidence suggesting a postsynaptic localization comes from studies in which intracellular injection of purified protein kinase C induced changes that mimicked (H comes from studies in which intracellular injection of purified protein kinase C induced changes that mimicked (Hu et al., 1987), whereas injection of a peptide inhibitor of protein kinase C prevented (Hvalby et al., in pr comes from studies in which intracellular injection of typurified protein kinase C induced changes that mimicked M<br>(Hu et al., 1987), whereas injection of a peptide inhibitor at of protein kinase C prevented (Hvalby et al. purified protein kinase C induced changes that mimicked (Hu et al., 1987), whereas injection of a peptide inhibitor of protein kinase C prevented (Hvalby et al., in preparation), several features of LTP. Thus, a role for p (Hu et al., 1987), whereas injection of a peptide i<br>of protein kinase C prevented (Hvalby et al., in<br>ration), several features of LTP. Thus, a role for<br>kinase C-catalyzed phosphorylation in the post<br>mechanisms involved in protein kinase C prevented (Hvalby et al., in prepation), several features of LTP. Thus, a role for protein posse C-catalyzed phosphorylation in the postsynaptic dechanisms involved in LTP appears probable. y Recent studie

ration), several features of LTP. Thus, a role for protein positions in the post extends the post of mechanisms involved in LTP appears probable. The mechanisms involved in LTP appears probable. The came is highly enriched kinase C-catalyzed phosphorylation in the postsynaptic denomechanisms involved in LTP appears probable. ylat<br>
Recent studies have also indicated a possible role for al.,<br>
CaM kinase II in LTP. This enzyme is highly enriche mechanisms involved in LTP appears probable.<br>
Recent studies have also indicated a possible role for<br>
CaM kinase II in LTP. This enzyme is highly enriched<br>
in many of those nerve cells that can generate LTP in<br>
response to Recent studies have also indicated a possible role f<br>CaM kinase II in LTP. This enzyme is highly enrich<br>in many of those nerve cells that can generate LTP<br>response to high frequency stimulation of afferent inpu<br>(Ouimet et

GREENGARD<br>over, CaM kinase II is present in postsynaptic densities<br>(section II.B.2) and would, therefore, be expected to be GREENGARD<br>over, CaM kinase II is present in postsynaptic densities<br>(section II.B.2) and would, therefore, be expected to be<br>exposed to the increases in Ca<sup>2+</sup> levels that follow NMDA GREENGARD<br>over, CaM kinase II is present in postsynaptic densities<br>(section II.B.2) and would, therefore, be expected to be<br>exposed to the increases in  $Ca^{2+}$  levels that follow NMDA<br>receptor activation under depolarizin over, CaM kinase II is present in postsynaptic densities (section II.B.2) and would, therefore, be expected to be exposed to the increases in Ca<sup>2+</sup> levels that follow NMDA receptor activation under depolarizing conditions over, CaM kinase II is present in postsynaptic densities (section II.B.2) and would, therefore, be expected to be exposed to the increases in  $Ca^{2+}$  levels that follow NMDA receptor activation under depolarizing conditio (section II.B.2) and would, therefore, be expected to be exposed to the increases in  $Ca^{2+}$  levels that follow NMDA receptor activation under depolarizing conditions. Recent studies, in which peptide inhibitors of this e exposed to the increases in  $Ca^{2+}$  levels that follow NMDA receptor activation under depolarizing conditions. Recent studies, in which peptide inhibitors of this enzyme were used, led the authors to conclude that CaM kin receptor activation under depolarizing conditions. Recent studies, in which peptide inhibitors of this enzyme were used, led the authors to conclude that CaM kinase II activation is a necessary requirement for LTP to deve cent studies, in which peptide inhibitors of this en<br>were used, led the authors to conclude that CaM k:<br>II activation is a necessary requirement for LT<br>develop (Malenka et al., 1989b; Malinow et al., 1<br>Thus, it seems poss were used, led the authors to conclude that CaM kinase II activation is a necessary requirement for LTP to develop (Malenka et al., 1989b; Malinow et al., 1989). Thus, it seems possible that both types of  $Ca^{2+}$ -dependen Thus, it seems possible that both types of  $Ca^{2+}$ -dependvelop (Malenka et al., 1989b; Malinow et al., 1989).<br>nus, it seems possible that both types of Ca<sup>2+</sup>-depend-<br>t protein kinases may be involved in the initial stages<br>LTP.<br>These protein kinases may also be involved in the<br>a

involvement of  $Ca^{2+}$ -dependent protein kinases in the been proposed that proteolytic removal of the regulatory<br>process. Both CaM kinase II and protein kinase C are domain from the relevant protein kinase(s), and the<br>hig 1983b,c), and the possible involvement of these enzymes  $Ca^{2+}$ -dependent protein kinases, may be involved in<br>in the generation of LTP has been the subject of analysis. maintenance of LTP (Malinow et al., 1988, 1989; R<br>Co Thus, it seems possible that both types of  $Ca^{2+}$ -dependent protein kinases may be involved in the initial stages of LTP.<br>These protein kinases may also be involved in the maintenance of LTP. Sphingosine, a kinase inhibi ent protein kinases may be involved in the initial stages<br>of LTP.<br>These protein kinases may also be involved in the<br>maintenance of LTP. Sphingosine, a kinase inhibitor<br>that acts on the regulatory site of protein kinase C a of LTP.<br>These protein kinases may also be involved in th<br>maintenance of LTP. Sphingosine, a kinase inhibite<br>that acts on the regulatory site of protein kinase C an<br>CaM kinase II (Jefferson and Schulman, 1988), is capa-<br>ble These protein kinases may also be involved in the<br>maintenance of LTP. Sphingosine, a kinase inhibitor<br>that acts on the regulatory site of protein kinase C and<br>CaM kinase II (Jefferson and Schulman, 1988), is capa-<br>ble of b that acts on the regulatory site of protein kinase C and that acts on the regulatory site of protein kinase C and CaM kinase II (Jefferson and Schulman, 1988), is capable of blocking LTP only if it is present during the inducing tetanus. In contrast, kinase inhibitors active at CaM kinase II (Jefferson and Schulman, 1988), is capa-<br>ble of blocking LTP only if it is present during the<br>inducing tetanus. In contrast, kinase inhibitors active at<br>the catalytic sites of protein kinase C and CaM kinase the catalytic sites of protein kinase C and CaM kinase II inducing tetanus. In contrast, kinase inhibitors active at<br>the catalytic sites of protein kinase C and CaM kinase II<br>(such as H-7) can block the initiation of LTP and also<br>reverse the phenomenon if added later. Therefore, the catalytic sites of protein kinase C and CaM kinase II<br>(such as H-7) can block the initiation of LTP and also<br>reverse the phenomenon if added later. Therefore, it has<br>been proposed that proteolytic removal of the regula (such as H-7) can block the initiation of LTP and also<br>reverse the phenomenon if added later. Therefore, it has<br>been proposed that proteolytic removal of the regulatory<br>domain from the relevant protein kinase(s), and the<br> reverse the phenomenon if added later. Therefore, it has<br>been proposed that proteolytic removal of the regulatory<br>domain from the relevant protein kinase(s), and the<br>resulting constitutive activation of one or both of thes been proposed that proteolytic removal of the regulatory<br>domain from the relevant protein kinase(s), and the<br>resulting constitutive activation of one or both of thes<br>Ca<sup>2+</sup>-dependent protein kinases, may be involved in the resulting constitutive activation of one or both of these Ca<sup>2+</sup>-dependent protein kinases, may be involved in the

The studies reviewed in the preceding sections have demonstrated that protein phosphorylation is involved mann et al., 1988).<br> **VI. Phosphoproteins and Clinical Disorders**<br>
The studies reviewed in the preceding sections have<br>
demonstrated that protein phosphorylation is involved<br>
in pleiotropic regulation of cell function in t VI. Phosphoproteins and Clinical Disorders<br>The studies reviewed in the preceding sections have<br>demonstrated that protein phosphorylation is involved<br>in pleiotropic regulation of cell function in the nervous<br>system as well VI. Phosphoproteins and Clinical Disorders<br>The studies reviewed in the preceding sections has<br>demonstrated that protein phosphorylation is involve<br>in pleiotropic regulation of cell function in the nervo<br>system as well as i The studies reviewed in the preceding sections have<br>demonstrated that protein phosphorylation is involve<br>in pleiotropic regulation of cell function in the nervor<br>system as well as in peripheral tissues. It should, ther<br>for demonstrated that protein phosphorylation is involved<br>in pleiotropic regulation of cell function in the nervous<br>system as well as in peripheral tissues. It should, there-<br>fore, not be surprising that a number of pharmacolo in pleiotropic regulation of cell function in the nervous system as well as in peripheral tissues. It should, therefore, not be surprising that a number of pharmacological agents have been found to achieve their actions th system as well as in peripheral tissues. It should, therefore, not be surprising that a number of pharmacological agents have been found to achieve their actions through perturbations of one or another protein phosphorylat fore, not be surprising that a number of pharmacological<br>agents have been found to achieve their actions through<br>perturbations of one or another protein phosphorylation<br>system. For the same reason, one might also anticipat agents have been found to achieve their actions through<br>perturbations of one or another protein phosphorylation<br>system. For the same reason, one might also anticipate<br>that abnormalities in protein phosphorylation could be<br> perturbations of one or another protein phosphorylation<br>system. For the same reason, one might also anticipate<br>that abnormalities in protein phosphorylation could be<br>involved in the etiology of a variety of clinical disord system. For the same reason, one might also anticipate<br>that abnormalities in protein phosphorylation could be<br>involved in the etiology of a variety of clinical disorders.<br>At present, such disorders include a subclass of di that abnormalities in protein phosphorylation could be<br>involved in the etiology of a variety of clinical disorders.<br>At present, such disorders include a subclass of diabetes,<br>which has been shown to be attributable to a mu involved in the etiology of a variety of clinical disorders.<br>At present, such disorders include a subclass of diabetes,<br>which has been shown to be attributable to a mutation<br>in the insulin receptor that renders it incapabl At present, such disorders include a subclass of diabe<br>which has been shown to be attributable to a mutat<br>in the insulin receptor that renders it incapable<br>undergoing autophosphorylation in the presence of<br>sulin (Odawara e which has been shown to be attributable to a mutation<br>in the insulin receptor that renders it incapable of<br>undergoing autophosphorylation in the presence of in-<br>sulin (Odawara et al., 1989; Taira et al., 1989). Further-<br>mo in the insulin receptor that renders it incapable of undergoing autophosphorylation in the presence of insulin (Odawara et al., 1989; Taira et al., 1989). Furthermore, several classes of oncogenic viruses have been shown t undergoing autophosphorylation in the presence of insulin (Odawara et al., 1989; Taira et al., 1989). Furthermore, several classes of oncogenic viruses have been shown to transform cells by virtue of expressing protein tyr sulin (Odawara et al., 1989; Taira et al., 1989). Furtl<br>more, several classes of oncogenic viruses have b<br>shown to transform cells by virtue of expressing prot<br>tyrosine kinase activities (for review, see Bishop, 19;<br>Moreov more, several classes of oncogenic viruses have b<br>shown to transform cells by virtue of expressing prot<br>tyrosine kinase activities (for review, see Bishop, 19<br>Moreover, cystic fibrosis has been shown to be attril<br>able to a shown to transform cells by virtue of expressing protein<br>tyrosine kinase activities (for review, see Bishop, 1982).<br>Moreover, cystic fibrosis has been shown to be attribut-<br>able to an inability of Cl<sup>-</sup> channels to respond tyrosine kinase activities (for review, see Bishop, 1982).<br>Moreover, cystic fibrosis has been shown to be attribut-<br>able to an inability of Cl<sup>-</sup> channels to respond appropri-<br>ately to cyclic AMP-dependent protein kinase a Moreover, cystic fibrosis has been shown to be attri<br>able to an inability of Cl<sup>-</sup> channels to respond appro<br>ately to cyclic AMP-dependent protein kinase an<br>protein kinase C (see below). Finally, a variety of<br>dence has ind able to an inability of Cl<sup>-</sup> channels to respond appropriately to cyclic AMP-dependent protein kinase and to protein kinase C (see below). Finally, a variety of evidence has indicated abnormalities of protein phosphor-<br>yl ately to cyclic AMP-c<br>protein kinase C (see<br>dence has indicated ab<br>ylation in Alzheimer's<br>al., 1990a; see below).<br>In this section, we otein kinase C (see below). Finally, a variety of evi-<br>nce has indicated abnormalities of protein phosphor-<br>ation in Alzheimer's disease (Selkoe, 1989; Gandy et<br>, 1990a; see below).<br>In this section, we will summarize resul

dence has indicated abnormalities of protein phosphor-<br>ylation in Alzheimer's disease (Selkoe, 1989; Gandy et<br>al., 1990a; see below).<br>In this section, we will summarize results of clinical<br>studies correlating variant forms ylation in Alzheimer's disease (Selkoe, 1989; Gandy en al., 1990a; see below).<br>
In this section, we will summarize results of clinics<br>
studies correlating variant forms of synapsin II with<br>
alcoholism and discuss certain s al., 1990a; see below).<br>In this section, we will summarize results of clinical<br>studies correlating variant forms of synapsin II with<br>alcoholism and discuss certain studies of protein phos-<br>phorylation relevant to cystic fi

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scribe recent studies indicating that dopamine, a diuretic<br>widely used clinically, induces natriuresis by a mecha-PROTEIN PHOSPHORYLA<br>scribe recent studies indicating that dopamine, a diure<br>widely used clinically, induces natriuresis by a mech<br>nism that involves a protein phosphorylation pathw PROTEIN PHOSPHORYLATIO<br>scribe recent studies indicating that dopamine, a diuretic<br>widely used clinically, induces natriuresis by a mecha-<br>nism that involves a protein phosphorylation pathway.<br>Finally, we will briefly discu scribe recent studies indicating that dopamine, a diuretic the widely used clinically, induces natriuresis by a mecha-<br>nism that involves a protein phosphorylation pathway. 19<br>Finally, we will briefly discuss the involveme scribe recent studies indicating that dopamine, a diuretic<br>widely used clinically, induces natriuresis by a mecha-<br>nism that involves a protein phosphorylation pathway.<br>Finally, we will briefly discuss the involvement of p The widespread in the pathogenesis of Alzheimer's<br>se.<br>Synapsin Variants and Alcoholism<br>The widespread involvement of protein phosphor<br>in a variety of neuronal functions suggests the

ease. occurses<br>
A. Synapsin Variants and Alcoholism with<br>
The widespread involvement of protein phosphoryla-<br>
tion in a variety of neuronal functions suggests that an indianalysis of neuronal protein phosphorylation system A. Synapsin Variants and Alcoholism<br>
The widespread involvement of protein phosphoryla-<br>
tia)<br>
tion in a variety of neuronal functions suggests that an<br>
analysis of neuronal protein phosphorylation systems in<br>
neuropsychia A. Synapsin Variants and Alconolism<br>The widespread involvement of protein phosphorylistion in a variety of neuronal functions suggests that a<br>analysis of neuronal protein phosphorylation systems is<br>neuropsychiatric disorde The widespread involvement of protein phosphorylation in a variety of neuronal functions suggests that an indically also allows analysis of neuronal protein phosphorylation systems in alcomorphosphorylation about molecular tion in a variety of neuronal functions suggests that an indi-<br>analysis of neuronal protein phosphorylation systems in alco-<br>neuropsychiatric disorders might yield important infor-<br>mation about molecular mechanisms involve analysis of neuronal protein phosphorylation systems in alcomorphism in the mation about molecular mechanisms involved in such potentials protein phosphorylation systems present in drawissue from human brain appear to com neuropsychiatric disorders might yield important information about molecular mechanisms involved in such possess. Protein phosphorylation systems present in tissue from human brain appear to comprise many of the same prote mation about molecular mechanisms involved in such podiceases. Protein phosphorylation systems present in dratissue from human brain appear to comprise many of the value of the phosphatase regulators previously seen in an diseases. Protein phosphorylation systems present in<br>tissue from human brain appear to comprise many of the<br>same protein kinases, phosphoproteins, and protein<br>phosphatase regulators previously seen in animal brain<br>(Routten tissue from human brain appear to comprise many of the<br>same protein kinases, phosphoproteins, and protein<br>phosphatase regulators previously seen in animal brain<br>(Routtenberg et al., 1981; Martinez-Millan and Rod-<br>night, 19 same protein kinases, phosphoproteins, and prot<br>phosphatase regulators previously seen in animal br<br>(Routtenberg et al., 1981; Martinez-Millan and R<br>night, 1982; Walaas et al., 1989d). Moreover, metho<br>for the detection of phosphatase regulators previously seen in animal brain of  $\epsilon$  (Routtenberg et al., 1981; Martinez-Millan and Rod-<br>night, 1982; Walaas et al., 1989d). Moreover, methods Greent for the detection of phosphoproteins in human (Routtenberg et al., 1981; Martinez-Millan and Rod-<br>night, 1982; Walaas et al., 1989d). Moreover, methods  $G_r$ <br>for the detection of phosphoproteins in human cerebro-<br>spinal fluid have recently been developed, and, in fact might, 1982; Walaas et al., 1989d). Moreover, methods<br>for the detection of phosphoproteins in human cerebro-<br>spinal fluid have recently been developed, and, in fact, a<br>phosphoprotein substrate for protein kinase C has been for the detection of phosphoproteins in human cerebro-<br>spinal fluid have recently been developed, and, in fact, a<br>phosphoprotein substrate for protein kinase C has been<br>found to be present in cerebrospinal fluid from pati spinal fluid have recently been developed, and, in fact, a<br>phosphoprotein substrate for protein kinase C has been<br>found to be present in cerebrospinal fluid from patients<br>with paraneoplastic cerebellar degeneration (Gandy phosphoprotein substrate for protein kinase C has been<br>found to be present in cerebrospinal fluid from patients<br>with paraneoplastic cerebellar degeneration (Gandy et<br>al., 1990b). It thus appears that, despite the considera found to be present in cerebrospinal fluid from patients<br>with paraneoplastic cerebellar degeneration (Gandy et<br>al., 1990b). It thus appears that, despite the considerable<br>problems encountered in studies of human CNS materi with paraneoplastic cerebellar degeneration (Gandy et al., 1990b). It thus appears that, despite the considerable  $B$  problems encountered in studies of human CNS material, particularly concerning postmortem proteolysis ( al., 1990b). It thus appears that, despite the considerable problems encountered in studies of human CNS material, particularly concerning postmortem proteolysis (Walaas et al., 1989d), studies of the possible involvement problems encountered in studies of human CNS material, particularly concerning postmortem proteolysis (Walaas<br>et al., 1989d), studies of the possible involvement of<br>protein phosphorylation in human neurological and/or<br>psyc et al., 1989d), studies of the possible involvement of in the affected cells are unable to respond to activation<br>protein phosphorylation in human neurological and/or in a physiological manner (Welsh, 1990). Given the im-<br>p et al., 1989d), studies of the possible involvement of in<br>protein phosphorylation in human neurological and/or<br>psychiatric diseases may now be feasible (for examples, p<br>see Raisman-Vozari et al., 1990; Girault et al., 1989 protein phosphorylation in human neurological and/or psychiatric diseases may now be feasible (for examples, see Raisman-Vozari et al., 1990; Girault et al., 1989b). In one such series of studies, it was found that variant psychiatric diseases may now be feasible (for examples, port see Raisman-Vozari et al., 1990; Girault et al., 1989b). In of the one such series of studies, it was found that variant forms C of synapsin II, a synaptic vesic one such series of studies, it was found that variant forms<br>of synapsin II, a synaptic vesicle-associated protein dis-<br>cussed in section IV.A.2, may have some connection to<br>alcoholism and possibly other neuropsychiatric di ders. synapsin II, a synaptic vesicle-associated protein dis-<br>ssed in section IV.A.2, may have some connection to<br>coholism and possibly other neuropsychiatric disor-<br>Bo<br>Synapsin II consists of two polypeptides, synapsin IIa<br>d sy cussed in section IV.A.2, may have some connection to<br>alcoholism and possibly other neuropsychiatric disor-<br>ders.<br>Synapsin II consists of two polypeptides, synapsin IIa<br>and synapsin IIb (see section IV). Brains from all su

alcoholism and possibly other neuropsychiatric disor-<br>ders. an<br>Synapsin II consists of two polypeptides, synapsin IIa thi<br>and synapsin IIb (see section IV). Brains from all sub-<br>thuman mammalian species studied to date hav ders. an an unity of two polypeptides, synapsin IIa this and synapsin IIb (see section IV). Brains from all sub-<br>human mammalian species studied to date have only one epit<br>form of synapsin IIa and one form of synapsin IIb. Synapsin II consists of two polypeptides, synapsin II<br>and synapsin IIb (see section IV). Brains from all sub<br>human mammalian species studied to date have only on<br>form of synapsin IIa and one form of synapsin IIb. II<br>contra and synapsin IIb (see section IV). Brains from all su<br>human mammalian species studied to date have only of<br>orm of synapsin IIa and one form of synapsin IIb.<br>contrast, postmortem human brain samples have ad<br>tional forms of human mammalian species studied to date have only one<br>form of synapsin IIa and one form of synapsin IIb. In<br>contrast, postmortem human brain samples have addi-<br>cional forms of synapsins IIa and IIb with higher appar-<br>ent form of synapsin IIa and one form of synapsin IIb.<br>contrast, postmortem human brain samples have ad<br>tional forms of synapsins IIa and IIb with higher appar<br>ent molecular weights (Perdahl et al., 1984). The form<br>designated contrast, postmortem human brain samples have additional forms of synapsins IIa and IIb with higher apparent molecular weights (Perdahl et al., 1984). The forms 1 designated synapsins  $IIa_1$  and  $IIb_1$  have the same appar tional forms of synapsins IIa and IIb with higher appar-<br>ent molecular weights (Perdahl et al., 1984). The forms 19<br>designated synapsins IIa<sub>1</sub> and IIb<sub>1</sub> have the same appar-<br>ent molecular masses as the nonhuman forms of ent molecular weights (Perdahl et al., 1984). The forms 1996<br>designated synapsins  $IIa_1$  and  $IIb_1$  have the same appar-<br>ent molecular masses as the nonhuman forms of synapsin scril<br>IIa and IIb, respectively, and are refe designated synapsins  $IIA_1$  and  $IIB_1$  have the same apparent molecular masses as the nonhuman forms of synapsin<br>IIa and IIb, respectively, and are referred to as the K<br>"normal" forms, and synapsins  $IIA_2$ ,  $IIA_3$ ,  $IIB_2$ ent molecular masses as the nonhuman forms of synapsin<br>IIa and IIb, respectively, and are referred to as the<br>"normal" forms, and synapsins  $IIa_2$ ,  $IIa_3$ ,  $IIIb_2$ , and  $IIIb_3$ <br>are referred to as the "variant" forms. Within IIa and IIb, respectively, and are referred to as the "normal" forms, and synapsins  $IIa_2$ ,  $IIa_3$ ,  $IIIb_2$ , and  $IIIb_3$  prese referred to as the "variant" forms. Within any single last human brain, the same forms of synaps "normal" forms, and synapsins  $IIa_2$ ,  $IIa_3$ ,  $IIIb_2$ , and  $IIb_3$  pro<br>are referred to as the "variant" forms. Within any single lari<br>human brain, the same forms of synapsin II are present al.,<br>throughout all brain regions. are referred to as the "variant" forms. Within any single<br>human brain, the same forms of synapsin II are present<br>throughout all brain regions. Moreover, in each human<br>brain, the presence or absence of synapsins  $IIa_1$ ,  $IIa$ human brain, the same forms of synapsin II are present althroughout all brain regions. Moreover, in each human morain, the presence or absence of synapsins  $IIa_1$ ,  $IIa_2$ , and cy  $IIIa_3$  parallels the presence or absence o throughout all brain regions. Moreover, in each human mee<br>brain, the presence or absence of synapsins  $IIa_1$ ,  $IIa_2$ , and cys<br> $IIa_3$  parallels the presence or absence of synapsins  $IIb_1$ , por<br> $IIb_2$ , and  $IIb_3$ , respectiv brain, the presence or absence of synapsins  $IIa_1$ ,  $IIa_2$ , and  $IIa_3$  parallels the presence or absence of synapsins  $IIb_1$ ,  $IIIb_2$ , and  $IIIb_3$ , respectively. Thus, an individual may have just one form of synapsin  $IIa$  a IIa<sub>3</sub> parallels the presence or absence of synapsins IIb<sub>1</sub>, IIb<sub>2</sub>, and IIb<sub>3</sub>, respectively. Thus, an individual may have just one form of synapsin IIa and synapsin IIb (e.g., IIa<sub>1</sub> and IIb<sub>1</sub>) or any two forms of syn

et al., 1984; Grebb et al., 1989;, Grebb and Greengard, and NEURONAL FUNCTION 329<br>three studies of human postmortem brain tissue (Perdah<br>et al., 1984; Grebb et al., 1989;, Grebb and Greengard<br>1990). In all three studies, a significant correlation was 1999). AND NEURONAL FUNCTION 329<br>
1990). In all three studies, a significant correlation was<br>
1990). In all three studies, a significant correlation was<br>
1990). In all three studies, a significant correlation was<br>
1990). I three studies of human postmortem brain tissue (Perdahl<br>et al., 1984; Grebb et al., 1989;, Grebb and Greengard,<br>1990). In all three studies, a significant correlation was<br>found between the presence of synapsin II variants three studies of human postmortem brain tissue (Perdahl<br>et al., 1984; Grebb et al., 1989;, Grebb and Greengard,<br>1990). In all three studies, a significant correlation was<br>found between the presence of synapsin II variants et al., 1984; Grebb et al., 1989;, Grebb and Greengard, 1990). In all three studies, a significant correlation was found between the presence of synapsin II variants and the diagnosis of alcoholism; in addition, an increas 1990). In all three studies, a significant correlation was<br>found between the presence of synapsin II variants and<br>the diagnosis of alcoholism; in addition, an increased<br>occurrence of synapsin II variants among individuals<br> found between the presence of synapsin II variants and<br>the diagnosis of alcoholism; in addition, an increased<br>occurrence of synapsin II variants among individuals<br>with various dementing illnesses (Alzheimer's disease,<br>mult the diagnosis of alcoholism; in addition, an increased<br>occurrence of synapsin II variants among individuals<br>with various dementing illnesses (Alzheimer's disease,<br>multiinfarct dementia, Parkinson's disease with demen-<br>tia) occurrence of synapsin II variants among individuals<br>with various dementing illnesses (Alzheimer's disease,<br>multiinfarct dementia, Parkinson's disease with demen-<br>tia) was also observed (Perdahl et al., 1984). These data<br>i with various dementing illnesses (Alzheimer's disease, multiinfarct dementia, Parkinson's disease with dementia) was also observed (Perdahl et al., 1984). These data indicate that synapsin II variants may not be specific f multiinfarct dementia, Parkinson's disease with dementia) was also observed (Perdahl et al., 1984). These data indicate that synapsin II variants may not be specific for alcoholism and that synapsin II variants may represe tia) was also observed (Perdahl et al., 1984). These data indicate that synapsin II variants may not be specific for alcoholism and that synapsin II variants may represent a specific genetic trait which may contribute to t indicate that synapsin II variants may not be specific for<br>alcoholism and that synapsin II variants may represent<br>a specific genetic trait which may contribute to the<br>polygenetic etiologies of several different clinical sy alcoholism and that synapsin II variants may represent<br>a specific genetic trait which may contribute to the<br>polygenetic etiologies of several different clinical syn-<br>dromes, including alcoholism. Additionally, synapsin II<br> a specific genetic trait which may contribute to the polygenetic etiologies of several different clinical syn-<br>dromes, including alcoholism. Additionally, synapsin II<br>variants have been found in postmortem brain samples<br>fr polygenetic etiologies of several different clinical syn-<br>dromes, including alcoholism. Additionally, synapsin II<br>variants have been found in postmortem brain samples<br>from infants and children who have died of a wide varie dromes, including alcoholism. Additionally, synapsin II<br>variants have been found in postmortem brain samples<br>from infants and children who have died of a wide variety<br>of accidents and medical illnesses, thus suggesting tha variants have been found in postmortem brain samples<br>from infants and children who have died of a wide variety<br>of accidents and medical illnesses, thus suggesting that<br>synapsin II variants can be present at birth (Grebb an from infants and children who have died of a wide variety<br>of accidents and medical illnesses, thus suggesting that<br>synapsin II variants can be present at birth (Grebb and<br>Greengard, 1990). Unfortunately, synapsin II varian of accidents and medical illnesses, thus suggesting that<br>synapsin II variants can be present at birth (Grebb and<br>Greengard, 1990). Unfortunately, synapsin II variants<br>have not been found in any of the 18 rodent models of<br>a synapsin II variants can be present at birth (Grebb and Greengard, 1990). Unfortunately, synapsin II variants have not been found in any of the 18 rodent models of alcoholism, aging, or vitamin B deficiency, making it diff Greengard, 199<br>have not been<br>alcoholism, age<br>difficult to deverthose variants.<br>B. Custic Eihro have not been found in any of the 18 rodent models of alcoholism, aging, or vitamin B deficiency, making it difficult to develop experimental models for the study of those variants.<br>*B. Cystic Fibrosis and Cl<sup>-</sup> Channel Re* 

Ficult to develop experimental models for the study of<br>ose variants.<br>Cystic Fibrosis and Cl<sup>-</sup> Channel Regulation<br>Recent studies have shown that cystic fibrosis is due<br>a defect in ion channel function, in that Cl<sup>-</sup> channe those variants.<br>
B. Cystic Fibrosis and C $\Gamma$  Channel Regulation<br>
Recent studies have shown that cystic fibrosis is due<br>
to a defect in ion channel function, in that C $\Gamma$  channels<br>
in the affected cells are unable to res B. Cystic Fibrosis and Cl<sup>-</sup> Channel Regulation<br>Recent studies have shown that cystic fibrosis is due<br>to a defect in ion channel function, in that Cl<sup>-</sup> channels<br>in the affected cells are unable to respond to activation<br>in B. Cystic Fibrosis and Cl<sup>-</sup> Channel Regulation<br>Recent studies have shown that cystic fibrosis is due<br>to a defect in ion channel function, in that  $Cl^-$  channels<br>in the affected cells are unable to respond to activation<br>in Recent studies have shown that cystic fibrosis is due<br>to a defect in ion channel function, in that Cl<sup>-</sup> channels<br>in the affected cells are unable to respond to activation<br>in a physiological manner (Welsh, 1990). Given the in a physiological manner (Welsh, 1990). Given the im-

Cystic fibrosis is a fatal, autosomal recessive genetic disease characterized by abnormalities in fluid and electrolyte transport in exocrine epithelia (Quinton, 1990). in a physiological manner (Welsh, 1990). Given the importance of ion channel function in the CNS, a discussion<br>of this disease seems warranted here.<br>Cystic fibrosis is a fatal, autosomal recessive genetic<br>disease character portance of ion channel function in the CNS, a discussion<br>of this disease seems warranted here.<br>Cystic fibrosis is a fatal, autosomal recessive genetic<br>disease characterized by abnormalities in fluid and elec-<br>trolyte tran of this disease seems warranted here.<br>Cystic fibrosis is a fatal, autosomal recessive genetic<br>disease characterized by abnormalities in fluid and elec-<br>trolyte transport in exocrine epithelia (Quinton, 1990).<br>Both absorpti Cystic fibrosis is a fatal, autosomal recessive genetic<br>disease characterized by abnormalities in fluid and elec-<br>trolyte transport in exocrine epithelia (Quinton, 1990).<br>Both absorptive and secretory processes are affecte disease characterized by abnormalities in fluid and electrolyte transport in exocrine epithelia (Quinton, 1990).<br>Both absorptive and secretory processes are affected by an underlying membrane defect in Cl<sup>-</sup> permeability, trolyte transport in exocrine epithelia (Quinton, 1990).<br>Both absorptive and secretory processes are affected by<br>an underlying membrane defect in Cl<sup>-</sup> permeability, and<br>this defect results in tissue-specific symptoms. Alt Both absorptive and secretory processes are affected<br>an underlying membrane defect in Cl<sup>-</sup> permeability, a<br>this defect results in tissue-specific symptoms. Althou<br>the defect is not fatal in and of itself, the effects in a an underlying membrane defect in Cl<sup>-</sup> permeability, and<br>this defect results in tissue-specific symptoms. Although<br>the defect is not fatal in and of itself, the effects in airway<br>epithelia ultimately lead to irreversible a this defect results in tissue-specific symptoms. Although<br>the defect is not fatal in and of itself, the effects in airway<br>epithelia ultimately lead to irreversible and fatal second-<br>ary pulmonary infections. Cystic fibrosi the defect is not fatal in and of itself, the effects in airway<br>epithelia ultimately lead to irreversible and fatal second-<br>ary pulmonary infections. Cystic fibrosis is the most<br>common fatal genetic disease in the United S 1990). y pulmonary infections. Cystic fibrosis is the most<br>mmon fatal genetic disease in the United States and<br>fects approximately 1 in 2000 Caucasians (Quinton,<br>90).<br>The cystic fibrosis gene was recently cloned and de-<br>ribed (Ro

 $b_2$ , and IIb<sub>3</sub>, respectively. Thus, an individual may have regulates the quantity and composition of the respiratory<br>st one form of synapsin IIa and synapsin IIb (e.g., IIa<sub>1</sub> tract fluid; this Cl<sup>-</sup> secretion is contr common fatal genetic disease in the United States and<br>affects approximately 1 in 2000 Caucasians (Quinton,<br>1990).<br>The cystic fibrosis gene was recently cloned and de-<br>scribed (Rommens et al., 1989; Riordan et al., 1989;<br>Ke affects approximately 1 in 2000 Caucasians (Quinton, 1990).<br>1990).<br>The cystic fibrosis gene was recently cloned and de-<br>scribed (Rommens et al., 1989; Riordan et al., 1989;<br>Kerem et al., 1989). The function of the encoded 1990).<br>The cystic fibrosis gene was recently cloned and de<br>scribed (Rommens et al., 1989; Riordan et al., 1989<br>Kerem et al., 1989). The function of the encoded gen<br>product is not clear, although the protein exhibits simi-<br> The cystic fibrosis gene was recently cloned and described (Rommens et al., 1989; Riordan et al., 1989; Kerem et al., 1989). The function of the encoded gene product is not clear, although the protein exhibits similarities scribed (Rommens et al., 1989; Riordan et al., 1989; Kerem et al., 1989). The function of the encoded gene product is not clear, although the protein exhibits similarities with a number of transport proteins (Riordan et a Kerem et al., 1989). The function of the encoded gene product is not clear, although the protein exhibits sim<br>larities with a number of transport proteins (Riordan<br>al., 1989). However, in recent studies, several biochemic<br>mechanisms have been identified that are defective<br>cys larities with a number of transport proteins (Riordan et al., 1989). However, in recent studies, several biochemical mechanisms have been identified that are defective in cystic fibrosis epithelia, all of which center on C al., 1989). However, in recent studies, several biochemical mechanisms have been identified that are defective in cystic fibrosis epithelia, all of which center on Cl<sup>-</sup> transport mechanisms. Cl<sup>-</sup> secretion by the airway mechanisms have been identified that are defective in<br>cystic fibrosis epithelia, all of which center on Cl<sup>-</sup> trans-<br>port mechanisms. Cl<sup>-</sup> secretion by the airway epithelium<br>regulates the quantity and composition of the r cystic fibrosis epithelia, all of which center on Cl<sup>-</sup> trans-<br>port mechanisms. Cl<sup>-</sup> secretion by the airway epithelium<br>regulates the quantity and composition of the respiratory<br>tract fluid; this Cl<sup>-</sup> secretion is contro port mechanisms. Cl<sup>-</sup> secretion by the airway epithelium<br>regulates the quantity and composition of the respiratory<br>tract fluid; this Cl<sup>-</sup> secretion is controlled by apical<br>membrane Cl<sup>-</sup> channels. A number of hormones an regulates the quantity and composition of the respiratory<br>tract fluid; this Cl<sup>-</sup> secretion is controlled by apical<br>membrane Cl<sup>-</sup> channels. A number of hormones and<br>secretagogues that increase intracellular levels of cycl

WALAAS AND GREENGARD<br>these Cl<sup>-</sup> channels (Welsh, 1990). Certain secretagogues Goldberg, 1<br>have also been found to increase diacylglycerol levels, for the clin waLAAS AND<br>these Cl<sup>-</sup> channels (Welsh, 1990). Certain secretagogues<br>have also been found to increase diacylglycerol levels,<br>indicating that protein kinase C also may regulate Cl<sup>-</sup> WALAAS AND GRE<br>these Cl<sup>-</sup> channels (Welsh, 1990). Certain secretagogues Go<br>have also been found to increase diacylglycerol levels, for<br>indicating that protein kinase C also may regulate Cl<sup>-</sup> um<br>channels, and, indeed, act channels (Welsh, 1990). Certain secretagogues Goldb<br>have also been found to increase diacylglycerol levels, for the<br>indicating that protein kinase C also may regulate Cl<sup>-</sup> ume he<br>channels, and, indeed, activators of prote these Cl<sup>-</sup> channels (Welsh, 1990). Certain secretagogues<br>have also been found to increase diacylglycerol levels,<br>indicating that protein kinase C also may regulate Cl<sup>-</sup><br>channels, and, indeed, activators of protein kinase have also been found to increase diacylglycerol levels, indicating that protein kinase C also may regulate Cl<sup>-</sup><br>channels, and, indeed, activators of protein kinase C levere found to either stimulate or inhibit Cl<sup>-</sup> secre indicating t<br>channels, a<br>were found<br>depending e<br>al., 1989).<br>In airway

depending on the physiological state of the cells (Li et al., 1989).<br>In airway epithelial cells from children with cystic fibrosis, Cl<sup>-</sup> channels were found to be present, but their regulation was defective. Activation of depending on the physiological state of the cells (Li et al., 1989).<br>
In airway epithelial cells from children with cystic<br>
fibrosis, Cl<sup>-</sup> channels were found to be present, but their<br>
regulation was defective. Activation al., 1989).<br>In airway epithelial cells from children with cystic<br>fibrosis, Cl<sup>-</sup> channels were found to be present, but their<br>regulation was defective. Activation of apical membrane<br>Cl<sup>-</sup> channels by cyclic AMP-mediated st In airway epithelial cells from children with cystic<br>fibrosis, Cl<sup>-</sup> channels were found to be present, but their<br>regulation was defective. Activation of apical membrane<br>Cl<sup>-</sup> channels by cyclic AMP-mediated stimuli was ab fibrosis, Cl<sup>-</sup> channels were found to be present, but their regulation was defective. Activation of apical membrane Cl<sup>-</sup> channels by cyclic AMP-mediated stimuli was absent, despite normal agonist-induced increases in cel regulation was defective. Activation of apical membrane Cl<sup>-</sup> channels by cyclic AMP-mediated stimuli was absent, despite normal agonist-induced increases in cellular cyclic AMP levels (Frizzell et al., 1986; Welsh, 1990). Cl<sup>-</sup> channels by cyclic AMP-mediated stimuli was absent, despite normal agonist-induced increases in cellular K cyclic AMP levels (Frizzell et al., 1986; Welsh, 1990). patches membrane patches. It was examined in cell-fr sent, despite normal agonist-induced increases in cellular K cyclic AMP levels (Frizzell et al., 1986; Welsh, 1990). The molecular mechanism underlying these observations sy was examined in cell-free membrane patches. It w cyclic AMP levels (Frizzell et al., 1986; Welsh, 1990).<br>The molecular mechanism underlying these observations<br>was examined in cell-free membrane patches. It was<br>found that application of the purified C subunit of cyclic<br>AM The molecular mechanism underlying these observations symples was examined in cell-free membrane patches. It was expound that application of the purified C subunit of cyclic  $\mu$  m AMP-dependent protein kinase plus ATP op was examined in cell-free membrane patches. It was<br>found that application of the purified C subunit of cyclic<br>AMP-dependent protein kinase plus ATP opened Cl<sup>-</sup><br>channels in patches from normal airway epithelial cells<br>but f found that application of the purified C subunit of cyclic and AMP-dependent protein kinase plus ATP opened Cl<sup>-</sup> schannels in patches from normal airway epithelial cells but failed to open such channels in patches from c AMP-dependent protein kinase plus ATP opened Cl<sup>-</sup><br>channels in patches from normal airway epithelial cells<br>but failed to open such channels in patches from cystic<br>fibrosis epithelial cells (Schoumacher et al., 1987; Li et<br> channels in patches from normal airway epithelial cells mead but failed to open such channels in patches from cystic religiorsis epithelial cells (Schoumacher et al., 1987; Li et diss al., 1988). Thus, the cystic fibrosis but failed to open such channels in patches from cystic<br>fibrosis epithelial cells (Schoumacher et al., 1987; Li et<br>al., 1988). Thus, the cystic fibrosis cells display an ina-<br>bility of the Cl<sup>-</sup> channel, or a modulator the fibrosis epithelial cells (Schoumacher et al., 1987; Li et al., 1988). Thus, the cystic fibrosis cells display an inability of the Cl<sup>-</sup> channel, or a modulator thereof, to dop respond to cyclic AMP-dependent protein kina secretion. bility of the Cl<sup>-</sup> channel, or a modulator thereof, to dopamine; moreover, as with proximal convoluted turespond to cyclic AMP-dependent protein kinase, a re-<br>sponse that is indispensable for normal regulation of Cl<sup>-</sup> bo

ing Cl<sup>-</sup> channels at low Ca<sup>2+</sup> concentrations and inactisponse that is indispensable for normal regulation of (secretion.<br>In cell-free membrane patches from normal airwepithelal cells, protein kinase C had dual effects, activing  $Cl^-$  channels at low  $Ca^{2+}$  concentrations and secretion.<br>
In cell-free membrane patches from normal airway<br>
epithelal cells, protein kinase C had dual effects, activat-<br>
ing Cl<sup>-</sup> channels at low Ca<sup>2+</sup> concentrations and inacti-<br>
vating the channels at high Ca<sup>2+</sup> c In cell-free membrane patches from normal airway<br>epithelal cells, protein kinase C had dual effects, activat-<br>ing Cl<sup>-</sup> channels at low  $Ca^{2+}$  concentrations and inacti-<br>vating the channels at high  $Ca^{2+}$  concentrations epithelal cells, protein kinase C had dual effects, activating Cl<sup>-</sup> channels at low  $Ca^{2+}$  concentrations and inactivating the channels at high  $Ca^{2+}$  concentrations (Li et al., 1989). In membrane patches from cystic f ing Cl<sup>-</sup> channels at low Ca<sup>2+</sup> concentrations and inactivating the channels at high Ca<sup>2+</sup> concentrations (Li et pl., 1989). In membrane patches from cystic fibrosis cells, reprotein kinase C-induced inactivation was no vating the channels at high  $Ca^{2+}$  concentrations (Li et al., 1989). In membrane patches from cystic fibrosis cells, reception kinase C-induced inactivation was normal, but production was defective. The data indicated th al., 1989). In membrane patches from cystic fibrosis cel<br>protein kinase C-induced inactivation was normal, b<br>activation was defective. The data indicated that one<br>more isoforms of protein kinase C phosphorylates a<br>regulate protein kinase C-induced inactivation was normal, but<br>activation was defective. The data indicated that one or<br>more isoforms of protein kinase C phosphorylates and<br>regulates different sites on the channel or on an associactivation was defective. The data indicated that one or<br>more isoforms of protein kinase C phosphorylates and<br>regulates different sites on the channel or on an associ-<br>ated membrane protein, one of which is defective in<br>c more isoforms of protein kinase C phosphorylates and regulates different sites on the channel or on an associated membrane protein, one of which is defective in cystic fibrosis (Li et al., 1989; Hwang et al., 1989). An imp more isolorms of protein kinase C phosphorylates and<br>regulates different sites on the channel or on an associ-<br>ated membrane protein, one of which is defective in<br>cystic fibrosis (Li et al., 1989; Hwang et al., 1989). An<br> protein(s) involved to become phosphorylated by the cystic fibrosis (Li et al., 1989; Hwang et al., 1989). An<br>important question that remains concerning the deficient<br>regulation mechanism in cystic fibrosis is whether the<br>defects are caused by an inability of the membrane<br> important question that remains concerning the deficient regulation mechanism in cystic fibrosis is whether the defects are caused by an inability of the membrane protein(s) involved to become phosphorylated by the respec regulation mechanism in cystic fibrosis is whether the defects are caused by an inability of the membrane protein(s) involved to become phosphorylated by the respective protein kinases, or whether the proteins are phosphor defects are caused by an inability of the membran<br>protein(s) involved to become phosphorylated by th<br>respective protein kinases, or whether the proteins are<br>phosphorylated in a normal way but are unable to re<br>spond with th protein(s) involved to become phosphoryl<br>respective protein kinases, or whether the<br>phosphorylated in a normal way but are u<br>spond with the conformational change neces<br>ulate Cl<sup>-</sup> permeability in a normal fashion.<br>C. Donam phosphorylated in a normal way but are unable to re-<br>spond with the conformational change necessary to mod-<br>ulate Cl<sup>-</sup> permeability in a normal fashion.<br>*C. Dopaminergic Regulation of Natriuresis*<br>Na<sup>+</sup>, K<sup>+</sup>-ATPase, an i spond with the conformational change necessary to modulate  $Cl^-$  permeability in a normal fashion.<br>C. Dopaminergic Regulation of Natriuresis<br>Na<sup>+</sup>, K<sup>+</sup>-ATPase, an integral membrane protein pres-<br>ent in virtually all mamma

ulate Cl<sup>-</sup> permeability in a normal fashion.<br>C. Dopaminergic Regulation of Natriuresis<br>Na<sup>+</sup>, K<sup>+</sup>-ATPase, an integral membrane protein pres-<br>ent in virtually all mammalian cells, regulates a number<br>of vital functions, in C. Dopaminergic Regulation of Natriuresis<br>Na<sup>+</sup>, K<sup>+</sup>-ATPase, an integral membrane protein pres-<br>ent in virtually all mammalian cells, regulates a number<br>of vital functions, including intracellular electrolyte ho-<br>meostasi C. *Dopaminergic Regulation of Natriuresis*<br>Na<sup>+</sup>, K<sup>+</sup>-ATPase, an integral membrane protein pre<br>ent in virtually all mammalian cells, regulates a numb<br>of vital functions, including intracellular electrolyte h<br>meostasis, Na<sup>+</sup>, K<sup>+</sup>-ATPase, an integral membrane protein pres-<br>ent in virtually all mammalian cells, regulates a number<br>of vital functions, including intracellular electrolyte ho-<br>meostasis, cell volume, membrane potential, and t ent in virtually all mammalian cells, regulates a number<br>of vital functions, including intracellular electrolyte ho-<br>meostasis, cell volume, membrane potential, and trans-<br>port of Na<sup>+</sup> and various other compounds. This en of vital functions, including intracellular electrolyte homeostasis, cell volume, membrane potential, and transport of Na<sup>+</sup> and various other compounds. This enzyme is particularly abundant in brain and kidney, and recens meostasis, cell volume, membrane potential, and trans-<br>port of Na<sup>+</sup> and various other compounds. This enzyme this particularly abundant in brain and kidney, and recent pistudies have shown that the enzyme is subject to re port of  $Na^+$  and various other compounds. This enzyme is particularly abundant in brain and kidney, and recent studies have shown that the enzyme is subject to regulation by dopamine, which can decrease the activity of t is particularly abundant in brain and kidney, and recent studies have shown that the enzyme is subject to regulation by dopamine, which can decrease the activity of the enzyme, in both renal tubule cells (Aperia et al., 19 studies have shown that the enzyme is subject to regulation by dopamine, which can decrease the activity of int the enzyme, in both renal tubule cells (Aperia et al., me 1987) and in neostriatal neurons (Bertorello et al.,

channels, and, indeed, activators of protein kinase C have made this catecholamine compound the diuretic<br>were found to either stimulate or inhibit  $Cl^-$  secretion, drug of choice in certain clinical situations when renal<br>d Goldberg, 1972; Schmidt et al., 1986), which are critical<br>for the clinical regulation of Na<sup>+</sup> and extracellular vol-FREENGARD<br>Goldberg, 1972; Schmidt et al., 1986), which are critical<br>for the clinical regulation of Na<sup>+</sup> and extracellular vol-<br>ume homeostasis and for the regulation of blood pressure, GREENGARD<br>Goldberg, 1972; Schmidt et al., 1986), which are critical<br>for the clinical regulation of Na<sup>+</sup> and extracellular vol-<br>ume homeostasis and for the regulation of blood pressure,<br>have made this catecholamine compoun Goldberg, 1972; Schmidt et al., 1986), which are critical<br>for the clinical regulation of  $Na<sup>+</sup>$  and extracellular vol-<br>ume homeostasis and for the regulation of blood pressure,<br>have made this catecholamine compound the Goldberg, 1972; Schmidt et al., 1986), which are critical<br>for the clinical regulation of Na<sup>+</sup> and extracellular vol-<br>ume homeostasis and for the regulation of blood pressure,<br>have made this catecholamine compound the diu for the clinical regulation of  $Na^+$  and extracellular volume homeostasis and for the regulation of blood pressure,<br>have made this catecholamine compound the diuretic<br>drug of choice in certain clinical situations when ren ume homeostasis and for the regulation of blood pressure,<br>have made this catecholamine compound the diuretic<br>drug of choice in certain clinical situations when renal<br>function is compromised (Schwartz and Gewertz, 1988;<br>Ape have made this catecholamine compound the diuret<br>drug of choice in certain clinical situations when ren<br>function is compromised (Schwartz and Gewertz, 198<br>Aperia et al., 1991). An understanding of the mechanis<br>by which do drug of choice in certain clinics<br>function is compromised (Schw<br>Aperia et al., 1991). An understa<br>by which dopamine inhibits Na<br>fore, of considerable importance<br>Studies of proximal convolute nction is compromised (Schwartz and Gewertz, 1988;<br>beria et al., 1991). An understanding of the mechanism<br>which dopamine inhibits Na<sup>+</sup>, K<sup>+</sup>-ATPase is, there-<br>re, of considerable importance.<br>Studies of proximal convoluted

Aperia et al., 1991). An understanding of the mechanism<br>by which dopamine inhibits  $Na^+$ ,  $K^+$ -ATPase is, there-<br>fore, of considerable importance.<br>Studies of proximal convoluted tubules from rat kidney<br>showed that the do by which dopamine inhibits Na<sup>+</sup>, K<sup>+</sup>-ATPase is, there-<br>fore, of considerable importance.<br>Studies of proximal convoluted tubules from rat kidney<br>showed that the dopamine-induced inhibition of Na<sup>+</sup>,<br>K<sup>+</sup>-ATPase was mediat fore, of considerable importance.<br>
Studies of proximal convoluted tubules from rat kidney<br>
showed that the dopamine-induced inhibition of Na<sup>+</sup>,<br>  $K^+$ -ATPase was mediated through both D1 and D2 do-<br>
pamine receptors (Ber Studies of proximal convoluted tubules from rat kidney<br>showed that the dopamine-induced inhibition of Na<sup>+</sup>,<br>K<sup>+</sup>-ATPase was mediated through both D1 and D2 do-<br>pamine receptors (Bertorello and Aperia, 1988). Such<br>synergis showed that the dopamine-induced inhibition of Na<br>K<sup>+</sup>-ATPase was mediated through both D1 and D2 do<br>pamine receptors (Bertorello and Aperia, 1988). Suc<br>synergism is similar to the mechanisms necessary for fu<br>expression of K<sup>+</sup>-ATPase was mediated through both D1 and D2 do-<br>pamine receptors (Bertorello and Aperia, 1988). Such<br>synergism is similar to the mechanisms necessary for full<br>expression of the electrophysiological actions of dopa-<br>min pamine receptors (Bertorello and Aperia, 1988). Such<br>synergism is similar to the mechanisms necessary for full<br>expression of the electrophysiological actions of dopa-<br>mine in the CNS (Carlson et al., 1987). Recent work has synergism is similar to the mechanisms necessary for full expression of the electrophysiological actions of dopa-<br>mine in the CNS (Carlson et al., 1987). Recent work has<br>shown that dopamine also inhibits the enzyme in per expression of the electrophysiological actions of dopa-<br>mine in the CNS (Carlson et al., 1987). Recent work has<br>shown that dopamine also inhibits the enzyme in per-<br>meabilized, intact nerve cells from neostriatum (Berto-<br> mine in the CNS (Carlson et al., 1987). Recent work<br>shown that dopamine also inhibits the enzyme in p<br>meabilized, intact nerve cells from neostriatum (Ber<br>rello et al., 1990). In that study, Na<sup>+</sup>, K<sup>+</sup>-ATPase<br>dissociated shown that dopamine also inhibits the enzyme in per-<br>meabilized, intact nerve cells from neostriatum (Berto-<br>rello et al., 1990). In that study,  $Na^+$ ,  $K^+$ -ATPase in<br>dissociated medium-sized spiny cells from the neostri meabilized, intact nerve cells from neostriatum (Berto-<br>rello et al., 1990). In that study, Na<sup>+</sup>, K<sup>+</sup>-ATPase in<br>dissociated medium-sized spiny cells from the neostria-<br>tum was found to be rapidly and potently inhibited b rello et al., 1990). In that study,  $Na^+$ ,  $K^+$ -ATPase in dissociated medium-sized spiny cells from the neostriatum was found to be rapidly and potently inhibited by dopamine; moreover, as with proximal convoluted tubule tum was found to be rapidly and potently inhibited by m was found to be rapidly and potently inhibited by<br>pamine; moreover, as with proximal convoluted tu-<br>les, dopamine acted through a synergistic effect on<br>th D1 and D2 receptors.<br>Evidence obtained from studies in kidney cel dopamine; moreover, as with proximal convoluted tubules, dopamine acted through a synergistic effect on both D1 and D2 receptors.<br>Evidence obtained from studies in kidney cells points to direct phosphorylation of the ATPas

bules, dopamine acted through a synergistic effect<br>both D1 and D2 receptors.<br>Evidence obtained from studies in kidney cells point<br>to direct phosphorylation of the ATPase and to mod<br>lation of protein phosphatase activity as both D1 and D2 receptors.<br>Evidence obtained from studies in kidney cells points<br>to direct phosphorylation of the ATPase and to modu-<br>lation of protein phosphatase activity as possible media-<br>tors behind these effects. Thus Evidence obtained from studies in kidney cells points<br>to direct phosphorylation of the ATPase and to modu-<br>lation of protein phosphatase activity as possible media-<br>tors behind these effects. Thus, recent studies of a high to direct phosphorylation of the ATPase and to mod<br>lation of protein phosphatase activity as possible medi<br>tors behind these effects. Thus, recent studies of a high<br>purified preparation of Na<sup>+</sup>, K<sup>+</sup>-ATPase from sha<br>rect lation of protein phosphatase activity as possible media-<br>tors behind these effects. Thus, recent studies of a highly<br>purified preparation of Na<sup>+</sup>, K<sup>+</sup>-ATPase from shark<br>rectal gland have shown that both cyclic AMP-depe tors behind these effects. Thus, recent studies of a highly<br>purified preparation of Na<sup>+</sup>, K<sup>+</sup>-ATPase from shark<br>rectal gland have shown that both cyclic AMP-dependent<br>protein kinase and protein kinase C can rapidly and<br> purified preparation of Na<sup>+</sup>, K<sup>+</sup>-ATPase from shark<br>rectal gland have shown that both cyclic AMP-dependent<br>protein kinase and protein kinase C can rapidly and<br>stoichiometrically phosphorylate the  $\alpha$ -1 subunit of the<br>e rectal gland have shown that both cyclic AMP-dependent<br>protein kinase and protein kinase C can rapidly and<br>stoichiometrically phosphorylate the  $\alpha$ -1 subunit of the<br>enzyme, while concomitantly inhibiting enzyme activity<br> protein kinase and protein kinase C can rapidly and<br>stoichiometrically phosphorylate the  $\alpha$ -1 subunit of the<br>enzyme, while concomitantly inhibiting enzyme activity<br>by 50 to 75% (Bertorello et al., submitted). In other<br>s stoichiometrically phosphorylate the  $\alpha$ -1 subunit of the<br>enzyme, while concomitantly inhibiting enzyme activity<br>by 50 to 75% (Bertorello et al., submitted). In other<br>studies, dopamine-regulated phosphorylation of<br>DARPPenzyme, while concomitantly inhibiting enzyme activity<br>by 50 to 75% (Bertorello et al., submitted). In other<br>studies, dopamine-regulated phosphorylation of<br>DARPP-32 was implicated in the mechanism of action<br>of dopamine on by 50 to 75% (Bertorello et al., submitted). In other studies, dopamine-regulated phosphorylation of DARPP-32 was implicated in the mechanism of action of dopamine on the Na<sup>+</sup>, K<sup>+</sup>-ATPase. Both renal tubular cells and n studies, dopamine-regulated phosphorylation of DARPP-32 was implicated in the mechanism of action<br>of dopamine on the Na<sup>+</sup>, K<sup>+</sup>-ATPase. Both renal tubular<br>cells and neostriatal neurons express D1 dopamine re-<br>ceptors and DARPP-32 was implicated in the mechanism of action<br>of dopamine on the Na<sup>+</sup>, K<sup>+</sup>-ATPase. Both renal tubular<br>cells and neostriatal neurons express D1 dopamine re-<br>ceptors and increase the levels of cyclic AMP in response<br> of dopamine on the Na<sup>+</sup>, K<sup>+</sup>-ATPase. Both renal tubular cells and neostriatal neurons express D1 dopamine receptors and increase the levels of cyclic AMP in response to dopamine (Forn et al., 1974; Bertorello, 1989), and cells and neostriatal neurons express D1 dopamine receptors and increase the levels of cyclic AMP in response<br>to dopamine (Forn et al., 1974; Bertorello, 1989), and<br>both contain high levels of DARPP-32 (Ouimet et al.,<br>1984 ceptors and increase the levels of cyclic AMP in response<br>to dopamine (Forn et al., 1974; Bertorello, 1989), and<br>both contain high levels of DARPP-32 (Ouimet et al.<br>1984b; Meister et al., 1989). Thus, cyclic AMP-regulated<br> to dopamine (Forn et al., 1974; Bertorello, 1989), an<br>both contain high levels of DARPP-32 (Ouimet et al<br>1984b; Meister et al., 1989). Thus, cyclic AMP-regulate<br>phosphorylation of DARPP-32 on Thr-34, which con<br>verts the pr both contain high levels of DARPP-32 (Ouimet et 1984b; Meister et al., 1989). Thus, cyclic AMP-regular phosphorylation of DARPP-32 on Thr-34, which werts the protein into a potent inhibitor of protein phatase-1 (section II 1984b; Meister et al., 1989). Thus, cyclic AMP-regulated<br>phosphorylation of DARPP-32 on Thr-34, which con-<br>verts the protein into a potent inhibitor of protein phos-<br>phatase-1 (section III), may be involved in the dopamin phosphorylation of DARPP-32 on Thr-34, which converts the protein into a potent inhibitor of protein phosphatase-1 (section III), may be involved in the dopamine-<br>induced regulation of Na<sup>+</sup>, K<sup>+</sup>-ATPase activity in both c verts the protein into a potent inhibitor of protein phos-<br>phatase-1 (section III), may be involved in the dopamine-<br>induced regulation of Na<sup>+</sup>, K<sup>+</sup>-ATPase activity in both<br>cell types. Support for this hypothesis has com phatase-1 (section III), may be involved in the dopamine-<br>induced regulation of Na<sup>+</sup>, K<sup>+</sup>-ATPase activity in both<br>cell types. Support for this hypothesis has come from<br>studies in which a peptide corresponding to residues induced regulation of  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase activity in both cell types. Support for this hypothesis has come from studies in which a peptide corresponding to residues 8–38 of DARPP-32 was used. The phosphorylated f cell types. Support for this hypothesis has come from<br>studies in which a peptide corresponding to residues 8–<br>38 of DARPP-32 was used. The phosphorylated form of<br>this peptide retains potency as an inhibitor of protein<br>phos studies in which a peptide corresponding to residues 8–38 of DARPP-32 was used. The phosphorylated form of this peptide retains potency as an inhibitor of protein phosphatase-1, whereas the dephosphoform is inactive in thi 38 of DARPP-32 was used. The phosphorylated form of<br>this peptide retains potency as an inhibitor of protein<br>phosphatase-1, whereas the dephosphoform is inactive<br>in this respect (Hemmings et al., 1990). When introduced<br>into this peptide retains potency as an inhibitor of prophosphatase-1, whereas the dephosphoform is inacin this respect (Hemmings et al., 1990). When introduction of Hanle, the phospin-permeabilized renal tubule cells from medu phosphatase-1, whereas the dephosphoform is inactive<br>in this respect (Hemmings et al., 1990). When introduced<br>into saponin-permeabilized renal tubule cells from the<br>medullary thick ascending loop of Henle, the phosphor-<br>yl in this respect (Hemmings et al., 1990). When introduced<br>into saponin-permeabilized renal tubule cells from the<br>medullary thick ascending loop of Henle, the phosphor-<br>ylated but not the dephosphorylated peptide decreased<br>N

or dibutyryl cyclic AMP. This effect was associated with **PROTEIN PHOSPHORYLATION AN**<br>optimal concentrations of D1 dopamine receptor agonists the<br>or dibutyryl cyclic AMP. This effect was associated with cyt<br>a decrease in the  $V_{max}$  and an increase in the  $K_m$  values ma **PROTEIN PHOSPHORYLATION** Applying the Vmax and an increase in the  $K_m$  values in the Vmax and an increase in the  $K_m$  values in the Na<sup>+</sup>, K<sup>+</sup>-ATPase for K<sup>+</sup> (Aperia et al., 1991). optimal concentrations of D1 dopamine receptor agoni<br>or dibutyryl cyclic AMP. This effect was associated w<br>a decrease in the  $V_{max}$  and an increase in the  $K_m$  value<br>of the Na<sup>+</sup>, K<sup>+</sup>-ATPase for K<sup>+</sup> (Aperia et al., 1991 timal concentrations of D1 dopamine receptor agonists<br>dibutyryl cyclic AMP. This effect was associated with<br>decrease in the V<sub>max</sub> and an increase in the  $K_m$  values<br>the Na<sup>+</sup>, K<sup>+</sup>-ATPase for K<sup>+</sup> (Aperia et al., 1991).<br>

or dibutyryl cyclic AMP. This effect was associated with cyt<br>a decrease in the  $V_{max}$  and an increase in the  $K_m$  values ma<br>of the Na<sup>+</sup>, K<sup>+</sup>-ATPase for K<sup>+</sup> (Aperia et al., 1991). a p<br>In summary, the results of these st a decrease in the  $V_{max}$  and an increase in the  $K_m$  values<br>of the Na<sup>+</sup>, K<sup>+</sup>-ATPase for K<sup>+</sup> (Aperia et al., 1991).<br>In summary, the results of these studies indicate that<br>dopamine, acting through D1 dopamine receptors, of the Na<sup>+</sup>, K<sup>+</sup>-ATPase for K<sup>+</sup> (Aperia et al., 1991).<br>In summary, the results of these studies indicate that<br>dopamine, acting through D1 dopamine receptors, may<br>stimulate cyclic AMP-regulated phosphorylation and in-<br>h In summary, the results of these studies indicate that dopamine, acting through D1 dopamine receptors, may stimulate cyclic AMP-regulated phosphorylation and indopamine, acting through D1 dopamine receptors, may to<br>stimulate cyclic AMP-regulated phosphorylation and in-<br>hibition of the Na<sup>+</sup>, K<sup>+</sup>-ATPase in situ. The data further<br>suggest that inhibition of phosphorotein dephosphor stimulate cyclic AMP-regulated phosphorylation and inhibition of the Na<sup>+</sup>, K<sup>+</sup>-ATPase in situ. The data further suggest that inhibition of phosphoprotein dephosphorylation by protein phosphatase-1, mediated through DARPP suggest that inhibition of phosphoprotein dephosphorylation by protein phosphatase-1, mediated through DARPP-32 phosphorylation, is also involved. The results are consistent with dopamine regulating  $Na^+$  reabsorption in ation by protein phosphatase-1, mediated through DARPP-32 phosphorylation, is also involved. The results pump. *D. Protein and decreased dephosphorylation of the Na<sup>+</sup>* pump.<br> *D. Protein Phosphorylation and Alzheimer's Disease* 

Musical dephosphorylation of the Na<sup>+</sup> example the Nature of the Na<sup>+</sup> example the Nosphorylation and Alzheimer's Disease the Alzheimer's disease, a progressive encephalopathy of the life, is characterized by initial amne pump.<br>
D. Protein Phosphorylation and Alzheimer's Disease<br>
Alzheimer's disease, a progressive encephalopathy of<br>
late life, is characterized by initial amnesia for recent<br>
events, progressing to complete loss of all cortic D. Protein Phosphorylation and Alzheimer's Disease<br>Alzheimer's disease, a progressive encephalopathy clate life, is characterized by initial amnesia for recen<br>events, progressing to complete loss of all cortical func<br>tions D. Protein Phosphorylation and Alzheimer's Disease<br>Alzheimer's disease, a progressive encephalopathy of<br>late life, is characterized by initial amnesia for recent<br>events, progressing to complete loss of all cortical func-<br>t late life, is characterized by initial amnesia for recent events, progressing to complete loss of all cortical functions, and ending in a vegetative state, with death ultimately ensuing (for review, see Katzman, 1986). A n late life, is characterized by initial amnesia for recent<br>events, progressing to complete loss of all cortical func-<br>tions, and ending in a vegetative state, with death ulti-<br>mately ensuing (for review, see Katzman, 1986) events, progressing to complete loss of all cortical functions, and ending in a vegetative state, with death ulti-<br>mately ensuing (for review, see Katzman, 1986). A number of neurotransmitter deficiencies have been report tions, and ending in a vegetative state, with death ulti-<br>mately ensuing (for review, see Katzman, 1986). A num-<br>ber of neurotransmitter deficiencies have been reported<br>in this disease, particularly a pronounced destructio mately ensuing (for review, see Katzman, 1986). A number of neurotransmitter deficiencies have been reported<br>in this disease, particularly a pronounced destruction of<br>the cholinergic cells and fibers which originate in the ber of neurotransmitter deficiencies have been reported<br>in this disease, particularly a pronounced destruction of<br>the cholinergic cells and fibers which originate in the<br>nucleus basalis of Meynert and innervate the cerebr in this disease, particularly a pronounced destruction of<br>the cholinergic cells and fibers which originate in the<br>nucleus basalis of Meynert and innervate the cerebral<br>cortex and hippocampal formation (for reviews, see<br>Bow the cholinergic cells and fibers which originate in the nucleus basalis of Meynert and innervate the cerebral cortex and hippocampal formation (for reviews, see Bowen, 1983; Hardy et al., 1985). A possible degeneration of nucleus basalis of Meynert and innervate the cerebral<br>cortex and hippocampal formation (for reviews, see<br>Bowen, 1983; Hardy et al., 1985). A possible degeneration<br>of the quantitatively dominating glutamate transmitter<br>syst cortex and hippocampal formation (for reviews, see<br>Bowen, 1983; Hardy et al., 1985). A possible degeneration<br>of the quantitatively dominating glutamate transmitter<br>systems in the brain has also been proposed as a factor<br>in Bowen, 1983; Hardy et al., 1985). A possible degenera<br>of the quantitatively dominating glutamate transm<br>systems in the brain has also been proposed as a fa<br>in this disease (Hyman et al., 1987; Palmer and Gers<br>1990), as hav of the quantitatively dominating glutamate transmitter<br>systems in the brain has also been proposed as a factor<br>in this disease (Hyman et al., 1987; Palmer and Gershon,<br>1990), as have deficiencies of serotonin and noradrena systems in the brain has also been proposed as a factor<br>in this disease (Hyman et al., 1987; Palmer and Gershon,<br>1990), as have deficiencies of serotonin and noradrena-<br>line neurons (for examples, see Hardy et al., 1985).<br> in this disease (Hyman et al., 1987; Palmer and Gershon, 1990), as have deficiencies of serotonin and noradrena-<br>line neurons (for examples, see Hardy et al., 1985).<br>Pathologically, both limbic and association cortices, in 1990), as have deficiencies of serotonin and noradrenaline neurons (for examples, see Hardy et al., 1985<br>Pathologically, both limbic and association cortices, ir<br>cluding the hippocampal formation, become involvee<br>with larg Pathologically, both limbic and association cortices, including the hippocampal formation, become involved, with large numbers of neurons ultimately degenerating.<br>The disease is invariably characterized by accumulation of Pathologically, both limbic and association cortices, including the hippocampal formation, become involved, with large numbers of neurons ultimately degenerating.<br>The disease is invariably characterized by accumulation of cluding the hippocampal formation, become involved,<br>with large numbers of neurons ultimately degenerating.<br>The disease is invariably characterized by accumulation<br>of poorly soluble structures within and outside neurons<br>an with large numbers of neurons ultimately degenerati<br>The disease is invariably characterized by accumulat<br>of poorly soluble structures within and outside neur<br>and in surrounding cerebral vessels, together with<br>extensive dis The disease is invariably characterized by accumulation<br>of poorly soluble structures within and outside neurons<br>and in surrounding cerebral vessels, together with an<br>extensive disruption of normal cerebral cortical archite of poorly soluble structures within and outside neurons<br>and in surrounding cerebral vessels, together with an<br>extensive disruption of normal cerebral cortical architec-<br>ture (Tomlinson and Corsellis, 1984). Extensive evide extensive disruption of normal cerebral cortical architecture (Tomlinson and Corsellis, 1984). Extensive evidence indicates that the major proteins present in the insoluble deposits found inside brain cells (the neurofibri extensive disruption of normal cerebral cortical architec-<br>ture (Tomlinson and Corsellis, 1984). Extensive evidence<br>indicates that the major proteins present in the insoluble<br>inghly phosphorylated (for examples, see Sternb ture (Tomlinson and Corsellis, 1984). Extensive evidence yis<br>indicates that the major proteins present in the insoluble<br>deposits found inside brain cells (the neurofibrillary tan-<br>gles) are derived from normal cytoskeletal indicates that the major proteins present in the insoluble<br>deposits found inside brain cells (the neurofibrillary tan-<br>gles) are derived from normal cytoskeletal proteins and<br>that at least part of their abnormal nature app deposits found inside brain cells (the neurofibrillary tangles) are derived from normal cytoskeletal proteins and that at least part of their abnormal nature appears to be caused by defective protein phosphorylation of the gles) are derived from normal cytoskeletal proteins and<br>that at least part of their abnormal nature appears to be<br>caused by defective protein phosphorylation of these<br>proteins (for reviews, see Selkoe, 1989; Gandy et al.,<br> that at least part of their abnormal nature appears to be<br>caused by defective protein phosphorylation of these<br>proteins (for reviews, see Selkoe, 1989; Gandy et al., pl<br>1990a). Similarly, recent evidence indicates that th caused by defective protein phosphorylation of these<br>proteins (for reviews, see Selkoe, 1989; Gandy et al.,<br>1990a). Similarly, recent evidence indicates that the ex-<br>tracellular deposits (the neuritic plaques) consist mai proteins (for reviews, see Selkoe, 1989; Gandy et al 1990a). Similarly, recent evidence indicates that the extracellular deposits (the neuritic plaques) consist mainl of a distinct protein, termed the  $\beta$ -amyloid/A4 prot 1990a). Similarly, recent evidence indicates that the ex-<br>tracellular deposits (the neuritic plaques) consist mainly<br>of a distinct protein, termed the  $\beta$ -amyloid/A4 protein, Ho<br>which derives from a  $\beta$ -amyloid precurso tracellular deposits (the neuritic plaques) consist mainly<br>of a distinct protein, termed the  $\beta$ -amyloid/A4 protein,<br>which derives from a  $\beta$ -amyloid precursor protein local-<br>ized in the cell membrane of a wide variety of a distinct protein, termed the  $\beta$ -amyloid/A4 protein,<br>which derives from a  $\beta$ -amyloid precursor protein local-<br>ized in the cell membrane of a wide variety of cells and<br>tissues. It appears that the processing of thi which derives from a  $\beta$ -amyloid precursor protein local-<br>ized in the cell membrane of a wide variety of cells and<br>igsues. It appears that the processing of this precursor<br>protein, which leads to the ultimate deposition ized in the cell membrane of a wide variety of cells and<br>tissues. It appears that the processing of this precursor<br>protein, which leads to the ultimate deposition of the  $\beta$ -<br>amyloid protein in the extracellular plaques, tissues. It appears that the processing of this precursor protein, which leads to the ultimate deposition of the  $\beta$ -<br>amyloid protein in the extracellular plaques, may be appears of regulated by protein phosphorylation s

cytoskeletal proteins and in neurofibrillary tangle formation and then present some observations concerning AND NEURONAL FUNCTION 331<br>the systems involved in the phosphorylation of neuronal<br>cytoskeletal proteins and in neurofibrillary tangle for-<br>mation and then present some observations concerning<br>a possible regulation of  $\beta$ the systems involved in the phosphorylation of neuronacytoskeletal proteins and in neurofibrillary tangle formation and then present some observations concerning possible regulation of  $\beta$ -amyloid precursor protein proce the systems involved in the phosphorylation of neuronal cytoskeletal proteins and in neurofibrillary tangle formation and then present some observations concerning a possible regulation of  $\beta$ -amyloid precursor protein p cytoskeletal proteins and in neurofibrillary tangle for<br>mation and then present some observations concerning<br>a possible regulation of  $\beta$ -amyloid precursor protein proc<br>essing by a phosphorylation mechanism that might re mation and then present so<br>a possible regulation of  $\beta$ -an<br>essing by a phosphorylation<br>to future therapeutic interversing to Alzheimer's disease.<br>1. Cytoskeletal protein ph **1. easing by a phosphorylation mechanism that might relate** to future therapeutic interventions in the processes leading to Alzheimer's disease.<br>
1. Cytoskeletal protein phosphorylation. Both actin filaments, intermediate

essing by a phosphorylation mechanism that might re<br>to future therapeutic interventions in the processes le<br>ing to Alzheimer's disease.<br>1. Cytoskeletal protein phosphorylation. Both actin<br>aments, intermediate filaments (co to future therapeutic interventions in the processes leading to Alzheimer's disease.<br>
1. Cytoskeletal protein phosphorylation. Both actin filaments, intermediate filaments (composed of neurofilament proteins in neurons, gl ing to Alzheimer's disease.<br>
1. Cytoskeletal protein phosphorylation. Both actin fil-<br>
aments, intermediate filaments (composed of neurofila-<br>
ment proteins in neurons, glial fibrillary acidic protein<br>
in astrocytes), and 1. Cytoskeletal protein phosphorylation. Both actin filaments, intermediate filaments (composed of neurofilament proteins in neurons, glial fibrillary acidic protein in astrocytes), and microtubules are widely distributed aments, intermediate filaments (composed of neurofila-<br>ment proteins in neurons, glial fibrillary acidic protein<br>in astrocytes), and microtubules are widely distributed<br>throughout neural cells. These proteins appear to be<br> ment proteins in neurons, glial fibrillary acidic protein<br>in astrocytes), and microtubules are widely distributed<br>throughout neural cells. These proteins appear to be<br>important in morphogenesis, in neuritic transport and<br>e in astrocytes), and microtubules are widely distribut<br>throughout neural cells. These proteins appear to limportant in morphogenesis, in neuritic transport an<br>extensions, in regulation of organelle interactions, an<br>in membr throughout neural cells. These proteins appear to be<br>important in morphogenesis, in neuritic transport and<br>extensions, in regulation of organelle interactions, and<br>in membrane-cytosol interactions (for reviews, see Olms-<br>t important in morphogenesis, in neuritic transport and<br>extensions, in regulation of organelle interactions, and<br>in membrane-cytosol interactions (for reviews, see Olms-<br>tedt, 1986; Matus, 1988a,b; Mitchison and Kirschner,<br>1 extensions, in regulation of organelle interactions, and<br>in membrane-cytosol interactions (for reviews, see Olms-<br>tedt, 1986; Matus, 1988a,b; Mitchison and Kirschner,<br>1988). Both microtubule proteins and neurofilament proin membrane-cytosol interactions (for reviews, see Olmstedt, 1986; Matus, 1988a,b; Mitchison and Kirschner, 1988). Both microtubule proteins and neurofilament proteins are known to be highly phosphorylated, whereas the ext tedt, 1986; Matus, 1988a,b; Mitchison and Kirschner, 1988). Both microtubule proteins and neurofilament proteins are known to be highly phosphorylated, whereas the extent of actin phosphorylation is less clear. Aspects of 1988). Both microtubule proteins and neurofilament proteins are known to be highly phosphorylated, whereas the extent of actin phosphorylation is less clear. Aspects of the role of actin in neuronal function have been disc teins are known to be highly phosphorylated, whereas the extent of actin phosphorylation is less clear. Aspects of the role of actin in neuronal function have been discussed together with the synapsins in section IV.A.2. N the extent of actin phosphorylation is less clear. Aspect of the role of actin in neuronal function have bediscussed together with the synapsins in section IV.<br>Neurofilament and microtubule protein phosphorylat will be dis

discussed together with the synapsins in section IV.A.2.<br>Neurofilament and microtubule protein phosphorylation<br>will be discussed here.<br>a. NEUROFILAMENT PROTEINS. The three neurofila-<br>ment proteins (apparent molecular masse Neurofilament and microtubule protein phosphorylation<br>will be discussed here.<br>a. NEUROFILAMENT PROTEINS. The three neurofila-<br>ment proteins (apparent molecular masses of 68, 140,<br>and 200 kDa), which make up the neuron-spec will be discussed here.<br>
a. NEUROFILAMENT PROTEINS. The three neurofila-<br>
ment proteins (apparent molecular masses of 68, 140,<br>
and 200 kDa), which make up the neuron-specific forms<br>
of intermediate filaments (for review, a. NEUROFILAMENT PROTEINS. The three neurofilament proteins (apparent molecular masses of 68, 140 and 200 kDa), which make up the neuron-specific forms of intermediate filaments (for review, see Williams and Runge, 1983), ment proteins (apparent molecular masses of 68, and 200 kDa), which make up the neuron-specific for of intermediate filaments (for review, see Williams Runge, 1983), appear to be specifically enriched in r ronal somata and and 200 kDa), which make up the neuron-specific forms<br>of intermediate filaments (for review, see Williams and<br>Runge, 1983), appear to be specifically enriched in neu-<br>ronal somata and axons (for examples, see Hammer-<br>schla Runge, 1983), appear to be specifically enriched in neuronal somata and axons (for examples, see Hammerschlag and Brady, 1989). A number of protein kinases can catalyze phosphorylation of the neurofilament proteins. These schlag and Brady, 1989). A number of protein kinases<br>can catalyze phosphorylation of the neurofilament pro-<br>teins. These include second messenger-regulated en-<br>zymes such as cyclic AMP-dependent protein kinase<br>(Leterrier e schlag and Brady, 1989). A number of protein kinases<br>can catalyze phosphorylation of the neurofilament pro-<br>teins. These include second messenger-regulated en-<br>zymes such as cyclic AMP-dependent protein kinase<br>(Leterrier e can catalyze phosphorylation of the neurofilament proteins. These include second messenger-regulated en-<br>zymes such as cyclic AMP-dependent protein kinase<br>(Leterrier et al., 1981) and CaM kinase II (Tanaka et al.,<br>1984; Va teins. These include second messenger-regulated<br>zymes such as cyclic AMP-dependent protein kii<br>(Leterrier et al., 1981) and CaM kinase II (Tanaka et<br>1984; Vallano et al., 1985), whereas others appear<br>represent enzymes dist zymes such as cyclic AMP-dependent protein k<br>(Leterrier et al., 1981) and CaM kinase II (Tanaka<br>1984; Vallano et al., 1985), whereas others appe<br>represent enzymes distinct from the second messe<br>regulated protein kinases (s (Leterrier et al., 1981) and CaM kinase II (Tanaka et al., 1984; Vallano et al., 1985), whereas others appear to represent enzymes distinct from the second messenger-<br>regulated protein kinases (section II. D). Immunohistorepresent enzymes distinct from the second messenger-<br>regulated protein kinases (section II. D). Immunohistorepresent enzymes distinct from the second messenger-<br>regulated protein kinases (section II. D). Immunohisto-<br>chemical studies indicate that the neurofilament proteins<br>present in neuronal somata are essentially dephosphorregulated protein kinases (section II. D). Immunohisto-<br>chemical studies indicate that the neurofilament proteins<br>present in neuronal somata are essentially dephosphor-<br>ylated, whereas the axonal forms of the proteins beco chemical studies indicate that the neurofilament proteins<br>present in neuronal somata are essentially dephosphor-<br>ylated, whereas the axonal forms of the proteins become<br>highly phosphorylated (for examples, see Sternberger<br> present in neuronal somata are essentially dephosphor-<br>ylated, whereas the axonal forms of the proteins become<br>highly phosphorylated (for examples, see Sternberger<br>and Sternberger, 1983; Matus, 1988a). It is, therefore,<br>po ylated, whereas the axonal forms of the proteins becomples, see Sternber and Sternberger, 1983; Matus, 1988a). It is, therefore possible that protein phosphorylation may be involuin regulating axonal maturation or transpor highly phosphorylated (for examples, see Sternberger and Sternberger, 1983; Matus, 1988a). It is, therefore, possible that protein phosphorylation may be involved in regulating axonal maturation or transport of neurofil-am and Sternberger, 1983; Matus, 1988a). It is, therefore possible that protein phosphorylation may be involve in regulating axonal maturation or transport of neurofile aments. The identities of the enzymes involved in this p possible that protein phosphorylation may be involved<br>in regulating axonal maturation or transport of neurofil-<br>aments. The identities of the enzymes involved in this<br>phenomenon remain uncertain, however, and the func-<br>tio aments. The identities of the enzymes involved in this phenomenon remain uncertain, however, and the functional importance of neurofilament phosphorylation also remains unclear (for examples, see Eagles et al., 1981; Honch aments. The identities of the enzymes involved in this<br>phenomenon remain uncertain, however, and the func-<br>tional importance of neurofilament phosphorylation also<br>remains unclear (for examples, see Eagles et al., 1981;<br>Hon phenomenon remain uncertain, however, and the functional importance of neurofilament phosphorylation also remains unclear (for examples, see Eagles et al., 1981; Honchar et al., 1982; Carden et al., 1985; Bignami et al., 1 1988a). mains unclear (for examples, see Eagles et al., 1981;<br>onchar et al., 1982; Carden et al., 1985; Bignami et al.,<br>986; Foster et al., 1987; Nixon et al., 1987; Matus,<br>988a).<br>b. MICROTUBULE PROTEINS. Microtubules are present<br>

Honchar et al., 1982; Carden et al., 1985; Bignami et 1986; Foster et al., 1987; Nixon et al., 1987; Mat<br>1988a).<br>b. MICROTUBULE PROTEINS. Microtubules are pres<br>throughout nerve cells, both in association with posts<br>aptic m 1986; Foster et al., 1987; Nixon et al., 1987; Matus, 1988a).<br>
b. MICROTUBULE PROTEINS. Microtubules are present<br>
throughout nerve cells, both in association with postsyn-<br>
aptic membranes and in dendrites, somata, axons, 1988a).<br>
b. MICROTUBULE PROTEINS. Microtubules are present<br>
throughout nerve cells, both in association with postsyn-<br>
aptic membranes and in dendrites, somata, axons, and<br>
less prominently, in presynaptic terminals (Olmst b. MICROTUBULE PROTEINS. Microtubules are present<br>throughout nerve cells, both in association with postsyn-<br>aptic membranes and in dendrites, somata, axons, and,<br>less prominently, in presynaptic terminals (Olmstedt,<br>1986;

 $332$  WALAAS AND GREENGARD<br>major protein components of microtubules include  $\alpha$ -<br>and  $\beta$ -tubulin and MAPs, many of which appear to be yet been de<br>phosphorylated. protein kina phosphorylated. *Tubulin* and MAPs, many of which appear to be yet osphorylated.<br>
Tubulin has been reported to be phosphorylated by the production has been reported to be phosphorylated by the th cyclic AMP-dependent protein kinase and C

major protein components of microtubules include  $\alpha$ -<br>and  $\beta$ -tubulin and MAPs, many of which appear to be yet been<br>phosphorylated.<br>Tubulin has been reported to be phosphorylated by the different<br>both cyclic AMP-depende and  $\beta$ -tubulin and MAPs, many of which appear to<br>phosphorylated.<br>Tubulin has been reported to be phosphorylated<br>both cyclic AMP-dependent protein kinase and C<br>kinase II in vitro (Burke and DeLorenzo, 1981; Golde<br>ing et phosphorylated. phosphorylated. Tubulin has been reported to be phosphorylated by the both cyclic AMP-dependent protein kinase and CaM un kinase II in vitro (Burke and DeLorenzo, 1981; Goldenring et al., 1983; Yamamoto et Tubulin has been reported to be phosphorylated by<br>both cyclic AMP-dependent protein kinase and CaM<br>kinase II in vitro (Burke and DeLorenzo, 1981; Goldenr-<br>ing et al., 1983; Yamamoto et al., 1985). Although tubulin<br>may not both cyclic AMP-dependent protein kinase and CaM unce kinase II in vitro (Burke and DeLorenzo, 1981; Goldenr-<br>ing et al., 1983; Yamamoto et al., 1985). Although tubulin mol<br>may not be a particularly good substrate for thes kinase II in vitro (Burke and DeLorenzo, 1981; Goldenring et al., 1983; Yamamoto et al., 1985). Although tubulin may not be a particularly good substrate for these en-zymes (Nairn et al., 1985a; Schulman, 1988), recent in ing et al., 1983; Yamamoto et al., 1985). Although tubuli<br>may not be a particularly good substrate for these er<br>zymes (Nairn et al., 1985a; Schulman, 1988), recent i<br>vitro studies have indicated that phosphorylation of tul may not be a particularly good substrate for these en-<br>zymes (Nairn et al., 1985a; Schulman, 1988), recent in<br>witro studies have indicated that phosphorylation of tub-<br>ulin increases its interaction with membranes (Har-<br>gr zymes (Nairn et al., 1985a; Schulman, 1988), recent in avitro studies have indicated that phosphorylation of tubulin increases its interaction with membranes (Harpgreaves et al., 1986) but decreases microtubule assembly m vitro studies have indicated that phosphorylation of tub-<br>ulin increases its interaction with membranes (Har-<br>greaves et al., 1986) but decreases microtubule assembly mic<br>(Yamamoto et al., 1985). Phosphorylation of tubulin ulin increases its interaction with membranes (Har-<br>greaves et al., 1986) but decreases microtubule assembly m<br>(Yamamoto et al., 1985). Phosphorylation of tubulin has<br>incendent observed in intact cells (for examples, see G greaves et al., 1986) but decreases microtubule assembly (Yamamoto et al., 1985). Phosphorylation of tubulin has been observed in intact cells (for examples, see Gard and Kirschner, 1985), but the significance and regulati understood. en observed in intact cells (for examples, see Gard and and<br> *irschner*, 1985), but the significance and regulation of be p<br>
vivo tubulin phosphorylation in brain is not well dep<br> *MAP-2*, a high molecular weight protein (

Kirschner, 1985), but the significance and regulation of<br>in vivo tubulin phosphorylation in brain is not well<br>understood.<br> $MAP-2$ , a high molecular weight protein (280,000 to<br>300,000) that is specifically enriched in neurona in vivo tubulin phosphorylation in brain is not well dependerstood.<br>
MAP-2, a high molecular weight protein (280,000 to 1984<br>
300,000) that is specifically enriched in neuronal den-<br>
drites (De Camilli et al., 1984b), was k<br>
MAP-2, a high molecular weight protein (280,000 to<br>
300,000) that is specifically enriched in neuronal den-<br>
drites (De Camilli et al., 1984b), was originally found to<br>
the a substrate for cyclic AMP-dependent protein k  $MAP-2$ , a high molecular weight protein  $(280,000 \text{ to } 19,000,000)$  that is specifically enriched in neuronal dentities (De Camilli et al., 1984b), was originally found to the a substrate for cyclic AMP-dependent protein k 300,000) that is specifically enriched in neuronal dendrites (De Camilli et al., 1984b), was originally found to be a substrate for cyclic AMP-dependent protein kinase (Sloboda et al., 1975). More recent studies have shown drites (De Camilli et al., 1984b), was originally found to the a substrate for cyclic AMP-dependent protein kinase to (Sloboda et al., 1975). More recent studies have shown tat that the protein can be phosphorylated on a l be a substrate for cyclic AMP-dependent protein kin<br>(Sloboda et al., 1975). More recent studies have show<br>that the protein can be phosphorylated on a large num<br>of sites by a variety of other protein kinases, wh<br>include CaM (Sloboda et al., 1975). More recent studies have sho<br>that the protein can be phosphorylated on a large num<br>of sites by a variety of other protein kinases, wh<br>include CaM kinase II, protein kinase C, and tyrosi<br>specific pro that the protein can be phosphorylated on a large number<br>of sites by a variety of other protein kinases, which<br>include CaM kinase II, protein kinase C, and tyrosine-<br>specific protein kinases (Islam and Burns, 1981; Theur-<br> of sites by a variety of other protein kinases, which<br>include CaM kinase II, protein kinase C, and tyrosine-<br>specific protein kinases (Islam and Burns, 1981; Theur-<br>kauf and Vallee, 1983; Akiyama et al., 1986; Tsuyama et<br>a include CaM kinase II, protein kinase C, and tyrosine-<br>specific protein kinases (Islam and Burns, 1981; Theur-<br>kauf and Vallee, 1983; Akiyama et al., 1986; Tsuyama et<br>al., 1986; Yamauchi and Fujisawa, 1982, 1988; Goldenrin specific protein kinases (Islam and Burns, 1981; Theur-<br>kauf and Vallee, 1983; Akiyama et al., 1986; Tsuyama et ica<br>al., 1986; Yamauchi and Fujisawa, 1982, 1988; Goldenring sev<br>et al., 1985; Larson et al., 1985; Schulman, kauf and Vallee, 1983; Akiyama et al., 1986; Tsuyama et<br>al., 1986; Yamauchi and Fujisawa, 1982, 1988; Goldenring<br>et al., 1985; Larson et al., 1985; Schulman, 1984; Walaas<br>et al., 1983b,c; Walaas and Nairn, 1989). The prote al., 1986; Yamauchi and Fujisawa, 1982, 1988; Goldenring<br>et al., 1985; Larson et al., 1985; Schulman, 1984; Walaas<br>et al., 1983b,c; Walaas and Nairn, 1989). The protein is<br>also phosphorylated on multiple sites in situ (Tsu et al., 1985; Larson et al., 1985; Schulman, 1984; Waliet al., 1983b,c; Walaas and Nairn, 1989). The protein<br>also phosphorylated on multiple sites in situ (Tsuya<br>et al., 1986), and evidence suggests that different typ<br>of p et al., 1983b,c; Walaas and Nairn, 1989). The protein is disease, Guam Parkinson-dementia complex, and de-<br>also phosphorylated on multiple sites in situ (Tsuyama mentia pugilistica (Selkoe, 1989). These tangles are not<br>et et al., 1986), and evidence suggests<br>of protein phosphatases are respone<br>phorylation of these phosphorylatio<br>al., 1986). Such phosphatase activ<br>extensively characterized, however.<br>Phosphorylation of MAP-2 by protein phosphatases are responsible for the dephotorylation of these phosphorylation sites (Tsuyama, 1986). Such phosphatase activities have not be tensively characterized, however.<br>Phosphorylation of MAP-2 by either cyc

al., 1986). Such phosphatase activities have not been<br>extensively characterized, however.<br>Phosphorylation of MAP-2 by either cyclic AMP-<br>dependent or Ca<sup>2+</sup>-dependent protein kinases appears to<br>induce disassembly of microt extensively characterized, however. The prediction of MAP-2 by either cyclic AMP-<br>dependent or  $Ca^{2+}$ -dependent protein kinases appears to (G<br>induce disassembly of microtubules (Yamauchi and Fu-<br>jisawa, 1983b) and to reg Phosphorylation of MAP-2 by either cyclic AM<br>dependent or Ca<sup>2+</sup>-dependent protein kinases appears<br>induce disassembly of microtubules (Yamauchi and I<br>jisawa, 1983b) and to regulate their interaction with ac<br>(Jameson et al. chi and Fujisawa, 1988). The prominent expression of being involved in the intracellular manifestations of Alz-<br>MAP-2 in postsynaptic, dendritic compartments has sug-<br>gested that  $Ca^{2+}$ -dependent phosphorylation of this induce disassembly of microtubules (Yamauchi and Fu-<br>jisawa, 1983b) and to regulate their interaction with actin<br>(Jameson et al., 1980; Selden and Pollard, 1983; Yamau-<br>chi and Fujisawa, 1988). The prominent expression of<br> jisawa, 1983b) and to regulate their interaction with actin (Jameson et al., 1980; Selden and Pollard, 1983; Yamau-<br>chi and Fujisawa, 1988). The prominent expression of MAP-2 in postsynaptic, dendritic compartments has sug (Jameson et al., 1980; Selden and Pollard, 1983; Yamau-<br>chi and Fujisawa, 1988). The prominent expression of botal<br>MAP-2 in postsynaptic, dendritic compartments has sug-<br>gested that  $Ca^{2+}$ -dependent phosphorylation of th chi and Fujisawa, 1988). The prominent expression of bein<br>MAP-2 in postsynaptic, dendritic compartments has sug-<br>gested that  $Ca^{2+}$ -dependent phosphorylation of this pro-<br>tein might be an efficient mechanism whereby thos MAP-2 in postsynaptic, dendritic compartments has suggested that  $Ca^{2+}$ -dependent phosphorylation of this protein might be an efficient mechanism whereby those neurotransmitters that could increase intracellular  $Ca^{2+}$  gested that  $Ca^{2+}$ -dependent phosphorylation of this protein might be an efficient mechanism whereby those neurotransmitters that could increase intracellular  $Ca^{2+}$  levels could regulate postsynaptic cytoskeletal funct tein might be an efficient mechanism whereby those the<br>neurotransmitters that could increase intracellular Ca<sup>2+</sup> dra<br>levels could regulate postsynaptic cytoskeletal functions pre<br>(Matus, 1988b). Interestingly, recent stu neurotransmitters that could increase intracellular  $Ca^{2+}$ <br>levels could regulate postsynaptic cytoskeletal functions<br>(Matus, 1988b). Interestingly, recent studies of intact<br>slices of rat brain have shown that activation levels could regulate postsynaptic cytoskeletal functions (Matus, 1988b). Interestingly, recent studies of intact slices of rat brain have shown that activation of the NMDA type of glutamate receptor, which induces  $Ca^{2+}$ (Matus, 1988b). Interestingly, recent studies of intact slices of rat brain have shown that activation of the NMDA type of glutamate receptor, which induces  $Ca^{2+}$ fluxes into the cells (Dingledine, 1983), induces a poten slices of rat brain have shown that activation of NMDA type of glutamate receptor, which induces C<br>fluxes into the cells (Dingledine, 1983), induces a pot<br>dephosphorylation of MAP-2 (Halpain and Greenga<br>1990), presumably NMDA type of glutamate receptor, which induces  $Ca^{2+}$  Originally, aberrant phosphorylation of the neurofila-<br>fluxes into the cells (Dingledine, 1983), induces a potent ment proteins was believed to be responsible for thi fluxes into the cells (Dingledine, 1983), induces a potent mer<br>dephosphorylation of MAP-2 (Halpain and Greengard, phe<br>1990), presumably through activation of the Ca<sup>2+</sup>/cal- becom<br>modulin-dependent protein phosphatase-2B dephosphorylation of MAP-2 (Halpain and Greengard, p. 1990), presumably through activation of the  $Ca^{2+}/cal$ -<br>modulin-dependent protein phosphatase-2B which can tedephosphorylate MAP-2 in vitro (Goto et al., 1985). In b.<br>co

phosphorylation of MAP-2 in intact nerve calls have not GREENGARD<br>phosphorylation of MAP-2 in intact nerve cells have not<br>yet been defined. The functional roles of the multiple<br>protein kinases and phosphatases capable of regulating GREENGARD<br>phosphorylation of MAP-2 in intact nerve cells have not<br>yet been defined. The functional roles of the multiple<br>protein kinases and phosphatases capable of regulating<br>the different phosphorylation sites in MAP-2 a phosphorylation of MAP-2 in intact nerve cells have not<br>yet been defined. The functional roles of the multiple<br>protein kinases and phosphatases capable of regulating<br>the different phosphorylation sites in MAP-2 also remain uncertain. *The functional roles of the multiple* otein kinases and phosphatases capable of regulating e different phosphorylation sites in MAP-2 also remain certain.<br>*Tau factor* is a group of four related MAPs (apparent plecular ma

protein kinases and phosphatases capable of regulative different phosphorylation sites in MAP-2 also remainter and the uncertain.<br>Tau factor is a group of four related MAPs (appare molecular masses of 55 to 68 kDa in adul the different phosphorylation sites in MAP-2 also remain<br>uncertain.<br>Tau factor is a group of four related MAPs (apparent<br>molecular masses of 55 to 68 kDa in adult brain) (Cleve-<br>land et al., 1977), which are predominantly uncertain.<br>
Tau factor is a group of four related MAPs (apparent<br>
molecular masses of 55 to 68 kDa in adult brain) (Cleve-<br>
land et al., 1977), which are predominantly found in<br>
axons where they appear to stabilize the cyt Tau factor is a group of four related MAPs (apparent<br>molecular masses of 55 to 68 kDa in adult brain) (Cleve-<br>land et al., 1977), which are predominantly found in<br>axons where they appear to stabilize the cytoskeletal<br>polym molecular masses of 55 to 68 kDa in adult brain) (Cleveland et al., 1977), which are predominantly found in axons where they appear to stabilize the cytoskeletal polymer lattice (Drubin and Kirschner, 1986). These proteins land et al., 1977), which are predominantly found in<br>axons where they appear to stabilize the cytoskeletal<br>polymer lattice (Drubin and Kirschner, 1986). These<br>proteins stimulate both nucleation and elongation of<br>microtubul axons where they appear to stabilize the cytoskeletal<br>polymer lattice (Drubin and Kirschner, 1986). These<br>proteins stimulate both nucleation and elongation of<br>microtubules, and tau factor has also been found to<br>interact wi polymer lattice (Drubin and Kirschner, 1986). These<br>proteins stimulate both nucleation and elongation of<br>microtubules, and tau factor has also been found to<br>interact with both actin and neurofilaments (Mitchison<br>and Kirsch proteins stimulate both nucleation and elongation<br>microtubules, and tau factor has also been found<br>interact with both actin and neurofilaments (Mitchis<br>and Kirschner, 1988). Tau factor has been reported<br>be phosphorylated o microtubules, and tau factor has also been found to<br>interact with both actin and neurofilaments (Mitchison<br>and Kirschner, 1988). Tau factor has been reported to<br>be phosphorylated on multiple sites by both cyclic AMP-<br>depen interact with both actin and neurofilaments (Mitchison<br>and Kirschner, 1988). Tau factor has been reported to<br>be phosphorylated on multiple sites by both cyclic AMP-<br>dependent protein kinase, CaM kinase II, and protein<br>kina and Kirschner, 1988). Tau factor has been reported to<br>be phosphorylated on multiple sites by both cyclic AMP-<br>dependent protein kinase, CaM kinase II, and protein<br>kinase C (Cleveland et al., 1977; Yamamoto et al., 1983,<br>19 be phosphorylated on multiple sites by both cyclic AMP-<br>dependent protein kinase, CaM kinase II, and protein<br>kinase C (Cleveland et al., 1977; Yamamoto et al., 1983,<br>1985; Hoshi et al., 1987). This phosphorylation appears<br> dependent protein kinase, CaM kinase II, and protein<br>kinase C (Cleveland et al., 1977; Yamamoto et al., 1983,<br>1985; Hoshi et al., 1987). This phosphorylation appears<br>to inhibit microtubule assembly, and tau factor may,<br>the kinase C (Cleveland et al., 1977; Yamamoto et al., 1983, 1985; Hoshi et al., 1987). This phosphorylation appears<br>to inhibit microtubule assembly, and tau factor may,<br>therefore, play a role in microtubule function analogous 1985; Hoshi et al., 1987). This phosphorylation appe<br>to inhibit microtubule assembly, and tau factor m<br>therefore, play a role in microtubule function analogou<br>to that of MAP-2 (Lindwall and Cole, 1984). Moreov<br>tau factor i to inhibit microtubule assembly, and tau factor metherefore, play a role in microtubule function analogous to that of MAP-2 (Lindwall and Cole, 1984). Moreov tau factor is a component of the intracellular neuro brillary ta *2. Phonometers, play a role in microtubule function analogously that of MAP-2 (Lindwall and Cole, 1984). Moreover, u factor is a component of the intracellular neurofi-<br>illary tangles characteristic of Alzheimer's dise* 

et al., 1986), and evidence suggests that different types fully characterized but appear, based on protein analysis<br>of protein phosphatases are responsible for the dephos-<br>and immunocytochemistry, to contain tau factor, to al., 1986). Such phosphatase activities have not been fied proteins (for review, see Selkoe, 1989). The tau<br>extensively characterized, however. proteins present in neurofibrillary tangles appear to be<br>Phosphorylation of M to that of MAP-2 (Lindwall and Cole, 1984). Moreover,<br>tau factor is a component of the intracellular neurofi-<br>brillary tangles characteristic of Alzheimer's disease.<br>2. Tau factor phosphorylation and neurofibrillary tan-<br>g tau factor is a component of the intracellular neurofi-<br>brillary tangles characteristic of Alzheimer's disease.<br>2. Tau factor phosphorylation and neurofibrillary tan-<br>gles. Neurofibrillary tangles represent intracellular a brillary tangles characteristic of Alzheimer's disease.<br>
2. Tau factor phosphorylation and neurofibrillary tan-<br>
gles. Neurofibrillary tangles represent intracellular ac-<br>
cumulations of proteins, usually organized in pair 2. Tau factor phosphorylation and neurofibrillary tan-<br>gles. Neurofibrillary tangles represent intracellular ac-<br>cumulations of proteins, usually organized in paired hel-<br>ical filaments, and present in degenerating neurons gles. Neurofibrillary tangles represent intracellular accumulations of proteins, usually organized in paired helical filaments, and present in degenerating neurons of several diseases, including Alzheimer's disease, trisom cumulations of proteins, usually organized in paired helical filaments, and present in degenerating neurons of several diseases, including Alzheimer's disease, trisomy 21, progressive supranuclear palsy, Hallervorden-Spatz ical filaments, and present in degenerating neurons of<br>several diseases, including Alzheimer's disease, trisomy<br>21, progressive supranuclear palsy, Hallervorden-Spatz<br>disease, Guam Parkinson-dementia complex, and de-<br>menti several diseases, including Alzheimer's disease, trisomy<br>21, progressive supranuclear palsy, Hallervorden-Spatz<br>disease, Guam Parkinson-dementia complex, and de-<br>mentia pugilistica (Selkoe, 1989). These tangles are not<br>ful 21, progressive supranuclear palsy, Hallervorden-Spatz<br>disease, Guam Parkinson-dementia complex, and de-<br>mentia pugilistica (Selkoe, 1989). These tangles are not<br>fully characterized but appear, based on protein analysis<br>an mentia pugilistica (Selkoe, 1989). These tangles are not be phosphorylated on multipe sites by both cyclic AMP-<br>dependent protein kinase  $C$ . Celveland et al., 1977; Yamamoto et al., 1983,<br>kinase  $C$ . (Cleveland et al., 1977; Yamamoto et al., 1983,<br>1985; Hoshi et al., 1987). Th fully characterized but appear, based on protein analysis<br>and immunocytochemistry, to contain tau factor, to-<br>gether with other MAPs, ubiquitin, and other, unidenti-<br>fied proteins (for review, see Selkoe, 1989). The tau<br>pr and immunocytochemistry, to contain tau factor, to-<br>gether with other MAPs, ubiquitin, and other, unidenti-<br>fied proteins (for review, see Selkoe, 1989). The tau<br>proteins present in neurofibrillary tangles appear to be<br>pho gether with other MAPs, ubiquitin, and other, unidenti-<br>fied proteins (for review, see Selkoe, 1989). The tau<br>proteins present in neurofibrillary tangles appear to be<br>phosphorylated in an unusual or aberrant manner<br>(Grundk fied proteins (for review, see Selkoe, 1989). The tap<br>ordeins present in neurofibrillary tangles appear to b<br>phosphorylated in an unusual or aberrant manne<br>(Grundke-Iqbal et al., 1986), and evidence from sever.<br>laboratori proteins present in neurofibrillary tangles appear to be<br>phosphorylated in an unusual or aberrant manner<br>(Grundke-Iqbal et al., 1986), and evidence from several<br>laboratories implicates  $Ca^{2+}/calmodulin-dependent pro-  
tein phosphorylation in the pathogenesis of these tangles. Evidence for cytoskeletal protein phosphorylation$ losphorylated in an unusual or aberrant manner<br>Frundke-Iqbal et al., 1986), and evidence from several<br>boratories implicates  $Ca^{2+}/calmodulin$ -dependent pro-<br>in phosphorylation in the pathogenesis of these tangles.<br>Evidence for (Grundke-Iqbal et al., 1986), and evidence from several laboratories implicates  $Ca^{2+}/cal$ calmodulin-dependent protein phosphorylation in the pathogenesis of these tangles.<br>Evidence for cytoskeletal protein phosphorylation

laboratories implicates  $Ca^{2+}/calmodulin-dependent$  protein phosphorylation in the pathogenesis of these tangle.<br>Evidence for cytoskeletal protein phosphorylatio<br>being involved in the intracellular manifestations of Ala<br>heimer's disease Evidence for cytoskeletal protein phosphorylation<br>being involved in the intracellular manifestations of Alz-<br>heimer's disease includes the observations that the bind-<br>ing to neurofibrillary tangles of antibodies specific f Evidence for cytoskeletal protein phosphorylation<br>being involved in the intracellular manifestations of Alz-<br>heimer's disease includes the observations that the bind-<br>ing to neurofibrillary tangles of antibodies specific f being involved in the intracellular manifestations of Alzheimer's disease includes the observations that the binding to neurofibrillary tangles of antibodies specific for the dephosphoform of certain cytoskeletal proteins heimer's disease includes the observations that the bind-<br>ing to neurofibrillary tangles of antibodies specific for<br>the dephosphoform of certain cytoskeletal proteins is<br>dramatically enhanced if Alzheimer brain sections ar ing to neurofibrillary tangles of antibodies specific for<br>the dephosphoform of certain cytoskeletal proteins is<br>dramatically enhanced if Alzheimer brain sections are<br>preincubated with alkaline phosphatase, whereas normal<br>b the dephosphoform of certain cytoskeletal proteins is<br>dramatically enhanced if Alzheimer brain sections are<br>preincubated with alkaline phosphatase, whereas normal<br>brain sections do not demonstrate this phenomenon<br>(Sternber dramatically enhanced if Alzheimer brain sections<br>preincubated with alkaline phosphatase, whereas nor<br>brain sections do not demonstrate this phenome<br>(Sternberger et al., 1985; Grundke-Iqbal et al., 19<br>Originally, aberrant preincubated with alkaline phosphatase, whereas normal<br>brain sections do not demonstrate this phenomenon<br>(Sternberger et al., 1985; Grundke-Iqbal et al., 1986).<br>Originally, aberrant phosphorylation of the neurofila-<br>ment p brain sections do not demonstrate this phenomenon<br>(Sternberger et al., 1985; Grundke-Iqbal et al., 1986).<br>Originally, aberrant phosphorylation of the neurofila-<br>ment proteins was believed to be responsible for this<br>phenome (Sternberger et al., 1985; Grundke-Iqbal et al., 1986).<br>Originally, aberrant phosphorylation of the neurofilament proteins was believed to be responsible for this<br>phenomenon (Sternberger et al., 1985). However, it has<br>beco Originally, aberrant phosphorylation of the neurofierent proteins was believed to be responsible for the<br>phenomenon (Sternberger et al., 1985). However, it is become clear that the antibodies to neurofilament p<br>tein that l ment proteins was believed to be responsible for this<br>phenomenon (Sternberger et al., 1985). However, it has<br>become clear that the antibodies to neurofilament pro-<br>tein that labeled paired helical filaments in the neurofiphenomenon (Sternberger et al., 1985). However, it has<br>become clear that the antibodies to neurofilament pro-<br>tein that labeled paired helical filaments in the neurofi-<br>brillary tangles cross-react with phosphorylated epit

**a**spet

PHARMACOLOGICAL REVIEWS

Ksiesak-Reding et al., 1987), and present evidence indicates that neurofilament immunoreactivity in neurofi-**EXECUTE PHOSPHORYLA**<br>Ksiesak-Reding et al., 1987), and present evidence in<br>cates that neurofilament immunoreactivity in neuro<br>brillary tangles is due to tau proteins, which poss PROTEIN PHOSPHORYLATION<br>Ksiesak-Reding et al., 1987), and present evidence indi-<br>cates that neurofilament immunoreactivity in neurofi-<br>brillary tangles is due to tau proteins, which possess<br>cross-reacting epitopes (Goedert Ksiesak-Reding et al., 1987), and present evidence indicates that neurofilament immunoreactivity in neurofibrillary tangles is due to tau proteins, which possess cross-reacting epitopes (Goedert et al., 1988; Selkoe, 1989) 1989). tes that neurofilament immunoreactivity in neurofi-<br>illary tangles is due to tau proteins, which possess to dim<br>oss-reacting epitopes (Goedert et al., 1988; Selkoe, protein<br>89). 1990a;<br>Other evidence shows that tau protein

brillary tangles is due to tau proteins, which possess<br>cross-reacting epitopes (Goedert et al., 1988; Selkoe,<br>1989).<br>Other evidence shows that tau proteins, extracted from<br>neurofibrillary tangles, migrate in an aberrant ma cross-reacting epitopes (Goedert et al., 1988; Selkoe<br>1989).<br>Other evidence shows that tau proteins, extracted from<br>neurofibrillary tangles, migrate in an aberrant manne<br>during sodium dodecyl sulfate-polyacrylamide gel ele 1989).<br>
Other evidence shows that tau proteins, extracted from<br>
neurofibrillary tangles, migrate in an aberrant manner<br>
during sodium dodecyl sulfate-polyacrylamide gel elec-<br>
trophoresis when compared to tau proteins from Other evidence shows that tau proteins, extracted from amy<br>neurofibrillary tangles, migrate in an aberrant manner by p<br>during sodium dodecyl sulfate-polyacrylamide gel elec-<br>nai trophoresis when compared to tau proteins fr during sodium dodecyl sulfate-polyacrylamide gel elec-<br>trophoresis when compared to tau proteins from normal 6<br>brain and that normal tau factor can be induced to p<br>assume the Alzheimer-type electrophoretic mobility by (<br>in trophoresis when compared to tau proteins from normal 6<br>brain and that normal tau factor can be induced to p<br>assume the Alzheimer-type electrophoretic mobility by (in<br>vitro phosphorylation of tau protein with CaM kinase<br>II brain and that normal tau factor can be induced to<br>assume the Alzheimer-type electrophoretic mobility by<br>in vitro phosphorylation of tau protein with CaM kinase<br>II (Baudier and Cole, 1987) but not with protein kinase<br>C (Ba assume the Alzheimer-type electrophoretic mobility by (G in vitro phosphorylation of tau protein with CaM kinase where II (Baudier and Cole, 1987) but not with protein kinase C or C (Baudier et al., 1987). Finally, antige in vitro phosphorylation of tau protein with CaM kind II (Baudier and Cole, 1987) but not with protein kind C (Baudier et al., 1987). Finally, antigenic changes si ilar to those seen in neurofibrillary tangles have be eli II (Baudier and Cole, 1987) but not with protein kin C (Baudier et al., 1987). Finally, antigenic changes s ilar to those seen in neurofibrillary tangles have b elicited by glutamate and  $Ca^{2+}$  influx in cultured hip cam C (Baudier et al., 1987). Finally, antigenic changes sim-<br>ilar to those seen in neurofibrillary tangles have been<br>elicited by glutamate and  $Ca^{2+}$  influx in cultured hippo-<br>campal neurons (Mattson, 1990). Although the re ilar to those seen in neurofibrillary tangles have be<br>elicited by glutamate and  $Ca^{2+}$  influx in cultured hipp<br>campal neurons (Mattson, 1990). Although the relatio<br>ship of aberrant tau protein phosphorylation in the<br>tang elicited by glutamate and  $Ca^{2+}$  influx in cultured hippocampal neurons (Mattson, 1990). Although the relationship of aberrant tau protein phosphorylation in these tangles to the tangle formation is unclear, these observ campal neurons (Mattson, 1990). Although the relation-<br>ship of aberrant tau protein phosphorylation in these<br>tangles to the tangle formation is unclear, these obser-<br>vations point to a component of CaM kinase II-catalyzed<br> ship of aberrant tau protein phosphorylation in th<br>tangles to the tangle formation is unclear, these obs<br>vations point to a component of CaM kinase II-cataly<br>protein phosphorylation, particularly of tau protei<br>possibly bei tangles to the tangles to the tangles of probability possibly being in brillary tangles.<br>Brillary tangles.<br> $\beta$ .  $\beta$ -Amyloid also tein phosphorylation, particularly of tau proteins, amy assibly being involved in the pathogenesis of neurofi-<br>*S. β-Amyloid precursor protein phosphorylation and* proteins.<br>*3. β-Amyloid precursor protein phosphoryl* 

protein phosphorylation, particularly of tau proteins possibly being involved in the pathogenesis of neurofic brillary tangles.<br>
3.  $\beta$ -*Amyloid precursor protein phosphorylation an neuritic plaques*. In Alzheimer's dis possibly being involved in the pathogenesis of neurofi-<br>brillary tangles. in<br>3.  $\beta$ -Amyloid precursor protein phosphorylation and<br>neuritic plaques. In Alzheimer's disease, deposits of amy-<br>loid protein outside the cell a brillary tangles.<br>
3.  $\beta$ -Amyloid precursor protein phosphorylation and protein neuritic plaques. In Alzheimer's disease, deposits of amy-<br>
loid protein outside the cell and in the cerebral and protein<br>
meningeal vessels 3.  $\beta$ -Amyloid precursor protein phosphorylation and<br>neuritic plaques. In Alzheimer's disease, deposits of amy-<br>loid protein outside the cell and in the cerebral and<br>meningeal vessels appear to consist mainly of the  $\beta/A$ neuritic plaques. In Alzheimer's disease, deposits of amy<br>loid protein outside the cell and in the cerebral and<br>meningeal vessels appear to consist mainly of the  $\beta/A4$ <br>amyloid protein (Selkoe, 1989). Such  $\beta/A4$  accumula loid protein outside the cell and in the cerebral a<br>meningeal vessels appear to consist mainly of the  $\beta$ /<br>amyloid protein (Selkoe, 1989). Such  $\beta$ /A4 accumulati<br>is detected only in Alzheimer's disease and related co<br>di meningeal vessels appear to consist mainly of the  $\beta$ /A4 amyloid protein (Selkoe, 1989). Such  $\beta$ /A4 accumulation is detected only in Alzheimer's disease and related conditions such as trisomy 21 (Down's syndrome), here amyloid protein (Selkoe, 1989). Such  $\beta/A4$  accumulation<br>is detected only in Alzheimer's disease and related con-<br>ditions such as trisomy 21 (Down's syndrome), heredi-<br>tary cerebral hemorrhage with amyloidosis (Dutch type is detected only in Alzheimer's disease and related conditions such as trisomy 21 (Down's syndrome), hereditary cerebral hemorrhage with amyloidosis (Dutch type), and, much less frequently, normal aging (Joachim et al., 19 ditions such as trisomy 21 (Down's syndrome), hereditary cerebral hemorrhage with amyloidosis (Dutch type), and, much less frequently, normal aging (Joachim et al., 1987). Although the role of the amyloid protein precurso tary cerebral hemorrhage with amyloidosis (Dutch ty, and, much less frequently, normal aging (Joachim et 1987). Although the role of the amyloid protein precurs in the pathogenesis of Alzheimer's disease is unclear is cle and, much less frequently, normal aging (Joachim et al., 1987). Although the role of the amyloid protein precursor in the pathogenesis of Alzheimer's disease is unclear, it is clear that aberrant amyloid precursor protein 1987). Although the rol<br>in the pathogenesis of<br>is clear that aberrant a<br>ing leading to  $\beta/A4$  pr<br>feature of the disease.<br>Amyloidogenic isofo. the pathogenesis of Alzheimer's disease is unclear, it<br>clear that aberrant amyloid precursor protein process-<br>g leading to  $\beta/A4$  protein accumulation is a constant<br>ature of the disease.<br>Amyloidogenic isoforms of the amyl is clear that aberrant amyloid precursor protein processing leading to  $\beta/A4$  protein accumulation is a constant feature of the disease.<br>Amyloidogenic isoforms of the amyloid precursor protein, integral transmembrane prot

ing leading to  $\beta$ /A4 protein accumulation is a constant feature of the disease.<br>Amyloidogenic isoforms of the amyloid precursor protein, integral transmembrane proteins of approximately 110 to 130 kDa which contain a si feature of the disease.<br>Amyloidogenic isoforms of the amyloid precursor p<br>tein, integral transmembrane proteins of approximat<br>110 to 130 kDa which contain a single transmembra<br>spanning domain (Selkoe et al., 1988), are wi Amyloidogenic isoforms of the amyloid precursor pro-<br>tein, integral transmembrane proteins of approximately<br>110 to 130 kDa which contain a single transmembrane<br>spanning domain (Selkoe et al., 1988), are widely distributed tein, integral transmembrane proteins of approximately 110 to 130 kDa which contain a single transmembrane spanning domain (Selkoe et al., 1988), are widely distributed in the brain (Card et al., 1988). The  $\beta/A4$  portion 110 to 130 kDa which contain a single transmembrane<br>spanning domain (Selkoe et al., 1988), are widely distributed in the brain (Card et al., 1988). The  $\beta/A4$  portion<br>of the amyloid precursor protein, which consists of ap spanning domain (Selkoe et al., 1988), are widely distributed in the brain (Card et al., 1988). The  $\beta$ /A4 portion of the amyloid precursor protein, which consists of approximately 40 amino acid residues, lies at the jun uted in the brain (Card et al., 1988). The  $\beta$ /A4 portion<br>of the amyloid precursor protein, which consists of ap-<br>proximately 40 amino acid residues, lies at the junction<br>of the extracellular domain and this transmembran of the amyloid precursor protein, which consists of approximately 40 amino acid residues, lies at the junction<br>of the extracellular domain and this transmembrane<br>domain, with 28 residues outside the cell and the rest<br>embed proximately 40 amino acid residues, lies at the junction<br>of the extracellular domain and this transmembrane<br>domain, with 28 residues outside the cell and the rest<br>embedded in the membrane (Selkoe, 1989). Present evi-<br>denc of the extracellular domain and this transmembrane<br>domain, with 28 residues outside the cell and the rest<br>embedded in the membrane (Selkoe, 1989). Present evi-<br>dence indicates that the normal constitutive cleavage of<br>the domain, with 28 residues outside the cell and the rembedded in the membrane (Selkoe, 1989). Present e dence indicates that the normal constitutive cleavage the amyloid precursor protein takes place within the A4 domain, he embedded in the membrane (Selkoe, 1989). Present evi-<br>dence indicates that the normal constitutive cleavage of<br>the amyloid precursor protein takes place within the  $\beta$ /<br>A4 domain, hence precluding generation of the amylo dence indicates that the normal constitutive cleavage of<br>the amyloid precursor protein takes place within the  $\beta$ /<br>A4 domain, hence precluding generation of the amyloi-<br>dogenic  $\beta$ /A4 protein (Sisodia et al., 1990; Esch the amyloid precursor protein takes place with A4 domain, hence precluding generation of the dogenic  $\beta$ /A4 protein (Sisodia et al., 1990; Es 1990). Failure of this normal cleavage represer sible biochemical basis for ce 4 domain, hence precluding generation of the amyloi-<br>genic  $\beta/\mathbf{A}4$  protein (Sisodia et al., 1990; Esch et al., in<br>900). Failure of this normal cleavage represents a pos-<br>ble biochemical basis for cerebral amyloidosis.

dogenic  $\beta$ /A4 protein (Sisodia et al., 1990; Esch et al.)<br>1990). Failure of this normal cleavage represents a pos<br>sible biochemical basis for cerebral amyloidosis.<br>Several possible mechanisms may contribute to failur<br>of 1990). Failure of this normal cleavage represents a possible biochemical basis for cerebral amyloidosis.<br>Several possible mechanisms may contribute to failure<br>of normal cleavage, including overexpression of the amy-<br>loid p

during sodium dodecyl sulfate-polyacrylamide gel elec-<br>trophoresis when compared to tau proteins from normal 655 have been identified as candidate sites for rapid<br>brain and that normal tau factor can be induced to phosphor AND NEURONAL FUNCTION 333<br>proteolytic processing of the amyloid precursor protein<br>or mutations within the amyloid precursor gene leading AND NEURONAL FUNCTION 333<br>proteolytic processing of the amyloid precursor protein<br>or mutations within the amyloid precursor gene leading<br>to diminished efficacy of the normal amyloid precursor AND NEURONAL FUNCTION 333<br>proteolytic processing of the amyloid precursor protein<br>or mutations within the amyloid precursor gene leading<br>to diminished efficacy of the normal amyloid precursor<br>protein degradative pathway in proteolytic processing of the amyloid precursor protein<br>or mutations within the amyloid precursor gene leading<br>to diminished efficacy of the normal amyloid precursor<br>protein degradative pathway in brain (Gandy et al.,<br>1990 proteolytic processing of the amyloid precursor protein<br>or mutations within the amyloid precursor gene leading<br>to diminished efficacy of the normal amyloid precursor<br>protein degradative pathway in brain (Gandy et al.,<br>1990 to diminished efficacy of the normal amyloid precursor<br>protein degradative pathway in brain (Gandy et al.,<br>1990a; Levy et al., 1990). Recent analysis has shown that<br>amyloid precursor protein processing may be regulated to diminished efficacy of the normal amyloid precursor<br>protein degradative pathway in brain (Gandy et al.,<br>1990a; Levy et al., 1990). Recent analysis has shown that<br>amyloid precursor protein processing may be regulated<br>by protein degradative pathway in brain (Gandy  $\epsilon$  1990a; Levy et al., 1990). Recent analysis has shown amyloid precursor protein processing may be reguly protein phosphorylation. Within the intracelluli mains of the amyloi 1990a; Levy et al., 1990). Recent analysis has shown that<br>amyloid precursor protein processing may be regulated<br>by protein phosphorylation. Within the intracellular do-<br>mains of the amyloid precursor protein, Thr-654/Ser-<br> amyloid precursor protein processing may be regulated<br>by protein phosphorylation. Within the intracellular do-<br>mains of the amyloid precursor protein, Thr-654/Ser-<br>655 have been identified as candidate sites for rapid<br>phos mains of the amyloid precursor protein, Thr-654/Ser-655 have been identified as candidate sites for rapid 655 have been identified as candidate sites for rephosphorylation by protein kinase C and CaM kinas (Gandy et al., 1988). Moreover, in pulse-chase studie which PC12 cells were used, activation of protein kin C with phorbol phosphorylation by protein kinase C and CaM kinase II<br>(Gandy et al., 1988). Moreover, in pulse-chase studies in<br>which PC12 cells were used, activation of protein kinase<br>C with phorbol esters or inhibition of protein phosph (Gandy et al., 1988). Moreover, in pulse-chase studies in<br>which PC12 cells were used, activation of protein kinase<br>C with phorbol esters or inhibition of protein phospha-<br>tases-1 and -2A with okadaic acid (Bialojan and Tak which PC12 cells were used, activation of protein kin C with phorbol esters or inhibition of protein phospletases-1 and -2A with okadaic acid (Bialojan and Tal 1988) greatly diminished recovery of the mature amyle precurso C with phorbol esters or inhibition of protein phosphatases-1 and -2A with okadaic acid (Bialojan and Takai, 1988) greatly diminished recovery of the mature amyloid precursor protein while enhancing recovery of a COOH-<br>te tases-1 and -2A with okadaic acid (Bialojan and Takai, 1988) greatly diminished recovery of the mature amyloid precursor protein while enhancing recovery of a COOH-<br>terminal fragment of approximately 15 kDa (Buxbaum et al. 1988) greatly diminished recovery of the mature amyloid<br>precursor protein while enhancing recovery of a COOH-<br>terminal fragment of approximately 15 kDa (Buxbaum<br>et al., 1990). Combination of phorbol ester and okadaic<br>acid precursor protein while enhancing recovery of a COOH-<br>terminal fragment of approximately 15 kDa (Buxbaum<br>et al., 1990). Combination of phorbol ester and okadaic<br>acid led to the generation of the 15-kDa fragment and<br>also to terminal fragment of approximately 15 kDa (Buxbaum<br>et al., 1990). Combination of phorbol ester and okadaic<br>acid led to the generation of the 15-kDa fragment and<br>also to a larger 19-kDa COOH-terminal fragment of the<br>amyloid et al., 1990). Combination of phorbol ester and okadaic<br>acid led to the generation of the 15-kDa fragment and<br>also to a larger 19-kDa COOH-terminal fragment of the<br>amyloid precursor protein. In other experiments, the<br>prote also to a larger 19-kDa COOH-terminal fragment of the amyloid precursor protein. In other experiments, the protein kinase inhibitor H-7 led to an apparent decrease in the basal rate of processing of the amyloid precursor p also to a larger 19-kDa COOH-terminal fragment of the amyloid precursor protein. In other experiments, the protein kinase inhibitor H-7 led to an apparent decrease in the basal rate of processing of the amyloid precursor p amyloid precursor protein. In other experiments, the protein kinase inhibitor H-7 led to an apparent decrease in the basal rate of processing of the amyloid precursor protein. These results provide direct evidence that pro protein kinase inhibitor H-7 led to an apparent decreasing in the basal rate of processing of the amyloid precuprotein. These results provide direct evidence that possible interpretary of the amyloid precursor protein is r in the basal rate of processing of the amyloid precurso<br>protein. These results provide direct evidence that processing of the amyloid precursor protein is regulated b<br>protein phosphorylation, with one possible interpret<br>t protein. These results provide direct evidence that processing of the amyloid precursor protein is regulated by protein phosphorylation, with one possible interpretation being that the 15-kDa fragment represents the "norm essing of the amyloid precursor protein is regulated by<br>protein phosphorylation, with one possible interpreta-<br>tion being that the 15-kDa fragment represents the "nor-<br>mal" constitutive intra- $\beta$ /A4 cleavage, whereas the protein phosphorylation, with one possible interpreta-<br>tion being that the 15-kDa fragment represents the "nor-<br>mal" constitutive intra- $\beta$ /A4 cleavage, whereas the 19-<br>kDa COOH-terminal fragment represents processing vi tion being that the 15-kDa fragment represents the "nor-<br>mal" constitutive intra- $\beta$ /A4 cleavage, whereas the 19-<br>kDa COOH-terminal fragment represents processing via<br>an alternative and potentially amyloidogenic pathway, mal" constitutive intra- $\beta$ /A4 cleavage, when<br>kDa COOH-terminal fragment represents pro<br>an alternative and potentially amyloidogen<br>perhaps by cleavage at or near the  $\beta$ /A4 NI<br>(Buxbaum et al., 1990; Gandy et al., 1990a) Da COOH-terminal fragment represents processing via<br>a diternative and potentially amyloidogenic pathway,<br>rhaps by cleavage at or near the  $\beta/A4 \text{ NH}_2$  terminus<br>buxbaum et al., 1990; Gandy et al., 1990a).<br>At present, the m

an alternative and potentially amyloidogenic pathway,<br>perhaps by cleavage at or near the  $\beta/\text{A4} \text{ NH}_2$  terminus<br>(Buxbaum et al., 1990; Gandy et al., 1990a).<br>At present, the mechanisms behind the observed ef-<br>fects of m perhaps by cleavage at or near the  $\beta/A4 \text{ NH}_2$  termin (Buxbaum et al., 1990; Gandy et al., 1990a).<br>At present, the mechanisms behind the observed fects of manipulations of protein phosphorylation stems remain speculative (Buxbaum et al., 1990; Gandy et al., 1990a).<br>At present, the mechanisms behind the observed ef-<br>fects of manipulations of protein phosphorylation sys-<br>tems remain speculative. Previous studies of the traffick-<br>ing of sever At present, the mechanisms behind the observed<br>fects of manipulations of protein phosphorylation s<br>tems remain speculative. Previous studies of the trafficing<br>of several cell surface receptors have shown tl<br>ligand-induced fects of manipulations of protein phosphorylation sys-<br>tems remain speculative. Previous studies of the traffick-<br>ing of several cell surface receptors have shown that<br>ligand-induced endocytosis of, for example, the epider tems remain speculative. Previous studies of the trafficking of several cell surface receptors have shown that ligand-induced endocytosis of, for example, the epidermal growth factor receptor is accompanied by protein kina ing of several cell surface receptors have shown tligand-induced endocytosis of, for example, the epid mal growth factor receptor is accompanied by prot kinase C-mediated phosphorylation in an intracellu domain homologous ligand-induced endocytosis of, for example, the epider-<br>mal growth factor receptor is accompanied by protein<br>kinase C-mediated phosphorylation in an intracellular<br>domain homologous to that found in the amyloid precur-<br>sor mal growth factor receptor is accompanied by protein<br>kinase C-mediated phosphorylation in an intracellular<br>domain homologous to that found in the amyloid precur-<br>sor protein (Hunter et al., 1984; Beguinot et al., 1985;<br>Gan kinase C-mediated phosphorylation in an intracellular<br>domain homologous to that found in the amyloid precur-<br>sor protein (Hunter et al., 1984; Beguinot et al., 1985;<br>Gandy et al., 1990a). Thus, the regulation of endocytoti domain homologous to that found in the amyloid pre<br>sor protein (Hunter et al., 1984; Beguinot et al., 1<br>Gandy et al., 1990a). Thus, the regulation of endocyt<br>processing of this type of membrane protein by pro<br>phosphorylati sor protein (Hunter et al., 1984; Beguinot et al., 1985; Gandy et al., 1990a). Thus, the regulation of endocytotic processing of this type of membrane protein by protein phosphorylation appears to be a widespread phenomeno Gandy et al., 1990a). Thus, the regulation of endocytotic processing of this type of membrane protein by protein phosphorylation appears to be a widespread phenomenon. Furthermore, protein phosphorylation may also be invol processing of this type of membrane protein by protein<br>phosphorylation appears to be a widespread phenome-<br>non. Furthermore, protein phosphorylation may also be<br>involved in the regulation of amyloid precursor protein<br>expre phosphorylation appears to be a widespread phenomenon. Furthermore, protein phosphorylation may also be involved in the regulation of amyloid precursor protein expression, possibly via phosphorylation of transcription fact non. Furthermore, protein phosphorylation may also<br>involved in the regulation of amyloid precursor prote<br>expression, possibly via phosphorylation of transcripti<br>factors such as the homeoprotein hox 1.3, a protein th<br>binds involved in the regulation of amyloid precursor protein<br>expression, possibly via phosphorylation of transcription<br>factors such as the homeoprotein hox 1.3, a protein that<br>binds to the amyloid precursor protein promoter (Go expression, possibly via phosphorylation of transcription<br>factors such as the homeoprotein hox 1.3, a protein that<br>binds to the amyloid precursor protein promoter (Gold-<br>gaber et al., 1989). Future work will be required to factors such as the homeoprotein hox 1.3, a protein that binds to the amyloid precursor protein promoter (Goldgaber et al., 1989). Future work will be required to determine whether any of these mechanisms are involved in gaber et al., 1989). Future work will be required to determine whether any of these mechanisms are involved in cerebral amyloidosis and whether they constitute possible targets for antiamyloid therapy.<br>VII. Summary and Con determine whether any of these mechanisms are involved<br>in cerebral amyloidosis and whether they constitute pos-<br>sible targets for antiamyloid therapy.<br>VII. Summary and Conclusion<br>Following the initial demonstration of phos in cerebral amyloidosis and whether they constitute pos-

tion of endogenous brain proteins (Johnson et al., 1971).

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que 334<br>two decades of work have shown that this biochemical<br>mechanism represents one of the most important means waLAAS AND G<br>two decades of work have shown that this biochemical<br>mechanism represents one of the most important means<br>by which extracellular signals are transduced into 334<br>waLAAS AND GRE<br>two decades of work have shown that this biochemical<br>mechanism represents one of the most important means<br>hy which extracellular signals are transduced into<br>changes in neuronal functions. Evidence discu two decades of work have shown that this biochemical<br>mechanism represents one of the most important means<br>by which extracellular signals are transduced into<br>changes in neuronal functions. Evidence discussed in<br>this review two decades of work have shown that this biochemical<br>mechanism represents one of the most important means<br>by which extracellular signals are transduced into<br>changes in neuronal functions. Evidence discussed in<br>this review mechanism represents one of the most important m<br>by which extracellular signals are transduced<br>changes in neuronal functions. Evidence discusse<br>this review shows that neural cells contain a plethor<br>protein kinases, protein by which extracellular signals are transduced into<br>changes in neuronal functions. Evidence discussed in<br>this review shows that neural cells contain a plethora of<br>protein kinases, protein phosphatases, and phosphory-<br>lated changes in neuronal functions. Evidence discussed in AK this review shows that neural cells contain a plethora of protein kinases, protein phosphatases, and phosphory-<br>lated proteins and that many of these systems appear this review shows that neural cells contain a plethora of protein kinases, protein phosphatases, and phosphory-<br>lated proteins and that many of these systems appear<br>essential for the regulation of cell functions as diverse protein kinases, protein phosphatases, and phosphory-<br>lated proteins and that many of these systems appear<br>essential for the regulation of cell functions as diverse as<br>membrane excitability, neuronal secretory processes, c lated proteins and that many of these systems appears essential for the regulation of cell functions as diverse a membrane excitability, neuronal secretory processes, cy toskeletal organization, neuronal morphology, and ce essential for the regulation of cell functions as diverse as<br>membrane excitability, neuronal secretory processes, cy-<br>toskeletal organization, neuronal morphology, and cell-<br>ular metabolism. Moreover, there exists intricat membrane excitability, neuronal secretory processes, cy-<br>toskeletal organization, neuronal morphology, and cell-<br>ular metabolism. Moreover, there exists intricate func-<br>tional relationships between many of the neuronal pro toskeletal organization, neuronal morphology, and cell-<br>ular metabolism. Moreover, there exists intricate func-<br>tional relationships between many of the neuronal pro-<br>tein phosphorylation systems, which allow "cross-talk" cells. The properties of protein phosphorylation systems to influence events taking<br>negation  $P$ . The 87-kDa protein, a major<br>tein phosphorylation systems, which allow "cross-talk"<br>between distinct signals to take place in tional relationships between many of the neuronal pro-<br>tein phosphorylation systems, which allow "cross-talk"<br>between distinct signals to take place in various brain<br>cells. The properties of protein phosphorylation system tein phosphorylation systems, which allow "cross-talk"<br>between distinct signals to take place in various brain<br>cells. The properties of protein phosphorylation systems<br>allow these regulatory systems to influence events tak between distinct signals to take place in various brain cells. The properties of protein phosphorylation systems allow these regulatory systems to influence events taking place on a microsecond scale (e.g., neurotransmitte cells. The properties of protein phosphorylation systems<br>allow these regulatory systems to influence events taking<br>place on a microsecond scale (e.g., neurotransmitter re-<br>lease) and events lasting for hours and days (e.g. allow these regulatory systems to influence events taking<br>place on a microsecond scale (e.g., neurotransmitter re-<br>lease) and events lasting for hours and days (e.g., LTP).<br>Our present knowledge concerning neuronal protein lease) and events lasting for hours and days (e.g., LTP).<br>Our present knowledge concerning neuronal protein<br>phosphorylation has also allowed studies to be initiated<br>regarding the possible involvement of protein phosphorlease) and events lasting for hours and days (e.g., LTP).<br>Our present knowledge concerning neuronal protein<br>phosphorylation has also allowed studies to be initiated<br>regarding the possible involvement of protein phosphor-<br>y Our present knowledge concerning neuronal protein<br>phosphorylation has also allowed studies to be initiated<br>regarding the possible involvement of protein phosphor-<br>ylation in various clinical disorders affecting signal<br>tran phosphorylation has also allowed studies to be init<br>regarding the possible involvement of protein phosphation in various clinical disorders affecting s<br>transduction and brain function. It seems safe to pr<br>that continued st regarding the possible involvement of protein phosphor-<br>ylation in various clinical disorders affecting signal<br>transduction and brain function. It seems safe to predict<br>that continued studies of neuronal protein phosphoryl ylation in various clinical disorders affecting sign<br>transduction and brain function. It seems safe to predi<br>that continued studies of neuronal protein phosphoryl<br>tion systems will continue to improve our understandi<br>of th transduction and brain function. It seems safe to predict<br>that continued studies of neuronal protein phosphoryla-<br>tion systems will continue to improve our understanding<br>of the anatomical, physiological, and pharmacologic disease. tion systems will continue to improve our understanding<br>of the anatomical, physiological, and pharmacological<br>basis for nervous system function in both health and<br>disease.<br>*Acknowledgments*. We thank Drs. A. C. Nairn, A. J

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