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Protein Phosphorylation and Neuronal Function*

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I. Introduction

A. Functional Importance of Protein Phosphorylation

The last decades have witnessed major advances in our understanding of the molecular mechanisms involved in signal transduction in neuronal tissues. Reversible protein 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 neurotransmitters that have been shown to achieve at least some of their actions in neural cells through protein phosphorylation/dephosphorylation is presented in table 1.

Early studies of carbohydrate metabolism (Walsh et al., 1968) demonstrated that enzyme phosphorylation could have a regulatory role (Robison et al., 1971; Nimmo and Cohen, 1977; Krebs and Beavo, 1979). Later work extended this concept (Kuo and Greengard, 1969) and led to the realization that this biochemical mechanism 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 the regulation of a wide variety of other cellular functions. A full molecular understanding of the role of protein phosphorylation in nervous tissue would require identification and characterization of the various protein phosphorylation systems present in the brain. The phosphoproteins that appear to be particularly important in neuronal function include enzymes involved in neurotransmitter biosynthesis, synaptic vesicle-associated 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 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 the protein kinases, protein phosphatases, and substrate proteins involved and discuss some of the evidence that 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 references will be given. Indeed, the vast literature that exists concerning protein phosphorylation makes it impossible to discuss all aspects of this topic in a single review. The reader is referred to a number of other reviews for additional information (for examples, see Browning et al., 1985; Greengard, 1976, 1978, 1987; Huganir and Greengard, 1990; Kandel and Schwartz, 1982; Kennedy, 1983, 1989; Kaczmarek and Levitan 1987; Nairn et al., 1985b; Nestler and Greengard, 1984; Reichardt and Kelly, 1983; Walaas and Greengard, 1987).

Conclusive evidence for involvement of protein phosphorylation in neuronal function was originally difficult to obtain. Early studies suggested that cyclic nucleotide-dependent protein phosphorylation might be of physiological importance in the nervous system, because cor-

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TABLE 1
*First messengers regulating brain protein phosphorylation**

First messenger	Receptor	Type enzyme involved	Substrate protein	References
Acetylcholine	mACh-R	PKC	MARCKS	Wang, Audigier and Greengard, unpublished data
			GAP-43	Van Hoof et al., 1989
Noradrenaline (adrenaline)	α-AR	PKC	MARCKS	Wang, Audigier and Greengard, unpublished data
	β-AR	PKA	Synapsin I	Mobley and Greengard, 1985
			GFAP	Browning and Ruina, 1984
			Vimentin	Groppi and Browning, 1980
Dopamine	D1	PKA	Synapsin I, II	Nestler and Greengard, 1980; Treiman and Greengard, 1985
			DARPP-32	Walaas et al., 1983c
Serotonin		PKA	Synapsin I	Dolphin and Greengard, 1981a
Adenosine	A_2	PKA	Synapsin I	Dolphin and Greengard, 1981b
Glutamate	NMDA	PP-2B	DARPP-32	Halpain et al., 1990
			MAP-2	Halpain and Greengard, 1990
Depolarization		CaM-I	Synapsin I, II	Huttner and Greengard, 1979; Wang et al., 1988
		CaM-II	Synapsin I	Huttner and Greengard, 1979
		PKC	MARCKS	Wu et al., 1982
			GAP-43	Wang et al., 1988
Vasoactive intestinal peptide		PKA	ARPP-16	Girault et al., 1988

* Protein phosphorylation systems shown to be regulated by extracellular signals in intact neural cells and/or nerve terminals are included. Not included are widespread, predominantly nonneuronal systems. Abbreviations: PKC, protein kinase C; PKA, cyclic AMP-dependent protein kinase; PP-2B, protein phospatase-2B; ARPP-16, cyclic AMP-regulated phosphoprotein, 16 kDa; mACh-R, muscarinic acetylcholine receptor; α-AR, β-AR, α- and β-adrenergic receptors, respectively; D1, D1 type of dopamine receptor; A_2, A_2 type of adenosine receptor.

relations between levels of cyclic AMP‡ or cyclic GMP and specific electrophysiological properties were observed (for reviews, see Bloom, 1975; Bloom et al., 1975; 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 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, see Kaczmarek et al., 1980; Castellucci et al., 1980, 1982; Llinas et al., 1985; Paupardin-Tritsch et al., 1986b; DeRiemer et al., 1985).

B. Protein Phosphorylation Systems

All protein phosphorylation systems consist minimally of three components. These include the *phosphoproteins* themselves, which change their biological properties during phosphorylation/dephosphorylation. In addition, two classes of enzymes are needed for the phosphorylation/dephosphorylation reactions. One set of these enzymes includes the *protein kinases*, phosphotransferases that 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, Edelman et al., 1987). The other set of enzymes includes the *phosphoprotein phosphatases*, which dephosphorylate the phosphoproteins and thereby return the particular protein phosphorylation system to its basal state (Ingebritsen and Cohen, 1983a,b; Cohen, 1989; Shenolikar and Nairn, 1991).

Increases in the state of phosphorylation of phosphoproteins 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. Present evidence suggests that increasing the activity of protein kinases represents the most common activation mechanism in both neuronal and nonneuronal tissues. However, it is increasingly clear that certain protein phosphatases are subject to rapid and reversible control mechanisms. Recent evidence also indicates that many substrates undergo phosphorylation by multiple protein kinases (table 2). Such phosphoproteins may change their properties as substrates for protein kinases or phosphatases as a result of phosphorylation or dephosphorylation in other regions of the molecule. These various phenomena will be discussed below.

Mammalian brain is an unusually rich source of pro-

‡ Abbreviations: cyclic AMP and cyclic GMP, cyclic adenosine and cyclic guanosine 3′:5′-monophosphate, respectively; CNS, central nervous system; C, catalytic subunit; R, regulatory subunit; CaM kinase; Ca^{2+}/calmodulin-dependent protein kinase; GABA, γ-aminobutyric acid; IP_3, inositol 1,4,5-trisphosphate; GAP-43, growth-associated protein, 43 kDa; MAP, microtubule-associated protein; Thr, threonine; Ser, serine; protein kinase C, Ca^{2+}/phospholipid/diacylglycerol-dependent protein kinase; LTP, long-term potentiation; MARCKS, myristoylated, alanine-rich C-kinase substrate; DARPP-32, dopamine- and cyclic AMP-regulated phosphoprotein, M_r 32,000; NMDA, N-methyl D-aspartate; ATP, adenosine triphosphate.

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TABLE 2
*Neuronal proteins phosphorylated on multiple sites**

Protein	Protein kinase						Selected references
	PKA	CaM II	PKC	Cas K-II	Tyr K	Other	
MAP-2	+	+	+	−	−	+	Walaas and Nairn, 1989
Tau	−	+	+	−	−	−	Baudier and Cole, 1987; Baudier et al., 1987
Neurofilament	+	+	−	−	−	+	Matus, 1988a
Na^+ channel	+	−	+	−	−	−	Costa and Catterall, 1984a,b
Ca^{2+} channel	+	−	+	−	−	−	Curtis and Catterall 1985; Hosey et al., 1986
Synapsin I	+	+	−	−	−	+	Huttner and Greengard, 1979
Tyrosine hydroxylase	+	+	+	−	−	+	Haycock, 1990
nACh-R	+	−	+	−	+	−	Huganir and Greengard, 1990
mACh-R	+	−	+			+	Kwatra et al., 1989
$GABA_A$-R	+	−	+	−	−	+	Sweetnam et al., 1988; Browning et al., 1990
β-AR	+	−	+	−	−	+	Lefkowitz et al., 1990
DARPP-32	+	−	−	+	−	−	Hemmings et al., 1984; Girault et al., 1990

* Table includes examples of major neuronal proteins specifically involved in signal transduction or other brain-specific functions, and subject to multisite protein phosphorylation in intact tissue. References include recent papers or reviews, where original data are described. Abbreviations: nACh-R, nicotinic acetylcholine receptor; $GABA_A$-R, γ-aminobutyric acid receptor type A; Tyr K, tyrosine-specific protein kinase; other abbreviations as in legend to Table 1.

tein phosphorylation systems, including diverse protein kinases, phosphoprotein substrates, phosphoprotein phosphatases, and modulators thereof (Nairn et al., 1985b). For example, comparison between the endogenous protein phosphorylation activities found in rat forebrain 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+}-dependent protein kinase activities and a much larger number of putative endogenous substrate proteins than do peripheral tissues (S. I. Walaas and P. Greengard, unpublished evidence presented in Nestler and Greengard, 1989, p. 378).

II. Protein Kinases in Brain

The number of protein kinases described has increased dramatically during the last decade. Most of these protein kinases appear to belong to a common superfamily 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 properties of those protein kinases in the mammalian brain that 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 concentrations and cellular and subcellular distributions of some of the enzymes (Walter and Greengard, 1981; 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 second messenger-regulated enzymes.

A. General Mechanisms for Activation of Protein Kinases

Most members of the protein kinase family appear to contain catalytic domains that have approximately 30- 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 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 underlying such regulation, the present consensus being that most protein kinases have latent catalytic activities and that removal of inhibitory constraints can induce activation of the enzymes. A number of the most thoroughly studied protein kinases have been found to contain pseudosubstrate "prototopes" within their regulatory domains (for reviews, see Kemp et al., 1989; Soderling, 1990). These prototopes, which may be located either on the same polypeptides as the catalytic domains or on distinct R subunits, have primary structures similar to those surrounding the authentic phosphorylation sites in the physiological substrates (Kemp and Pearson, 1990). The prototope domains may, therefore, under basal conditions, be tightly bound to catalytic domains within the kinase. Activation of such enzymes is achieved through 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, either singly or working in concert, have thus far been defined in mammalian brain: second messenger generation, enzyme autophosphorylation, and direct binding of first messengers to a receptor-kinase

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complex. Activation through second messenger generation is the best studied of these mechanisms in brain tissue.

1. Activation by second messengers. Brain cells use several mechanisms for generating second messengers. These include neurotransmitter receptors which activate or inhibit adenylyl cyclase and guanylyl cyclase and alter the synthesis of cyclic AMP and cyclic GMP, respectively (for reviews, see Daly, 1977; Ferrendelli, 1978; Bockaert, 1981; Birnbaumer and Iyengar, 1982; Drummond, 1983) (table 3). Other neurotransmitter receptors appear coupled to activation or inhibition of phospholipase C, which generates IP_3 and diacylglycerol from phosphatidylinositol-4,5-bisphosphate (Brown et al., 1984; Berridge, 1984, 1987; Berridge and Irvine, 1989; Downes, 1982, 1988; Fisher and Agranoff, 1987). IP_3 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 neurotransmitter receptors are coupled to the influx of Ca^{2+}, through ligand-operated channels (Reuter, 1983; Miller, 1987; Hess, 1990). Another signal transduction system appears to involve receptors 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). Finally, the nerve impulse itself is involved in signal transduction via Ca^{2+} influx through voltage-sensitive channels (for reviews, see Augustine et al., 1987; Hess, 1990). Strong evidence indicates that many or most of the effects of the compounds generated by these various mechanisms are achieved through direct or indirect regulation of protein phosphorylation systems, particularly the second messenger-dependent protein kinases (table 4). These enzymes are activated by binding of the intracellular messengers to distinct sites on the enzymes which thereby undergo conformational changes.

TABLE 3
*First messengers regulating second messenger generation in brain**

First messenger	Second messengers				
	cAMP	cGMP	Ca^{2+}	DAG	AA
Glutamate	(↑)	↑	↑	↑	
GABA	↓				
Acetylcholine	↓	↑	↑	↑	↑
Norepinephrine	↑↓		↑	↑	↑
Dopamine	↑↓		↑	(↑)	
Serotonin	↑↓	↑		↑	
Histamine	↑	↑			
Adenosine	↑				
Vasoactive intestinal peptide	↑				
Opioids	↓				
Somatostatin	↓				
Substance P			↑	↑	
Atrial natriuretic factor		↑			
Depolarization		(↑)	↑	(↑)	

* The table includes major groups of first messengers reported to change levels of second messengers in preparations containing intact neural cells. Data compiled from: Daly (1977), 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, diacylglycerol; AA, arachidonic acid or metabolites thereof.

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 autophosphorylation sites, the phosphorylation of which may profoundly change the activity of the enzyme in question (for a recent review, see Blackshear et al., 1988). Well-known examples include cyclic AMP-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 $pp60^{c\text{-}src}$ (Okada and Nakagawa, 1989), all of which are enriched in brain. These enzymes will be discussed in greater detail below.

3. Activation by ligand binding. A third important mechanism for protein kinase activation is used by a group of receptor-associated protein kinases. These enzymes, most of which appear to phosphorylate their substrate proteins on tyrosine residues rather than on the more commonly phosphorylated serine or threonine residues, are often associated with receptors for various growth factors, hormones, and mitogens. Well-known examples include the epidermal and platelet-derived growth factor receptors, the insulin receptor, and the 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 appears to directly activate the protein kinase, which often is an integral part of the receptor itself, without any intervening second messenger generation. In other cases, such tyrosine-specific protein kinases may be distinct from the receptors themselves, although they often are associated with membranes and functionally linked to membrane receptors through unknown mechanisms. Examples include the tyrosine protein kinase present in *Torpedo electroplax*, which is capable of phosphorylating the nicotinic acetylcholine receptor (Huganir et al., 1984), and the recently described protein kinase $pp56^{lck}$ present in lymphocytes which appears to be activated by the CD4 or CD8 transmembrane complexes and which can phosphorylate the antigen receptors in T-lymphocytes (Barber et al., 1989; Veillette et al., 1989).

B. Second Messenger-regulated Protein Kinases

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 kinases, which have been found to be the principal

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TABLE 4
*Protein kinases involved in nervous system function**

Protein kinase	Major physiological functions	Selected references
Cyclic AMP-dependent protein kinase	Ion channel regulation	Kaczmarek and Levitan, 1986
	Transmitter synthesis	Zigmond et al., 1988
	Transmitter release	Kandel and Schwartz, 1982
	Receptor desensitization	Huganir and Greengard, 1990
	Intermediary metabolism	Wilkening and Makman, 1977
Cyclic GMP-dependent protein kinase	Ion channel regulation	Paupardin-Tritsch et al., 1986a,b
	Input resistance regulation	Woody et al., 1986
CaM-II	Transmitter synthesis	Zigmond et al., 1989
	Transmitter release	Llinas et al., 1985
	LTP	Malinow et al., 1988
	Cytoskeletal organization	Baudier and Cole, 1987
Protein kinase C	Ion channel regulation	Kaczmarek, 1987
	Transmitter synthesis	Zigmond et al., 1988
	Transmitter release	Nichols et al., 1987
	Receptor desensitization	Huganir and Greengard, 1990
	LTP	Hu et al., 1987

* Table includes second messenger-regulated protein kinases which have been shown to mediate or modulate major classes of functional processes in intact neural cells.

intracellular "receptor" proteins for cyclic AMP and cyclic GMP, respectively, in eukaryotic cells (for reviews, see Nimmo and Cohen, 1977; Walter and Greengard, 1981; Døskeland and Øgreid, 1981; Lincoln and Corbin, 1983). Some structural homologies between these enzymes exist (Corbin and Lincoln, 1978), but the differences in substrate specificities, activation mechanisms, quaternary structures, immunological cross-reactivities, and tissue distributions indicate that they have distinct physiological roles (Walter et al., 1980; Walter and Greengard, 1981; Nairn et al., 1985b).

a. CYCLIC AMP-DEPENDENT PROTEIN KINASE. This enzyme, first described by Walsh et al. (1968), is present in a number of isoforms (Cadd and McKnight, 1989) and is highly enriched in brain (Miyamoto et al., 1969; Nairn et al., 1985b). The main properties of the brain enzyme are identical with those of the enzyme prepared from peripheral tissues. It exists as a tetramer composed of two R subunits (49 to 55 kDa apparent molecular masses) joined by a disulfide bond and two C subunits (40 kDa apparent molecular mass), all of which, in the absence of cyclic AMP, bind together to produce an inactive complex (for examples, see Nimmo and Cohen, 1977).

The two main isozymic forms of cyclic AMP-dependent 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 RII subunits (51 to 55 kDa) (Hofmann et al., 1975; Nimmo and Cohen, 1977). Further studies, in which molecular genetic approaches were used, have shown that there are multiple forms of RI, RII and C, which have distinct properties and tissue distributions. Two clones from mouse genomic and complementary DNA libraries have been found to encode distinct forms of RI, designated RI-α and RI-β (Kuno et al., 1987; Clegg et al., 1988). Moreover, two forms of RII, designated RII-α and RII-β, 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-α and C-β, 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). In each of these cases, the α-forms of the different subunits appear to have a widespread tissue distribution, whereas the β-forms are restricted to brain and a few other, usually reproductive tissues (Cadd and McKnight, 1989). Such differences may reflect adaptions of the isoenzymes for specific neuronal functions or localizations.

i. **Regulation of activity.** The general mechanism for regulation of cyclic AMP-dependent protein kinase activity in brain appears to be similar to that described in peripheral tissues. Adenylyl cyclase, the membrane-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, including the brain, also by Ca^{2+}/calmodulin (Brostrom 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 nucleotide (for examples, see Øgreid et al., 1983; Robison-Steiner and Corbin, 1983; Døskeland and Øgreid, 1984). The newly formed intracellular cyclic AMP binds to the R subunits of the enzyme, thereby inducing the C sub-

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units to dissociate from the holoenzyme and making the 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 holoenzyme. Autophosphorylation of RII, which is stimulated by cyclic AMP, retards reassociation of the type II holoenzyme and thereby enhances its response to cyclic AMP (Rubin and Rosen, 1975; Rangel-Aldao and Rosen, 1976).

In addition to the R subunits, many tissues contain a small, heat-stable protein inhibitor of cyclic AMP-dependent 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 inhibitor may play a role in more protracted regulation of cyclic AMP-dependent protein kinase activity (for examples, see Costa, 1977).

ii. Distribution in brain. Both type I and type II cyclic AMP-dependent protein kinases are widely distributed throughout the brain (Walter et al., 1978; De Camilli et al., 1986; Cadd and McKnight, 1989). Total cyclic AMP-dependent protein kinase activity is highest in basal ganglia and cortical regions, with lowest activity found in brain stem and spinal cord (Walaas et al., 1983b,c). Analysis of kinase levels (Walter et al., 1979) agrees with results obtained in studies of gene expression in mouse brain, which indicates that transcripts for both types I and II of cyclic AMP-dependent protein kinase are present in neuronal cells, and type I in addition appears to be enriched in myelin and glial cells (Stein et al., 1987).

Analysis of messenger RNAs for the different isoforms 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-α, RI-α, and RI-β, showed preferential enrichment in neocortex, caudatoputamen, hypothalamus, thalamus, and hippocampus. Another pattern, which was shared by C-β and RII-β, was distinguished from the C-α pattern by a lower expression in the thalamus and in the CA1-3 regions of the hippocampus. RII-α was unique in being highly expressed only in the medial habenular nucleus of the epithalamus. Although these transcript levels do not necessarily reflect protein levels, they suggest that isoform-specific holoenzymes of cyclic AMP-dependent protein kinase exist in distinct brain regions (Cadd and McKnight, 1989).

In contrast to most other tissues, in which cyclic AMP-dependent protein kinase is found almost exclusively in the soluble fraction, mammalian brain has a high activity of the enzyme in both particulate and soluble fractions, with highest specific activities in the synaptic membrane and cytosol fractions (for examples, see Maeno et al., 1971; Walter et al., 1978; Kelly et al., 1979). The association of the enzyme with membranes appears to be achieved through the R subunits (Rubin et al., 1972; Corbin et al., 1977). Type II cyclic AMP-dependent protein kinase is also bound through the RII subunits to several cytoplasmic brain proteins, including the calmodulin-binding protein p75, the cytoskeletal protein MAP-2, calcineurin, a Ca^{2+}- and calmodulin-dependent protein phosphatase, and a number of proteins of unknown 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 cytosolic 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).

iii. Functional importance in nerve cells. The response of any cell to increases in cyclic AMP is determined by the identity and localization of the proteins in the cell that are phosphorylated by cyclic AMP-dependent 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 neurotransmitter 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 sequence around the phosphorylation site(s) consists of two or more basic amino acids (arginine and/or lysine), followed by another amino acid immediately NH_2-terminal to the phosphorylated residue (Kemp et al., 1975; Kemp and Pearson, 1990).

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 neurophysiological phenomena. For example, injection of this enzyme into bag cell neurons from the mollusk *Aplysia* regulated the frequency of firing of action potentials, 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 regulation of a different type of K^+ channel (Castellucci et al., 1980, 1982; Siegelbaum et al., 1982). K^+ channels 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 photoreceptor cells in *Hermissenda* (Alkon et al., 1983), and 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). Regulation of ion channels by protein phosphorylation is further discussed in section V.B.

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b. CYCLIC GMP-DEPENDENT PROTEIN KINASE. Cyclic GMP-dependent protein kinase, which was initially found in invertebrates (Kuo and Greengard, 1970), is present in several mammalian tissues, including brain (Greengard and Kuo, 1970; Walter, 1981; Walter and Greengard, 1981). The brain enzyme, partially purified from the cerebellum (Takai et al., 1975), has properties similar to the lung and heart enzymes. Other isozymic forms found in intestine (de Jonge, 1981) and smooth muscle (Wolfe et al., 1989) have also been studied. The cyclic GMP-dependent protein kinase enzymes exist as homodimers, each subunit (molecular mass approximately 74 kDa) of which has two binding sites for cyclic GMP (Corbin et al., 1986) and one catalytic domain (for reviews, see Walter and Greengard, 1981; Lincoln and Corbin, 1983; Nairn and Greengard, 1983).

i. Regulation of activity. When cyclic GMP binds to the enzyme, a conformational change in the protein is induced, inhibitory domains are removed, and the catalytic domain can proceed to phosphorylate substrates (Lincoln et al., 1978). A variety of neurotransmitters, drugs, hormones, or increases in neuronal activity cause Ca^{2+}-dependent increases in the formation of cyclic GMP 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 conversion of arginine to citrulline, can increase the levels of cyclic GMP in brain (Böhme et al., 1984; Garthwaite et al., 1988; Bredt and Snyder, 1989; Wood et al., 1990). Inactivation of cyclic GMP-dependent protein kinase is caused by cyclic nucleotide phosphodiesterase-catalyzed hydrolysis of the cyclic nucleotide (Appleman et al., 1982; Strada et al., 1984; Beavo, 1988).

ii. Distribution in brain. Cyclic GMP-dependent protein kinase has a very uneven tissue distribution, with 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 in Purkinje cells (Schlichter et al., 1980; Lohmann et al., 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 throughout the cytosol in cell bodies, dendrites, axons, and axon terminals (De Camilli et al., 1984a). This is in agreement with the cytosolic distribution of this enzyme observed in most peripheral tissues (Lincoln and Corbin, 1983). Cyclic GMP-dependent protein kinase also appears to be present, albeit at lower levels, in 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 described (Ariano, 1983; Walaas et al., 1989b).

iii. Functional importance in nerve cells. Little is known about physiological substrates for cyclic GMP-dependent protein kinase in brain, although it appears that the enzyme has a much more narrow substrate specificity than does the cyclic AMP-dependent enzyme (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), has been well characterized (Aswad and Greengard, 1981a,b; Aitken et al., 1981). Under certain conditions, this phosphoprotein has been found to be active as a protein phosphatase inhibitor (Nairn et al., 1985b; A. C. Nairn, P. Simonelli, H. C. Li and P. Greengard, unpublished results; see also section III.A).

Intracellular injection of activated cyclic GMP-dependent protein kinase has been found to induce distinct 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 cerebral cortex, the enzyme induced increases in input resistance (Woody et al., 1986), an effect that mimicked some of the effects of acetylcholine and cyclic GMP on these cells (Stone et al., 1975; Woody et al., 1978; Swartz and Woody, 1979).

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). When such preparations were prelabeled with [^{32}P]orthophosphate, and subsequently subjected to K^+ depolarization, several proteins showed Ca^{2+}-dependent increases in levels of phosphorylation. Studies of broken cell preparations confirmed and extended these findings, because addition of Ca^{2+} ions to synaptosomal membranes increased the phosphorylation of several proteins (DeLorenzo, 1976; Schulman 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, 1979; O'Callaghan et al., 1980). Ca^{2+}- and calmodulin-dependent protein phosphorylation appears to be particularly important in brain (Schulman, 1988; Kennedy, 1989), with high levels of CaM kinase activity and a large number of brain-specific endogenous substrates being present (Walaas et al., 1983b,c).

a. CA^{2+}/CALMODULIN-DEPENDENT PROTEIN KINASE II. Following the observation that synaptosomal membranes contain Ca^{2+}-dependent protein phosphorylation systems, 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 substrates for cyclic AMP-dependent protein kinase in the

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nervous system (Johnson et al., 1971; Ueda and Greengard, 1977). Synapsin I can be phosphorylated by two distinct CaM kinases, CaM kinase I, which phosphorylates the same serine residue (site 1) as does cyclic AMP-dependent protein kinase in the NH_2-terminal "head" region of the protein, and CaM kinase II, which phosphorylates two serine residues (sites 2 and 3) in the COOH-terminal "tail" region of the protein (Huttner and Greengard, 1979; Huttner et al., 1981; Kennedy and 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).

CaM kinase II has been purified from rat brain and characterized by a number of investigators (Fukunaga et al., 1982; Bennett et al., 1983; Goldenring et al., 1983; Yamauchi and Fujisawa, 1983a; Schulman, 1984; McGuinness et al., 1985a). Purified CaM kinase II exhibits a broad substrate specificity, with synapsin I (sites 2 and 3) being the most efficient substrate tested. In addition, the MAPs, MAP-2 and tau factor, together with glycogen synthase, smooth muscle myosin light chain, tyrosine hydroxylase, calcineurin, myelin basic protein, ribosomal protein S6, and Ca^{2+}/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; 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).

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 isolated and characterized and their deduced amino acid sequences described (Bennett and Kennedy, 1987; Lin et al., 1987; Bulleit et al., 1988; Tobimatsu et al., 1988; Tobimatsu and Fujisawa, 1989). These studies showed that the enzyme is composed of major α-subunits of 54 kDa, together with β- and β'-subunits of 60 and 58 kDa, respectively, and γ- and δ-subunits of 59 and 60 kDa, respectively. Moreover, these subunits are the products of highly homologous transcription units, with the presence or absence of amino acid insertions at the COOH-terminal side of the calmodulin-binding domain accounting for the different sizes of the subunits (Schulman, 1988; Tobimatsu and Fujisawa, 1989). All subunits contain three domains, designated the catalytic protein kinase domain, the regulatory, calmodulin-binding domain, and the association domain (Schulman, 1988). All subunits can be autophosphorylated in a Ca^{2+}/calmodulin-dependent manner and can bind calmodulin and ATP (for examples, see McGuinness et al., 1985a).

The enzyme appears to be present in heteromeric or homomeric complexes containing 10 to 12 subunits (Bennett et al., 1983). Transcripts for the α- and β-subunits are primarily found in brain, whereas transcripts for the γ- and δ-subunits are present in a number of tissues (Tobimatsu and Fujisawa, 1989). Both the α- and β-subunits have been expressed in nonneuronal cells, and these studies have shown that the α-subunit, expressed alone, behaves identically with the holoenzyme with respect to aggregation, autophosphorylation, and ensuing calmodulin independence (Hanson et al., 1989; Yamauchi et al., 1989). In contrast, expression of the β-subunit alone led to an enzyme that did not aggregate, although autophosphorylation and the ensuing Ca^{2+}/calmodulin independence (see below) was also seen with this isozymic form (Yamauchi et al., 1989). Thus, both enzyme activity and modulatory properties appear to be inherent to the different subunits.

A number of CaM kinases prepared from tissues other 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 (Schulman 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^{2+}/calmodulin-dependent glycogen synthase kinase from skeletal muscle displays a substrate specificity identical 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 with apparent molecular masses of 59, 58, and 54 kDa, all of which cross-react with monoclonal antibodies prepared against CaM kinase II from rat forebrain (McGuinness et al., 1983). These various Ca^{2+}/calmodulin-dependent enzymes, therefore, appear to represent isozymic forms of CaM kinase II.

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 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, see Manalan and Klee, 1984). Recent studies have shown that autophosphorylation further modulates CaM kinase II. Ca^{2+}/calmodulin-induced activation leads to a rapid phosphorylation of threonine residues (Thr-286 in the α-subunit, Thr-287 in the β-subunit), and this leads to the enzyme becoming largely independent of Ca^{2+} 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 et al., 1987; Fukunaga et al., 1989; Waxham et al., 1989). Such autophosphorylation may prolong the activation of

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the enzyme and, thus, prolong the duration of the cellular response to a transient elevation of Ca^{2+}. However, the generation of the Ca^{2+}/calmodulin-independent form of the enzyme is reversed by the action of protein phosphatases (Saitoh et al., 1987; Shields et al., 1985), and in intact nerve terminals both the autophosphorylation of Thr-286 in the α-subunit and the generation of the Ca^{2+}/calmodulin-independent form of the enzyme were found 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 arachidonic acid and lipoxygenase derivatives can inhibit CaM kinase II both in vitro and in preparations containing isolated nerve terminals, suggesting a role for these second messengers in regulating this protein phosphorylation system in intact nerve cells (Piomelli et al., 1989).

ii. Distribution in brain. CaM kinase II is present 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 (Ouimet et al., 1984a; Erondu and Kennedy, 1985), but also being concentrated in certain populations 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 in the cerebellum, brain stem, and spinal cord (Walaas et al., 1983b,c). Moreover, the α- and β-subunits of the enzyme differ in their regional and cellular localizations (McGuinness et al., 1985a; Miller and Kennedy, 1985; Walaas et al., 1988b).

The subunits of the enzyme have been found to be present in postsynaptic density fractions, which are submembranous postsynaptic fibrous structures enriched in asymmetrical excitatory synapses in mammalian brain. Indeed, the α-subunit of the kinase is identical with the "major postsynaptic density protein" (Kelly and Cotman, 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 et al., 1985b) and the insoluble postsynaptic density structure appears intriguing. Although the regulation of 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 intrinsic postsynaptic density proteins are physiological substrates for CaM kinase II (Gurd, 1985) remains unclear. Therefore, the high levels and tight association of CaM kinase II with the postsynaptic density remain unexplained, and possible structural, nonenzymatic roles of the protein in this structure have been suggested (Kelly and Cotman, 1978; Rostas et al., 1986).

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 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., 1990), and introduction of the enzyme into transiently permeabilized synaptosomes from rat cerebral cortex (Nichols et al., 1990) indicate that depolarization-induced neurotransmitter release from nerve terminals is potentiated 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 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 postsynaptic compartments. Injection of peptide inhibitors of CaM kinase II into hippocampal pyramidal cells has been reputed to prevent certain neurophysiological responses (Malenka et al., 1989a,b; Malinow et al., 1989). 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 possible substrates for CaM kinase II. Nevertheless, the exact nature of the postsynaptic responses mediated by this enzyme is presently unknown.

b. CA^{2+}/CALMODULIN-DEPENDENT PROTEIN KINASE I. This enzyme has been purified to apparent homogeneity from bovine brain, using synapsin I (site 1) as substrate (Nairn and Greengard, 1987). At present, CaM kinase I 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 proteins that show extensive homologies to each other (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 tissues examined, suggesting that additional physiological substrates for the enzyme exist (Nairn and Greengard, 1987).

c. CA^{2+}/CALMODULIN-DEPENDENT PROTEIN KINASE III. This enzyme, which is highly enriched in pancreas and specifically phosphorylates a 100-kDa protein identified 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 ribosomal protein synthesis in vitro (Nairn and Palfrey, 1987). Because CaM kinase III appears to be rapidly regulated in a variety of cells and tissues (Haycock et al., 1988a; Palfrey et al., 1987; Mackie et al., 1989a) by neurotrans-

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mitters, neuropeptides, and hormones that can regulate the levels of intracellular Ca^{2+}, protein synthesis in these cells may be regulated by such extracellular stimuli. Moreover, nerve growth factor has been found to regulate not the activity but the levels of the enzyme in PC12 cells, a pheochromocytoma cell line with neuron-like properties, indicating that this enzyme may also be involved in long-term regulation of protein synthetic activity (Nairn et al., 1987).

d. MYOSIN LIGHT CHAIN KINASE. This enzyme has been purified from forebrain and has been found to have properties similar to those of the smooth muscle enzyme, including the specific phosphorylation of smooth muscle myosin light chain (Dabrowska and Hartshorne, 1978; Dabrowska et al., 1978; Hathaway et al., 1981; Bartelt et al., 1987). Such phosphorylation is believed to be a prerequisite for interaction between myosin and actin (Sellers and Adelstein, 1987), and the brain enzyme is probably involved in the same function in nerve cells. As mentioned above, CaM kinase II can also phosphorylate isolated myosin light chains as well as intact myosin (Tanaka et al., 1986). Given the enrichment of CaM kinase II in brain as compared to myosin light chain kinase, it is possible that myosin light chain phosphorylation in situ may be catalyzed by both enzymes (Edelman et al., 1985).

e. PHOSPHORYLASE KINASE. This enzyme has been identified in brain (Ozawa, 1973). The brain form of phosphorylase kinase, which appears to express certain immunological differences from the muscle enzyme and 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 kinase regulates glycogen breakdown in neurons, a process that has been shown to be enhanced by electrical stimulation (King et al., 1967).

3. Ca^{2+}/phospholipid-dependent protein kinases. Another type of Ca^{2+}-dependent protein phosphorylation 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). This protein phosphorylation system, which mediates effects of those Ca^{2+}-mobilizing hormones and neurotransmitters that act through increased phosphatidylinositol turnover (for examples, see Michell, 1975; Nishizuka, 1984; Berridge and Irvine, 1989), is present in brain in 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.

Protein kinase C was first purified from cerebellum as a cyclic nucleotide-independent protein kinase activity, which could be proteolytically activated by a Ca^{2+}-dependent protease (Inoue et al., 1977; Takai et al., 1977). It now appears that protein kinase C exists as a number of distinct isoenzymes, which exhibit slightly different properties (Coussens et al., 1986; Knopf et al., 1986; Huang et al., 1986; Jaken and Kiley, 1987; Woodgett and Hunter, 1987; Kikkawa et al., 1987; Akita et al., 1990; for review, see Nishizuka, 1988).One group of protein kinase C isoenzymes, termed group A and including types I, II, and III, is derived from genes termed γ, β, and α, respectively (Nishizuka, 1988; Huang, 1989). These enzymes have been purified from brain and other tissues (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 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 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 enzymes display distinct autophosphorylation sites and distinct immunological characteristics (Huang and Huang, 1986; Huang et al., 1986) but appear to have similar substrate specificities, which are different from those of both cyclic nucleotide-dependent and CaM kinases.

Another group of isoenzymes (group B), derived from genes designated δ, ϵ, and ζ (Ono et al., 1987), has apparently not yet been characterized in nervous tissue, despite their messenger RNAs being abundant in brain (Ono et al., 1989; Ohno et al., 1988), and little is known about their role in nervous system function.

a. REGULATION OF ACTIVITY. The group A isoforms of protein kinase C were found to be activated by the addition of membrane phospholipids (e.g., phosphatidylserine), Ca^{2+}, and low concentrations of unsaturated 1,2-diacylglycerols, which (under optimal conditions) were found to decrease the apparent activation constant for Ca^{2+} 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 diacylglycerol (for review, see Bell, 1986; Woodgett et al., 1987; Nishizuka, 1986, 1988; Huang, 1989). In this way, diacylglycerol, generated from the receptor-induced breakdown either of polyphosphoinositides (Downes, 1982; Berridge, 1987; Fisher and Agranoff, 1987), of phosphatidylcholine (Billah and Anthes, 1990), or of inositol-containing glycolipids (Saltiel et al., 1986), can act as a second messenger together with Ca^{2+} in activating these 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 derivatives (Sekiguchi et al., 1987; for review, see Huang, 1989). Moreover, this group of protein kinase C isoen-

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zymes has been found to represent the major receptor for the tumor-promoting phorbol esters, which apparently can substitute for diacylglycerol and induce a prolonged activation of the enzyme (Castagna et al., 1982; Kikkawa et al., 1983; Parker et al., 1986; Baraban, 1987).

The group B enzymes, which are less well characterized, also appear to be regulated by phospholipids and, in some cases, diacylglycerol [depending on the type of substrate used to assay the enzyme (Ono et al., 1989)] but to be independent of Ca^{2+} (Nishizuka, 1988; Huang, 1989). For example, the translational products of the ϵ- and δ-genes, when expressed in COS-7 cells, did not show an absolute requirement for Ca^{2+}, diacylglycerol, and phospholipids (Ono et al., 1987, 1989), and the translational product of the ζ 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 ϵ gene, when expressed by the baculovirus system, appears to be regulated by phospholipids and, possibly, diacylglycerol, but to be insensitive to Ca^{2+} (Schaap and Parker, 1990).

b. DISTRIBUTION IN BRAIN. The group A isoenzymes have broad species, tissue, and cellular distributions, and 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 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 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 phorbol ester binding in the CNS showed a comparable enzyme distribution (Worley et al., 1986). Certain cell types, such as Purkinje cells and striatonigral cells, may have particularly high concentrations of the enzyme (Worley et al., 1986; Walaas et al., 1989f).

Recent immunochemical, immunocytochemical, and in situ hybridization studies have indicated that different protein kinase C isoenzymes have widespread, but distinct, regional and cellular distributions (Huang et al., 1987, 1988; Mochly-Rosen et al., 1987; Kitano et al., 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 III being predominantly cytosolic under unstimulated conditions (for examples, see Kitano et al., 1987; Kose et al., 1988).

c. FUNCTIONAL IMPORTANCE IN NERVE CELLS. Protein kinase C appears to be involved in a number of physiological and pathological functions (Nishizuka, 1986; Woodgett et al., 1987). A variety of brain proteins, including myelin basic protein (Turner et al., 1982, 1984), MAP-2 (Akiyama et al., 1986; Walaas and Nairn, 1989), tyrosine hydroxylase (Albert et al., 1984), the growth-associated protein GAP-43 (Aloyo et al., 1983; Coggins and Zwiers, 1989; Nielander et al., 1990), the MARCKS protein (Wu et al., 1982) (see below), and several other 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 good substrates for the enzyme (for examples, see Kikkawa 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 functions (Huang, 1989; Marais et al., 1990). In particular, the ϵ-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 substrates for the ϵ enzyme (Schaap and Parker, 1990).

Analysis of intact nerve terminal preparations has shown that protein kinase C-catalyzed protein phosphorylation is activated by depolarization-induced Ca^{2+} 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 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 demonstrated in brain slices containing intact neurons (Yip and Kelly, 1990).

Extensive evidence indicates that activators of protein 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, 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 neurons, 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+}-conductances in certain *Helix* neurons (Hammond et al., 1987), while a voltage-sensitive Cl^- 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 elicits (Hu et al., 1987), whereas injection of a peptide inhibitor of the kinase blocks (Hvalby et al., in preparation), several features of LTP. The phenomenon of LTP has been used as a model for the early phases of learning and memory in mammalian brain (Nicoll et al., 1988; Malenka et al., 1989b). These few examples, some of which will be discussed further below, suffice to indicate that this protein phosphorylation system is involved in the regulation of a variety of neurophysiological phenomena.

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C. Second Messenger-independent Protein Kinases

Mammalian brain contains a variety of other protein 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 their involvement in specific neuronal functions remains to be established. Therefore, although some of them are highly enriched in nervous tissue, indicating that they are functionally important, only a few will be briefly described.

Casein kinase I and *casein kinase II* are widespread protein kinases that preferentially phosphorylate acidic proteins like casein and phosvitin in vitro (Hathaway and Traugh, 1982). Recent studies indicate that DARPP-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 of this protein (Girault et al., 1989a; 1990). Casein kinase II, which can be activated by insulin both in peripheral tissues (Sommercorn et al., 1987) and in brain (Zorn et al., 1989), may, therefore, be involved in specific regulatory functions in DARPP-32-containing nerve cells.

Glycogen synthase kinase 3 has recently been found to catalyze the *in vitro* phosphorylation of the neuronal cell adhesion molecule N-CAM, suggesting that it may be involved in regulation of cell-cell interactions in the CNS (Mackie et al., 1989b).

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 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; Sternberger and Sternberger, 1983; Matus, 1988a). However, the physiological importance of neurofilament phosphorylation is not well understood (see section VI.D.1).

Myelin basic protein kinase has been reported as a protein kinase activity independent of the known second messengers, highly enriched in myelin fractions and very active toward myelin basic protein (Miyamoto, 1975, 1976). However, the relationship of this enzyme to proteolytically activated fragments of protein kinase C, which phosphorylates myelin basic protein in vitro and in vivo (Turner et al., 1982, 1984), is not known, and the functional effects of phosphorylation of myelin basic protein are also unclear (for examples, see Agrawal et al., 1982).

Pyruvate dehydrogenase kinase, a mitochondrial enzyme, specifically phosphorylates and inactivates the α-subunit of pyruvate dehydrogenase (Reed et al., 1985; Reed and Yeaman, 1987). This kinase, which appears to 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 et al., 1979, 1981), the latter effect presumably being caused by metabolic changes induced by the electrical stimulation.

D. Tyrosine-specific Protein Kinases

In addition to protein serine and threonine kinases, all tissues including brain contain another class of protein kinase that is probably of great functional importance (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 which is represented by *protooncogene products* and the other by *growth factor receptors*.

1. Protooncogene products. The best known of the brain protooncogene products is pp60$^{c\text{-}src}$, the 60-kDa gene product of the protooncogene c-*src* which is the cellular homolog of v-*src*, the transforming gene of the Rous 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 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 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 represents the major tyrosine kinase in synaptic vesicles purified from adult rat brain (Pang et al., 1988a). The neuron-specific form of the enzyme, which has a six-amino acid 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., 1990). These data indicate that pp60$^{c\text{-}src}$ may be involved in both pre- and postsynaptic functions in mature neurons. The activity of pp60$^{c\text{-}src}$ appears to be regulated by enzyme phosphorylation (for examples, see Okada and Nakagawa, 1989), with phosphorylation on tyrosine residues being strongly inhibitory.

The endogenous substrates for this enzyme in brain and its role(s) in neuronal function are not yet known. The enrichment of the c-*src* gene product in nerve terminals and somata of postmitotic neurons suggests that the enzyme may be involved in pleiotropic functions not restricted to growth and proliferation. The enrichment of the enzyme in synaptic vesicles and the prominent tyrosine phosphorylation obtained in synaptic vesicle preparations of both synaptophysin (Pang et al., 1988a,b; Barnekow et al., 1990) and p29 (Baumert et al., 1990), two intrinsic synaptic vesicle membrane proteins (for review, see De Camilli and Jahn, 1990), indicate that

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synaptic vesicle functions may be regulated by tyrosine phosphorylation. In fact, it has recently been found that the c-*src* protein is largely responsible for the endogenous phosphorylation of synaptophysin on tyrosine residues (Pang et al., 1988a; Barnekow et al., 1990).

In other studies, a link between this class of enzymes and activation of membrane receptors has been obtained. A pp60$^{c\text{-}src}$-related tyrosine kinase termed pp56^{lck}, present in T-lymphocytes (Barber et al., 1989), has been found to be activated by the CD4 or CD8 transmembrane proteins involved in transmembrane signaling in these cells (Veillette et al., 1989). Activation of these signaling systems in intact T-lymphocytes apparently induces pp56^{lck}-catalyzed tyrosine phosphorylation of a subunit 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 the membrane protein CD45, a tyrosine phosphatase (section III.B), is able to activate pp56^{lck} (Mustelin et al., 1989). Whether pp60$^{c\text{-}src}$-related proteins are involved in similar regulation mechanisms in neural cells is not known.

2. *Growth factor receptors.* The other class of tyrosine-specific protein kinases is intrinsic to receptors for a 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 tyrosine 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 the signal transduction pathways used by the relevant first messengers (for examples, see Rosen, 1987; Yarden and Ullrich, 1988) (see further discussion in section V.A.3).

III. Phosphoprotein Phosphatases in Brain

A. Serine/Threonine-specific Protein Phosphatases

Although protein phosphorylation systems in the brain appear in many cases to be regulated by activation of protein kinases, protein phosphatases also constitute targets for regulatory agents. The protein phosphatases involved in cellular regulation that dephosphorylate serine and/or threonine residues have been divided into two major types and further subclassified into four enzymatic activities (table 5), all of which have been found in brain (Ingebritsen and Cohen, 1983a,b; Ingebritsen et al., 1983). More recent evidence, mainly gained from molecular cloning studies, indicates that a large number of isozymic forms of these enzymes exist (for reviews, see Cohen, 1989; Cohen and Cohen, 1989; Shenolikar and Nairn, 1991; Guerini et al., 1990). However, the basic classification scheme (Ingebritsen and Cohen, 1983a,b) still appears valid and greatly simplifies a discussion of the properties of the main phosphatase activities found in brain. For more detailed information about protein

TABLE 5
*Serine/threonine-specific protein phosphatases in brain**

Enzyme	Regulator	Substrate specificity
Protein phosphatase-1	Inhibitor-1, inhibitor-2, DARPP-32	Broad
Protein phosphatase-2A	Unknown, (G-substrate)	Broad
Protein phosphatase-2B	Ca^{2+}/calmodulin	Narrow
Protein phosphatase-2C	Mg^{2+}	Broad

* The major classes of protein phosphatase activities in neural and peripheral tissues are presented. Data compiled from Ingebritsen and Cohen (1983a,b) and Shenolikar and Nairn (1991). Further details are described in the text, section III.

phosphatases, particularly in nonneuronal tissues, the reader is referred to several recent reviews of this topic for more detail (Li, 1982; Yang, 1986; Cohen, 1989; Cohen and Cohen, 1989; Shenolikar and Nairn, 1991).

Type 1 phosphatase (*protein phosphatase-1*) selectively dephosphorylates the β-subunit of phosphorylase kinase and is inhibited by certain heat-stable inhibitor proteins, and type 2 phosphatases (*protein phosphatases -2A, -2B, and -2C*) selectively dephosphorylate the α-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 phosphatases 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 pyruvate dehydrogenase phosphatase, which is activated by Ca^{2+} (Reed et al., 1985), and the branched chain α-keto acid dehydrogenase phosphatase (Damuni and Reed, 1987), which appears to be regulated through the binding of a heat-stable inhibitor protein (Reed et 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 (Gordon et al., 1979; Miyamoto and Kakiuchi, 1975; McNamara and Appel, 1977; Teichberg and Changeux, 1977; Coughlin et al., 1980). The identities of the latter types of phosphatases are not known.

The presence of these enzymes in brain indicates their physiological importance in dephosphorylating endogenous phosphoproteins. Phosphatase-1, -2A, and -2C all have relatively broad substrate specificities, whereas that of phosphatase -2B is more restricted (Shenolikar and Nairn, 1991). Despite this, protein phosphatase-2B, also known as calcineurin (Stewart et al., 1982; Yang 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 (King et al., 1984) It is, therefore, of considerable interest that the phosphorylated forms of phosphatase

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inhibitor-1 and of DARPP-32 are potent inhibitors of protein phosphatase-1 (see below). This suggests that phosphatase-2B indirectly regulates the activity of phosphatase-1, thereby extending its influence to phosphoproteins which are not direct substrates for phosphatase-2B itself.

1. Regulation of activity. Phosphatases-1, -2A, and -2B appear to be targets for regulation in brain. Regulation of type-1 phosphatase appears particularly interesting. Although little is known about phosphatase inhibitor-2 in neural tissues (Shenolikar and Nairn, 1991), brain 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 protein phosphatase-1 (Hemmings et al., 1984a, 1990). Phosphatase inhibitor-1 and DARPP-32 share partial 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., 1988). Phosphatase inhibitor-1 is also present in many peripheral, nonneuronal tissues (for examples, see Elbrecht et al., submitted). In contrast, DARPP-32 appears generally to be restricted to neuronal and peripheral cells that contain the D1 subclass of dopamine receptor, such as the medium-sized spiny neurons of the neostriatum (Ouimet 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 of the effects of dopamine acting on dopamine D1 receptors (for review, see Walaas et al., 1986a; Hemmings et al., 1987a,b,c).

Characterization of the type-2 phosphatases has shown that phosphatase-2A does not require divalent cations, phosphatase-2B requires Ca^{2+}/calmodulin, and phosphatase-2C requires Mg^{2+} for activity (Ingebritsen and Cohen, 1983a,b; Klee and Cohen, 1988; Shenolikar 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 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, 1981a,b; Aitken et al., 1981; Hemmings et al., 1984b,c), including being a good substrate for protein phosphatase-2B (King et al., 1984). However, in contrast 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 (A. C. Nairn, P. Simonelli, H. C. Li and P. Greengard, unpublished results). Therefore, neuronal cells express a number of distinct protein phosphatase inhibitors, some of which appear to be neuron specific. It appears probable that additional phosphatase inhibitors will be found in brain.

The data summarized above indicate that the activities of certain phosphatases in brain are regulated, directly or indirectly, by second messengers such as cyclic AMP, cyclic GMP, and Ca^{2+} and that these regulatory systems have distinct cellular and regional distributions in the brain. Indeed, recent data indicate that certain neurotransmitters may produce some of their physiological effects in brain by regulating protein phosphatase inhibitors in specific cells, 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 of the NMDA type of glutamate receptor has been found to decrease (Halpain et al., 1990), phosphorylation of DARPP-32 in situ. These changes occurred on that phosphorylation site that is preferentially phosphorylated by cyclic AMP-dependent protein kinase and dephosphorylated by phosphatase-2B in vitro and that determines the potency of DARPP-32 as an inhibitor of phosphatase-1 (Hemmings et al., 1984a,c, 1990). Therefore, the neurotransmitters dopamine and glutamate may achieve some of their actions in these cells through DARPP-32 phosphorylation and dephosphorylation and, thus, through regulation of the activity of protein phosphatase-1. (DARPP-32 is further discussed in section V. C, and NMDA-induced dephosphorylation of MAP-2 is discussed in section VI.D.1.)

B. Tyrosine-specific Protein Phosphatases

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 one study, seven forms of tyrosine-specific phosphatases were separated from bovine brain extracts and partially characterized (Jones et al., 1989). These activities could all be distinguished from the major serine/threonine phosphatases by their relative sensitivity to vanadate, NaF, inorganic phosphate, and the heat-stable inhibitor proteins described above (Jones et al., 1989). Two heat-stable tyrosine phosphatase inhibitor proteins were also found in the brain extracts, both of which were distinct from the heat-stable inhibitor proteins regulating the type-1 serine/threonine phosphatases (Ingebritsen, 1989).

One of the brain protein tyrosine phosphatases, designated PTP-5 (Jones et al., 1989), displayed a number of similarities with the major phosphotyrosine protein phosphatase previously purified from both soluble and particulate fractions from human placenta (Tonks et al., 1988b). The latter enzyme has recently been found to have similarities in primary structure with the intracellular domain of the CD45 transmembrane glycoprotein(s), previously shown to be enriched in cells of he-

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matopoietic lineages (Charbonneau et al., 1988; Tonks et al., 1988a). CD45 is known to regulate signal transduction and lymphocyte activation by specific association with lymphocyte receptors (Ledbetter et al., 1989). CD45 may, therefore, represent a prototype of membrane-associated, receptor-linked tyrosine phosphatases that could mediate or modulate signal transduction by 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 epidermal growth factor receptor (Yarden and Ullrich, 1988; Carpenter and Cohen, 1990). Putative phosphorylation sites for both protein kinase C and casein kinase II are also present in the intracellular domain of both CD45 and the epidermal growth factor receptor (Hunter et al., 1984; Cochet et al., 1984; Davis and Czech, 1986; Tonks et al., 1989). Hence, phosphotyrosine protein phosphatases such as CD45 may be regulated directly by extracellular ligands and, indirectly, by phosphorylation catalyzed by protein kinase C or casein kinase II. This would represent a parallel to the growth factor receptor-associated tyrosine-specific protein kinases discussed above. Whether such membrane-bound tyrosine phosphatases exist in brain is not yet known.

IV. Phosphoproteins and Presynaptic Function

Many physiological processes in brain are regulated by protein phosphorylation. These include neuronal excitability, receptor-mediated signal transduction, neurotransmitter biosynthesis and release, regulation of intermediary metabolism, and regulation of neuronal growth, differentiation, and morphology (for review, see Nestler and Greengard, 1984). In this section, examples of major 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 in section V.

A. Regulation of Neurotransmitter Synthesis and Release

1. Tyrosine hydroxylase and regulation of neurotransmitter synthesis. The activity of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of the catecholamine neurotransmitters (dopamine, noradrenaline, adrenaline), is subject to regulation by multiple 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 be activated (Morgenroth et al., 1975) and directly phosphorylated (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 additional, uncharacterized enzymes (Albert et al., 1984; 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 to induce multisite phosphorylation and activation of the enzyme (for examples, see Haycock et al., 1982; Nose et al., 1985; Tachikawa et al., 1986). Analysis of the mechanisms involved in intact cells indicated that four serine 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 a regulatory domain which, in the dephosphorylated state, inhibits the catalytic domain; phosphorylation of the NH_2-terminal region then relieves inhibitory constraints (Haycock, 1990).

Comparisons between the results obtained following in situ phosphorylation in PC12 cells and that obtained 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 enzyme (Albert et al., 1984; Campbell et al., 1986; Griffith 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, 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 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 hydroxylase have also been found to be phosphorylated in situ, but the kinase(s) responsible for the latter reactions are presently less well characterized (see Haycock, 1990). Thus, 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 receptor types present and may be different in distinct cells and tissues.

Less extensive evidence indicates that other enzymes involved in neurotransmitter biosynthesis, such as tryptophan hydroxylase and phenylalanine hydroxylase, are 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). It may be expected that other neurotransmitter-synthesizing enzymes are also regulated by protein phosphorylation.

2. Synapsins and regulation of neurotransmitter release. Ca^{2+}-dependent transmitter release from nerve terminals is subject to multiple regulatory mechanisms in both 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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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). 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^{2+} influx (Llinás et al., 1985, in press;). Recent studies have shown similar effects following loading of permeabilized synaptosomes from rat brain with this kinase (Nichols et al., 1990). The release of neurotransmitters is thus one of the neuronal functions for which there is particularly strong evidence for regulation by protein phosphorylation.

Several studies of protein phosphorylation in nerve terminals have been performed (for examples, see Krueger et al., 1977; Robinson and Dunkley, 1983; Dunkley et al., 1986; Wang et al., 1988). Studies of intact synaptosome preparations prelabeled with radioactive inorganic phosphate show that both depolarization-induced Ca^{2+} influx and addition of the tumor-promoting phorbol 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 depolarization-induced, Ca^{2+}-dependent protein phosphorylation seen in such isolated nerve terminals comprise six major phosphoproteins (table 6). These include four synaptic vesicle-associated proteins, the synapsins, which are substrates for CaM kinases and which are described in this 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.

The *synapsins* are a family of neuron-specific synaptic vesicle-associated proteins (for reviews, see De Camilli and Greengard, 1986; De Camilli et al., 1990), which in mammalian brain consist of synapsin Ia and synapsin Ib (collectively referred to as synapsin I and previously termed proteins Ia and Ib, respectively) and synapsin IIa and synapsin IIb (collectively referred to as synapsin II and previously termed proteins IIIa and IIIb, respectively). All of the synapsins are major substrates for cyclic AMP-regulated and Ca^{2+}/calmodulin-regulated protein kinases (Ueda et al., 1973; Ueda and Greengard, 1977; Forn and Greengard, 1978; Huttner and Greengard, 1979; Kennedy and Greengard, 1981; Walaas et al., 1983c; Nairn and Greengard, 1987). Cyclic AMP-dependent protein kinase and CaM kinase I both phosphorylate a single serine residue (site 1) in the collagenase-resistant "head" region of both synapsin I and synapsin II. CaM kinase II, in contrast, phosphorylates a pair of serine residues in the collagenase-sensitive "tail" region of synapsin I (sites 2 and 3) (Ueda and Greengard, 1977; Huttner and Greengard, 1979; Huttner et al., 1981) but does not phosphorylate synapsin II (Südhof et al., 1989).

A variety of physiological and pharmacological manipulations of intact nerve cell preparations produce increases in the state of phosphorylation of synapsin I. Such manipulations include electrical stimulation of intact nerve fibers (Nestler and Greengard, 1982a,b; Tsou and Greengard, 1982), depolarization of isolated nerve 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 intact animals (Strömbom et al., 1979), and application of neurotransmitter candidates such as serotonin (Dolphin and Greengard, 1981a,b), noradrenaline (Mobley and Greengard, 1985), and dopamine (Nestler and Greengard, 1980; Treiman and Greengard, 1985; Walaas et al., 1989e) to peripheral nervous tissue or slices from defined brain regions. In each of these systems, treatments that are known to increase the levels of cyclic AMP in the tissue have been found to increase 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 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+}-dependent phosphorylation of synapsin I also caused increased neurotransmitter release (Llinás et al., 1985, in press; Nichols et al., 1990).

Analysis of the nucleotide sequences of cloned complementary DNA for the four synapsins has revealed that synapsins Ia and Ib display extensive sequence homology, as do synapsins IIa and IIb. Synapsins I and II also have common domains, composed of similar NH_2-terminal 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-terminal regions: synapsins Ia and Ib, but not synapsins IIa or IIb, have long, extremely basic "tails" which contain the serine residues comprising phosphorylation sites 2 and 3 (Südhof et al., 1989).

Synapsins Ia, Ib, IIa, and IIb are all enriched in a 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 nerve terminals (Südhof et al., 1989; E. Mugnaini, personal communication). For example, the posterior pituitary and olfactory bulb contain relatively less of synapsin IIb than do most CNS regions (Walaas et al., 1988a). Moreover, all mossy fiber terminals of the hippocampal granule cells contain all four synapsins, whereas Purkinje cell axon terminals do not contain detectable amounts of synapsin IIa (Südhof et al., 1989). In the vertebrate retina, further differences have been observed. In this tissue, two types of vesicle-containing synapses are pres-

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TABLE 6

*Characteristics of proteins phosphorylated in isolated nerve terminals by depolarization-induced Ca^{2+} influx**

	Phosphoproteins					
	Synapsins				MARCKS	GAP-43
	Ia	Ib	IIa	IIb		
Molecular properties						
Molecular mass (sodium dodecyl sulfate-polyacrylamide gel electrophoresis)	86 kDa	80 kDa	74 kDa	55 kDa	68–87 kDa	43–57 kDa
Molecular mass (composition)	74 kDa	70 kDa	63.3 kDa	52.3 kDa	31.9 kDa	24.7 kDa
Amino acid residues	704	668	586	479	335	239
Charge (isoelectric focusing)	Basic	Basic	Neutral	Neutral	Acidic	Acidic
Calmodulin binding	−	−	−	−	+	+
Salt extractable	+	+	+	+	−	−
Hydrophobic domains	+	+	+	+	−	−
Fatty acid acylated	−	−	−	−	Myristate	Palmitate
Substrate for						
CaM kinase I	+	+	+	+	−	−
CaM kinase II	+	+	−	−	−	−
Protein kinase C	−	−	−	−	+	+
Localization						
Neuron specific	+	+	+	+	−	+
Growth cone enriched	−	−	−	−	+	+
Synaptic vesicle associated	+	+	+	+	−	−
Plasma membrane associated	−	−	−	−	+	+
Cytosolic	−	−	−	−	+	−
Actin binding	+	+	+	+	+	(+)

* Summary of main properties of the major, Ca^{2+}-dependent phosphoproteins found in isolated nerve terminal preparations. Data compiled 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. (1985), Ouimet et al. (1990), Liu and Storm (1990).

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 synapses differed in their content of synapsins, with only conventional synapses containing these proteins. 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 specifically enriched in a subset of amacrine nerve terminals 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 conventional presynaptic terminals (Mandell et al., 1990).

Considerable evidence indicates that the synapsins are involved in regulation of neurotransmitter release. Thus, 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., in press;). Similar observations have been reported for the goldfish Mauthner cell (Hackett et al., 1990). The cell biological basis for such regulation of neurotransmitter release by synapsin I and CaM kinase II has been investigated in some detail.

The synapsins appear to be associated with the external surface of small, electron-lucent synaptic vesicles, i.e., those vesicles that contain classical, nonpeptide neurotransmitters (De Camilli et al., 1983b, 1990). Synapsin I is bound to a specific, high-affinity saturable site on these synaptic vesicles through its tail region, and the central hydrophobic domain appears to be partly buried in the lipid environment of the vesicle membrane (Huttner et al., 1983; Schiebler et al., 1986; Bähler et al., 1989; 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; Schiebler et al., 1986). Thus, the interaction between synapsin I and synaptic vesicles may be regulated by CaM kinase II.

Synapsin I also interacts with cytoskeletal elements such as actin, microtubules, and spectrin in vitro (Bähler and Greengard, 1987; Bähler et al., 1989; Bennett et al., 1985; Goldenring et al., 1986; Petrucci and Morrow, 1987; Steiner et al., 1987). In fact, dephosphosynapsin I causes the bundling of F-actin (Bähler and Greengard, 1987; Petrucci and Morrow, 1987). Evidence indicates that synapsin I contains two binding sites for actin, that CaM kinase II-catalyzed phosphorylation of the protein inhibits its actin binding to one of these sites, and that this phosphorylation, therefore, prevents F-actin bundling

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from taking place (Bähler and Greengard, 1987; Petrucci and Morrow, 1987; Bähler et al., 1989).

It has been proposed that a tertiary complex, comprised 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 of this complex would allow vesicles to move from such a reserve pool to a releasable pool. Such a disruption could be achieved either through a decrease in the interaction between synapsin I and synaptic vesicle or through a decrease in the interaction between synapsin I and actin. Computer modeling of synapsin I binding to synaptic vesicles and F-actin, based upon the experimentally determined binding constants, indicates that dissociation of a synapsin I/synaptic vesicle binary complex from actin could account for the severing of the tertiary complex (Benfenati et al., 1991).

Synapsin II is also a major substrate for Ca^{2+}-dependent protein phosphorylation in nerve terminals (Wang et al., 1988). Synapsin II can be phosphorylated on that serine residue that corresponds to site 1 in synapsin I, and this reaction can be catalyzed by either cyclic AMP-dependent protein kinase or CaM kinase I (Huang et al., 1982; Browning et al., 1987; Nairn and Greengard, 1987). Synapsin II can also be phosphorylated in intact cells in response to any of several neurotransmitters and stimuli that increase cyclic AMP or Ca^{2+} levels in nerve terminals (Forn and Greengard, 1978; Tsou and Greengard, 1982; Haycock et al., 1988b; Wang et al., 1988; Walaas et al., 1989e).

Studies in which recombinant DNA technology was used have indicated that synapsin II can bind to a protein in small synaptic vesicles through a domain located close to the NH_2-terminal region, although the extreme NH_2 terminus appears unnecessary for such binding (Thiel et al., 1990). Because the region of synapsin II that binds to synaptic vesicles is common to synapsins I and II, it seems likely that the binding observed with synapsin II also applies to synapsin I.

Much less is known about the possible functions of synapsin II than of synapsin I. In view of the structural similarities (common domains), as well as the structural differences (variable domains), between synapsin I and synapsin II, it will be of great interest to determine which functions are held in common and which functions are unique to these two subclasses of synaptic vesicle-associated proteins.

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 protein kinase C (Wu et al., 1982; Wang et al., 1988). The phosphorylation of this protein has been found to correlate qualitatively with the phorbol ester-induced increase in release of transmitter from such synaptosomes (Nichols et al., 1987). However, this protein, which recently has been purified to homogeneity 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 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 tissues (Rozengurt et al., 1983; Albert et al., 1986; Blackshear et al., 1986).

Analysis of the biochemical properties of the protein 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 electrophoresis systems (Blackshear et al., 1986; Aderem et al., 1988). The protein contains a high proportion of alanine, it 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 residues (Stumpo et al., 1989; Graff et al., 1989a), whereas other kinases appear ineffective both in vitro and in situ (Walaas 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 (Rozengurt et al., 1983; Blackshear et al., 1986). In rat brain, the protein is enriched in both synaptosomal membranes and cytosol (Albert et al., 1986). The subcellular distribution of the protein appears to be determined by its phosphorylation state, because protein kinase C-catalyzed phosphorylation was able both to release the protein from synaptosomal membranes in vitro and to translocate the protein from membranes to cytosol in intact synaptosomes (Wang et al., 1989). The deduced primary structure of the protein does not show any hydrophobic domains (Stumpo et al., 1989). Therefore, the membrane association of the protein is believed to be caused by fatty acid acylation of the protein with myristic acid, an acylation that has been demonstrated in macrophages and muscle cells (Aderem et al., 1988; James and Olson, 1989). Finally, the protein appears to be able to bind calmodulin, and this binding can be 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 cellular release mechanisms, is unknown. Given the ubiquitous presence of this protein in both neuronal and nonneuronal cells, an involvement in widespread functions not restricted to nerve terminals is to be expected. Recent ultrastructural immunocytochemical studies of rat brain indicate that the protein is highly

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enriched in both dendrites and axons of certain neurons and in glial cells (Ouimet et al., 1990). In these cell types, 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 protein could be involved in both pre- and postsynaptic functions.

In other studies, MARCKS has been observed to be able to bind actin and to be associated with membrane-bound actin filaments associated with focal adhesion plaques at the plasma membrane in nonstimulated cultured neutrophils and macrophages (Rosen et al., 1990). Following protein kinase C-catalyzed phosphorylation, the actin-MARCKS complex was released from these membrane plaques (Rosen et al., in preparation). These data support the possibility that MARCKS may be functionally involved in regulation of cytoskeleton-plasma membrane interactions.

4. GAP-43 (B-50, F1, pp46, p57, neuromodulin). The other major protein phosphorylated by Ca^{2+} influx or protein kinase C activators in nerve terminals (Wang et al., 1988; Dekker et al., 1990) is a protein that, during sodium dodecyl sulfate-polyacrylamide gel electrophoresis, usually displays an approximate molecular mass of 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 protein, which has been extensively characterized, represents a neuron-specific (Kristjansson et al., 1982), membrane-associated phosphoprotein whose expression is greatly 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 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 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 24,000, which contrasts with the apparent molecular mass of 43 to 57 kDa observed on various sodium dodecyl sulfate-polyacrylamide gel electrophoresis systems (Basi et al., 1987; Benowitz et al., 1987; Karns et al., 1987; Kosik et al., 1988). Moreover, the protein can be phosphorylated 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 protein during subcellular fractionation (Mahler et al., 1982), the deduced primary structure does not contain any hydrophobic domains (for examples, see Basi et al., 1987; Karns et al., 1987; Wakim et al., 1987). Instead, fatty acid acylation of the protein with palmitic acid (Skene and Virag, 1989) appears to be at least partly responsible for the membrane localization of GAP-43. Other studies have indicated a tight association of GAP-43 with actin-rich submembranous cytoskeleton structures in neurons (Meiri and Gordon-Weeks, 1990; Moss et al., 1990).

Recent comparison of primary structures has shown that GAP-43 is identical with p57 or neuromodulin, a neuronal protein that has the unusual property of binding calmodulin with high affinity in the absence of Ca^{2+} (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 between the two proteins (Table 6), GAP-43 does not appear to have any sequence homology with the MARCKS protein.

The functions of GAP-43 remain essentially unknown. Localization studies of this neuron-specific protein have indicated that it is specifically enriched in axons and presynaptic terminals, and it has not been found in 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 protein may be involved in additions to rapidly growing 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). 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 modulated by GAP-43 (Strittmatter et al., 1990). Phosphorylation of GAP-43 appears to be correlated with neurotransmitter release in rat hippocampal slices (Dekker et al., 1989b), whereas introduction of antibodies against GAP-43 into permeabilized nerve terminals may decrease transmitter release (Dekker et al., 1989a).

A number of studies have indicated that ^{32}P labeling of GAP-43 during in vitro phosphorylation of membrane fractions with [γ-^{32}P]ATP is increased in preparations 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 related to the changes in synaptic function 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 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 enriched in neurons or nerve terminals (see above),

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also incorporates more ^{32}P during in vitro phosphorylation following LTP (Nelson et al., 1989) would suggest that changes in protein kinase C activity may be responsible. The functional importance of this phenomenon is not understood (see section V.D for further discussion of LTP).

B. Use of Nerve Terminal Phosphoproteins to Study Presynaptic Receptors

Use of the phosphoproteins described above has allowed examination of presynaptic receptors coupled to distinct second messenger-regulated protein phosphorylation 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 and fibers can be used to characterize presynaptic receptors capable of activating cyclic AMP-dependent protein kinase, CaM kinase I or CaM kinase II. This approach has been used to demonstrate presynaptic receptors for serotonin on nerve fibers in the facial motor nucleus (Dolphin and Greengard, 1981a,b), β-adrenergic receptors on a large number of nerve terminals in the neocortex (Mobley and Greengard, 1985), dopamine D1 and D2 receptors on hypothalamopituitary fibers in the neurohypophysis (Tsou and Greengard, 1982; Treiman and Greengard, 1985), and dopamine D1 receptors on nerve terminals in the superior cervical ganglion (Nestler and Greengard, 1980, 1982b), the neostriatum, and the substantia nigra (Walaas et al., 1989e).

The MARCKS protein appears to be widely, but unevenly, 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, when studied in such preparations, can be used to demonstrate the presence of presynaptic α_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 exclusive presynaptic localization of GAP-43 (Gispen et al., 1985), this phosphoprotein should also prove useful for analysis of presynaptic receptors linked to protein kinase C activation (for examples, see van Hooff et al., 1989).

V. Phosphoproteins and Postsynaptic Function

It is now abundantly clear that most, if not all, neurotransmitter receptors and ion channels are regulated by phosphorylation. Because most studies of receptors and ion channels have been carried out on neuronal somata, this topic is discussed in this section. However, it should be kept in mind that the principles elucidated by the study of cell body receptors and ion channels are probably generally applicable to receptors and ion channels on dendrites and axon terminals.

A. Regulation of Receptor Function

Three general classes of plasma membrane receptors have so far been defined in brain (table 7), all of which appear to be associated with protein phosphorylation 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; 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 receptors that transduce information through activation of tyrosine-specific protein kinase activity, which often is an integral part of the receptor itself (Yarden and Ullrich, 1988). Several receptors that are located in the cell nucleus, and which are regulated by phosphorylation, will also be mentioned.

1. Ion channel-coupled receptors. Recent studies have demonstrated that some major ion channel-coupled receptors (i.e., the $GABA_A$, glycine, nicotinic acetylcholine, and, possibly, different types of glutamate receptors) display considerable similarities in their structures and membrane topologies and appear to belong to the same gene superfamily of chemically gated ion channels (Schofield 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), the regulation of the nicotinic acetylcholine receptor and the $GABA_A$ receptor by phosphorylation has been most thoroughly studied. We will, therefore, restrict our discussion to these receptor types.

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, termed α, β, γ, and δ. Postsynaptic membranes from *Torpedo* contain at least three protein kinases capable of phosphorylating this receptor, i.e., cyclic AMP-dependent protein kinase, protein kinase C, and an endogenous tyrosine-specific protein kinase immunologically related to $pp60^{c\text{-}src}$ (Huganir and Greengard, 1983; Huganir et al., 1983, 1984; Safran et al., 1987). The cyclic AMP-dependent protein kinase phosphorylates the γ- and δ-subunits, protein kinase C phosphorylates the δ- and, more slowly, the α-subunits, and the protein tyrosine kinase phosphorylates the β-, γ-, and δ-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 these phosphorylation sites are all located in homologous regions in the major intracellular loop of the subunits and that multiple phosphorylation sites within a loop are located in close proximity to each other (for reviews, see Huganir, 1987; Miles and Huganir, 1988; Huganir and Greengard, 1990).

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TABLE 7
*Regulation of plasma membrane receptors by protein phosphorylation**

Receptor type	Protein kinase	Functional importance
Ion channel-associated receptors		
nACh-R	PKA	Increased response (neural type)
	PKA, PKC, Tyr-K	Increased rate of desensitization (muscle, electric organ)
$GABA_A$-R	PKA, PKC	Increased rate of desensitization
Glycine	PKA	Increased response
G-protein-associated receptors		
β-AR, α-AR	PKA, PKC	Heterologous desensitization
	β-ARK	Homologous desensitization
mACh-R	PKA, PKC	Heterologous desensitization
	β-ARK	Homologous desensitization
Tyrosine kinase receptors		
Insulin-R	Insulin-R	Signal transduction
	PKA, PKC	Down-regulation

* Summary of major types of transmitter receptors regulated by protein phosphorylation. Data compiled from: Huganir and Greengard (1990), Benovic et al. (1988), Rosen (1987), Song and Huang (1990). Abbreviations: β-ARK, β-adrenergic receptor kinase; insulin-R, insulin receptor; others as in legend to Tables 1 and 2.

The functional consequences of phosphorylation of the nicotinic cholinergic receptor have been examined. Reconstituted receptor that had been phosphorylated either 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 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 myotube 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 Zempel, 1987; Huganir and Greengard, 1987; 1990; Smith et al., 1989). This probably also holds true for tyrosine kinase-mediated phosphorylation, because phosphorylation by the latter kinase appears to occur between the sites phosphorylated by cyclic AMP-dependent protein kinase and by protein kinase C, at least on the δ-subunit (Huganir and Greengard, 1990). In contrast, recent data indicate that cyclic AMP-dependent phosphorylation of a neuronal acetylcholine receptor α-type subunit increases the response to ligand binding (Vijayaraghavan et al., 1990). Hence, phosphorylation of distinct isoforms of the nicotinic receptor may induce different types of responses.

Determination of the identities of the neurotransmitter(s) or hormone(s) responsible for the physiological regulation of the activity of the three protein kinases that phosphorylate the nicotinic acetylcholine receptor is currently the subject of investigation in several laboratories. In muscle cells, calcitonin gene-related peptide, a cotransmitter with acetylcholine in motor neurons, raises the levels of cyclic AMP (Laufer and Changeux, 1987), increases the rate of receptor desensitization, and stimulates the phosphorylation of the nicotinic acetylcholine receptor on the same subunits as does cyclic AMP-dependent protein kinase (Miles et al., 1987, 1989; Mulle et al., 1988). Other evidence suggests that acetylcholine, by causing both Ca^{2+} influx and diacylglycerol formation through activation of muscarinic and possibly nicotinic acetylcholine receptors, causes the activation of protein kinase C and thereby the phosphorylation of the nicotinic acetylcholine receptor (Adamo et al., 1985; 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 receptor has not yet been determined (Qu et al., 1990).

The *$GABA_A$ receptor* from rat brain consists of α- and β-subunits, and molecular cloning has shown that several isoforms of these subunits exist (for review, see Olsen and Towbin, 1990). This receptor also appears to be organized in a pentameric structure, the α- and β-subunits apparently having four transmembrane domains and displaying membrane topologies similar to those of the nicotinic acetylcholine receptor. Moreover, clones for additional γ- and δ-subunits have also been reported (Olsen and Towbin, 1990). There are predicted consensus sequences for phosphorylation by cyclic AMP-dependent protein kinase and by protein kinase C in the α- and β-subunits, and a γ-subunit clone has demonstrated a predicted consensus sequence for protein tyrosine kinases (Olsen and Towbin, 1990). Studies of the purified $GABA_A$ 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 protein kinase preparation (Sweetnam et al., 1988).

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The functional properties of the $GABA_A$ receptor, which constitutes a ligand-gated Cl^- channel (Schofield et al., 1987; Olsen and Towbin, 1990), are also regulated by phosphorylation (Stelzer et al., 1988). Activation of cyclic AMP-dependent protein kinase has been reported to increase the rate of desensitization of the receptor, analogous to the observations made with the nicotinic acetylcholine receptor (Tehrani et al., 1989; Heuschneider and Schwartz, 1989). Moreover, activation of protein kinase C by phorbol esters decreased the amplitude of the $GABA_A$ receptor current in oocytes expressing ion channels from total messenger RNA from chick forebrain (Sigel and Baur, 1988). Thus, both cyclic AMP-dependent protein kinase and protein kinase C may regulate the activity of the $GABA_A$ receptor.

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; Hall, 1987). These receptors, which include, inter alia, adrenergic receptors, dopamine receptors, muscarinic acetylcholine receptors, serotonin receptors, and tachykinin receptors, do not themselves contain the machinery for transduction of the signal across the membrane. Instead, these receptors interact with and activate various membrane-associated guanine nucleotide-binding proteins (G-proteins), which in turn can interact with and regulate enzymes such as adenylyl cyclase or phospholipase C, or other types of effector systems such as ion channels (Rodbell, 1980; Gilman, 1987). Although most, and possibly all, of these receptors are regulated by phosphorylation, the regulation of the β-adrenergic receptor and the muscarinic acetylcholine receptor by phosphorylation has been most thoroughly studied. We will, therefore, restrict most of our discussion to these receptor types.

The *β-adrenergic receptor*, the prototype of this receptor class, can be phosphorylated by both cyclic AMP-dependent protein kinase and by protein kinase C, as well as by a newly discovered protein kinase specific for the agonist-occupied receptor (for examples, see Benovic and Lefkowitz, 1987; Benovic et al., 1985, 1986b, 1987b, 1988; Bouivier et al., 1987; Sibley et al., 1987). Such phosphorylations appear to be intimately involved in the coupling of the receptor to adenylyl cyclase and the desensitization of the receptor (Sibley et al., 1986; Lefkowitz 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 to occur with this receptor type (Benovic and Lefkovitz, 1987). Evidence from studies of phosphorylation of the purified β-adrenergic receptor, as well as studies of intact cells, indicate that heterologous desensitization may be mediated, at least partly, by phosphorylation of the receptor on multiple sites by cyclic AMP-dependent protein kinase; similarly, activators of protein kinase C can also induce desensitization of β-adrenergic receptors in intact cells, suggesting that phospholipase C-coupled receptors promote another form of heterologous desensitization (Lefkowitz et al., 1990).

Homologous desensitization of the β-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 purified from bovine brain, appears to be specific for the β-adrenergic receptor and has, therefore, been designated β-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 distinct phosphorylation sites but only when agonist is bound to the receptor. This phosphorylation mechanism, therefore, represents substrate-activated phosphorylation, which is a highly effective mechanism for limiting desensitization to the homologous type.

Homologous desensitization of the β-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, 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 β-adrenergic receptor kinase (Kelleher and Johnson, 1990). For example, rhodopsin kinase phosphorylates light-exposed 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 β-adrenergic receptor in its agonist-bound form; conversely, the β-adrenergic receptor kinase can phosphorylate bleached, but not unbleached, rhodopsin in vitro (Benovic et al., 1986a). Phosphorylation of rhodopsin by rhodopsin kinase attenuates the interaction of rhodopsin with transducin, apparently through a mechanism involving a cytosolic protein termed arrestin, which binds to phosphorylated rhodopsin and prevents its binding and interaction with transducin (Stryer, 1986). This mechanism, which appears to be analogous to the one responsible for desensitization of the β-adrenergic receptor (Benovic et al., 1987a,b; Lohse et al., 1990), may be responsible for the termination of visual signal transduction.

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 phosphoinositide turnover, or activate K^+ channels, have been cloned and sequenced and have been found to be homologous to the β-adrenergic receptor in their amino acid sequences and topologies (for review, see Nathanson, 1987). The β-adrenergic receptor kinase has recently been reported to phosphorylate the purified M_2 muscarinic receptor from heart in an agonist-dependent man-

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ner (Kwatra et al., 1989). Moreover, treatment of chick hearts with muscarinic agonists both increased the phosphorylation and decreased the affinity of the muscarinic receptor for agonist (Kwatra and Hosey, 1986; Kwatra et al., 1987; Ho et al., 1987). In addition, both cyclic AMP-dependent protein kinase and protein kinase C have been reported to phosphorylate purified muscarinic receptors (Rosenbaum et al., 1987; Uchiyama et al., 1990; Haga et al., 1990). These results, therefore, indicate that the muscarinic acetylcholine receptors are subject to regulation by protein phosphorylation. β-Adrenergic receptor kinase, or a similar protein kinase, may regulate homologous desensitization of the muscarinic acetylcholine receptor in response to acetylcholine, whereas protein kinase C and cyclic AMP-dependent protein kinase may regulate heterologous desensitization in response to other extracellular signals.

Other G-protein-coupled receptors are also subject to phosphorylation. For example, the α_2-adrenergic receptor, which is coupled to inhibition of adenylyl cyclase, can be phosphorylated by the β-adrenergic receptor kinase (Benovic et al., 1987c). This phosphorylation is also agonist dependent and may be involved in the same type of homologous desensitization as the β-adrenergic receptor. Similarly, the *dopamine D1 receptor*, recently cloned and expressed, belongs to the same class of G-protein-linked receptors and possesses potential phosphorylation sites on intracellular domains, suggesting that this receptor type will be regulated by similar mechanisms (Dearry et al., 1990; Monsma et al., 1990; Sunahara et al., 1990; Zhou et al., 1990). Similar data have been presented for *tachykinin receptors* (Yokota et al., 1989; Guard and Watson, 1991).

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 Ullrich, 1988). This receptor, which is enriched in brain (Rees-Jones et al., 1984; Zahniser et al., 1984; Adamo et al., 1989), is composed of α-subunits, which are located extracellularly and contain the insulin-binding site, and β-subunits, which are transmembrane proteins and presumably convey the insulin signal into the cells (Rosen, 1987). The COOH-terminal part of the β-subunit contains tyrosine kinase activity and has extensive homology with other tyrosine kinases (Rosen, 1987; Yarden and Ullrich, 1988). Binding of insulin increases the tyrosine kinase activity of the receptor and is manifested by autophosphorylation of the β-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 (for reviews, see Rosen, 1987; Yarden and Ullrich, 1988). Agonist-induced activation of receptor tyrosine kinases also appears to be part of the signal transduction mechanism used by a variety of other growth factors and their receptors (Yarden and Ullrich, 1988).

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 is independent of insulin (Kasuga et al., 1982a,b; Rosen et 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 insulin-regulated protein kinases responsible for the serine phosphorylation are not clear. However, evidence indicates that both cyclic AMP-dependent protein kinase and protein kinase C regulate the receptor. Thus, treatment of intact cells with agents that increase cyclic AMP levels has been reported to increase serine and threonine phosphorylation of the receptor, presumably through indirect mechanisms (Stadtmauer and Rosen, 1986), and at the same time decrease the effect of insulin on tyrosine phosphorylation, thereby effectively causing a functional 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 serine and threonine residues (Takayama et al., 1984) and decreases the effect of insulin on tyrosine phosphorylation. The insulin receptor can be phosphorylated by protein kinase C in vitro, and this phosphorylation decreases the tyrosine kinase activity of the receptor (Bollag et al., 1986). Therefore, agents working through cyclic AMP-dependent protein kinase or protein kinase C may down-regulate this type of receptor.

4. Intracellular receptors. Several hormones and regulatory agents influence cellular function through intracellular receptors, which may be regulated by phosphorylation mechanisms. Thus, a superfamily of receptors present in cell nuclei consists of receptors for steroids, 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, see Weigel et al., 1981; Housley and Pratt, 1983; Singh and Moudgil, 1985; Tienrungroj et al., 1987; Auricchio et al., 1988; Brown and DeLuca, 1990; Denner et al., 1990; Hoeck and Groner, 1990; Moudgil, 1990). Whether such modifications of these receptor types take place in brain, and whether such phosphorylations lead to changes in neuronal function, remain to be examined.

B. Regulation of Ion Channels

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 mechanisms differ among distinct cell types (table 8) (for review, see Kaczmarek and Levitan, 1986). Physiological studies, usually using intracellular recordings or patch clamp analysis together with applications

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TABLE 8
Regulation of ion channels following intracellular injection of protein kinases, activators, or inhibitors, in intact nerve cells

Protein kinase involved	Cell type	Injected compound	Physiological consequence of kinase activation	Regulated ion channel
PKA	Bag cells (*Aplysia*)	PKA, PKI	After discharge ↑	K^+ channel
	Sensory neurons (*Aplysia*)	PKA, PKI	Transmitter release ↑	K^+ channel
	Neuron R 15 (*Aplysia*)	PKI	Bursting ↓	K^+ channel
	Helix neuron	PKA	Action potential duration ↓	K^+ channel
			After hyperpolarization ↑	K^+ channel
	Photoreceptor (*Hermissenda*)	PKA	Regulation of light-induced membrane depolarization	K^+ channel
PKG	*Helix* neuron	PKG + cGMP	Serotonin-induced depolarization ↑	Ca^{2+} channel
PKC	Bag cells (*Aplysia*)	PKC, DAG	Ca^{2+} current ↑	Ca^{2+} channel
	Photoreceptor (*Hermissenda*)	PKC, DAG	K^+ current ↑↓	K^+ channel
	Helix neuron	PKC	CCK-regulated Ca^{2+} current ↓	Ca^{2+} channel
CaM kinase II	Photoreceptor (*Hermissenda*)	CaM kinase II	K^+ current inactivation ↑	K^+ channel

* Summary of data from intracellular injection experiments where activated protein phosphorylation systems have been found to regulate ion channel properties. Data compiled from Kaczmarek and Levitan (1986), Kaczmarek (1987, 1988), Paupardin-Tritsch et al. (1986a,b), Woody et al. (1986), Siegelbaum et al. (1982). Further details are given in text. Abbreviations: PKI, protein inhibitor of cyclic AMP-dependent protein kinase; CCK, cholecystokinin; PKG, cyclic GMP-dependent protein kinase; others as in legend to Tables 1 and 3.

of second messengers and/or protein kinases, and biochemical investigations of purified channel proteins as targets for protein kinases have shown that various types of ion channels, including Na^+, K^+, Ca^{2+}, and Cl^- channels, are regulated by protein phosphorylation (for reviews, see Rossie and Catterall, 1987a; Huganir, 1986a,b; Levitan, 1985, 1988; Kaczmarek, 1987, 1988). In some cases, phosphorylation of the channel proteins themselves 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 channel properties, leading to changes in the electrical behavior of the cells (for examples, see Kaczmarek and Levitan, 1986; Levitan, 1985, 1988). In other cases the exact physiological importance of ion channel phosphorylation 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^+ channels, a number of K^+ channels, or various Ca^{2+} channels. Ligand-gated ion channels such as the nicotinic acetylcholine receptor and $GABA_A$ receptors have been discussed in section V.A.1, and the epithelial Cl^- channel defective in cystic fibrosis will be discussed in section VI.B. Certain aspects of the regulation of ionic conductances by distinct protein kinases were discussed briefly in section II.

1. Na^+ channels. The *voltage-sensitive Na^+* channel from rat brain, which has been extensively characterized (Agnew, 1984; Barchi, 1984; Catterall, 1986), contains a major α-subunit of approximately 260 kDa. This subunit has been found to be phosphorylated by both cyclic AMP-dependent protein kinase and protein kinase C (Costa and Catterall, 1984a,b; Costa et al., 1982; Rossie 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 cultures of rat brain neurons (Rossi and Catterall, 1987b, 1989). This suggests that physiological changes 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^+ channels was not observed, and the physiological importance of this phenomenon remains to be established (Costa and Catterall, 1984a,b; Rossie and Catterall, 1987a).

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 of several of these K^+ currents has been found to be regulated by protein phosphorylation.

The regulation of the voltage-dependent *delayed rectifier K^+* current, which in many instances is responsible 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 K^+ 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 added to the perfusing medium (Bezanilla et al., 1985; Perozo et al., 1986; Perozo and Bezanilla, 1990). Thus, cyclic AMP-catalyzed phosphorylation of the channel itself or of an associated protein appears to be important in determining the behavior of this channel.

In sensory neurons of *Aplysia*, voltage-dependent K^+

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channels that contribute to the repolarization phase of action potentials have been termed *S channels* (Siegelbaum et al., 1982). The closure of these channels by serotonin and by endogenous neuropeptides enhances action potentials and appears to be partly responsible for 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 kinase (Castellucci et al., 1980, 1982): application of the C subunit of this enzyme to the cytoplasmic face of membrane patches closes about one-third of the S channels monitored in the patches (Siegelbaum et al., 1982; Shuster et al., 1985).

Other types of voltage-dependent K^+ channels appear to be subject to regulation by protein phosphorylation. These include the transient inactivating *A current*, the amplitude of which has been reported to be decreased by the intracellular application of various protein kinases 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 bullfrog sympathetic neurons has been found to be diminished by activators of protein kinase C (Adams and Brown, 1984).

Multiple types of Ca^{2+}-activated K^+ currents, including the K^+ current responsible for the prolonged afterhyperpolarization that follows action potential bursts in many neurons (Pennefather et al., 1985), appear to be regulated by protein phosphorylation. Both positive and negative modulation of such channels by cyclic AMP-dependent protein kinase and by protein kinase C have been reported (for review, see Kaczmarek, 1988). One example of such regulation has been found in intact *Helix* neurons (De Peyer et al., 1982; Ewald et al., 1985). Intracellular application of the C subunit of cyclic AMP-dependent protein kinase into these neurons increased the amplitude of the Ca^{2+}-activated K^+ current that was recorded during depolarization. When membrane fractions from *Helix* were reconstituted into phospholipid bilayers, single Ca^{2+}-activated K^+ channels were detected. Application of the C subunit of cyclic AMP-dependent protein kinase in the presence of ATP produced a dramatic increase in the probability of opening of the channels (Ewald et al., 1985). The results were consistent with the hypothesis that this type of phosphorylation of the channel increased its sensitivity to Ca^{2+} ions.

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). This effect, which leads to an enhancement of the interburst hyperpolarization and is caused by an increase in the number of functional K^+ channels, appears to be mediated by cyclic AMP-dependent protein kinase and can be blocked by the protein inhibitor of this enzyme (Adams and Levitan, 1982; Lemos et al., 1985).

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 by mediating voltage-dependent increases in the cytosolic concentration of Ca^{2+} (Catterall et al., 1988), are present in 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^{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 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^{2+} channel, termed the L channel (Nowycky et al., 1985), has been found to be subject to phosphorylation by several protein kinases in vitro (for examples, see Curtis and Catterall, 1985; Hosey et al., 1986; Imagawa et al., 1987; Hosey and Lazdunski, 1988; Tsien et al., 1988; De Jongh et al., 1989; Röhrkasten et al., 1990).

Other studies have indicated that similar Ca^{2+} channels in invertebrate neurons (Kostyuk, 1984; Doroshenko et al., 1984; Eckert et al., 1986) and in the mammalian pituitary cell line GH_3 (Armstrong and Eckert, 1987) may maintain their responsiveness through cyclic AMP-dependent protein phosphorylation (Armstrong, 1989). When excised patches from GH_3 cells were incubated with the C subunit of cyclic AMP-dependent protein kinase together with ATP, the L-type Ca^{2+} channels were found to open normally, and they rapidly stopped responding to membrane depolarization in the absence of reagents that could support such protein phosphorylation (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 opening times of the individual channels following depolarization, in contrast to the brief opening responses seen in the presence of cyclic AMP-dependent protein 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+} channels are known to be rapidly inactivated by the Ca^{2+} ions which enter through the channels during depolarization, thereby reducing the opening frequency of the channels and reducing the accumulation of intracellular Ca^{2+} (Eckert and Chad, 1984; Chad and Eckert, 1986; Kalman et al., 1988; Armstrong, 1989). This phenomenon, which can be prevented by agents that promote cyclic AMP-dependent protein phosphorylation (Armstrong and Eckert, 1985), is caused at least partly by dephosphorylation

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of the Ca^{2+} channel, catalyzed by the Ca^{2+}/calmodulin-dependent protein phosphatase-2B (Hosey et al., 1986; Kalman et al., 1988). In addition, protein phosphatases-1 or -2A have also been reported to inactivate such Ca^{2+} channels (Hescheler et al., 1987).

Another type of voltage-dependent Ca^{2+} channel is 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 inward current, without affecting voltage-dependent K^+ currents (DeRiemer et al., 1985). Further analysis indicated that this increase was due to an apparent recruitment of 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 same neurons without affecting the inward Ca^{2+} current (Kaczmarek et al., 1980).

Neurotransmitter-induced regulation of Ca^{2+} channels mediated by protein phosphorylation also occurs in *Helix* neurons. In these snails, serotonin induced an increase of Ca^{2+} currents in a set of ventral neurons, with this effect apparently being mediated through cyclic GMP-dependent protein kinase, because the effect could be mimicked by intracellular injection of cyclic GMP or of an inhibitor of cyclic GMP phosphodiesterase (Paupardin-Tritsch et al., 1986a,b). Further evidence for protein phosphorylation being involved was obtained when it was found that the effect of serotonin was potentiated by injection of activated cyclic GMP-dependent protein kinase (Paupardin-Tritsch et al., 1986b). These data indicate that serotonin in these cells causes an increase in cyclic GMP levels, thereby activating cyclic GMP-dependent protein kinase and inducing phosphorylation of the Ca^{2+} channel or some associated protein, which in turn modulates the response of the channel to depolarization.

In other *Helix* neurons, cholecystokinin, a widely distributed neuropeptide, appeared to modulate Ca^{2+} currents through protein kinase C (Hammond et al., 1987). Extracellular application of sulfated cholecystokinin octapeptide or activators of protein kinase C, or intracellular injection of protein kinase C, shortened the Ca^{2+}-dependent action potential and decreased the amplitude of the Ca^{2+} 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 octapeptide on the Ca^{2+} current (Hammond et al., 1987). Similar results have been obtained in chick dorsal root ganglion cells with noradrenaline and activators of protein kinase C, agents that shortened the duration of action potentials and decreased the amplitude of voltage-dependent Ca^{2+} current (Rane and Dunlap, 1986).

IP_3-dependent Ca^{2+} channels, which are located intracellularly (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 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). Recent studies have shown that Purkinje cells in the cerebellum 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 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-dependent protein kinase (Walaas et al., 1983b, 1986b; 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-dependent phosphorylation of the protein appeared to decrease the capacity for Ca^{2+} release from cerebellar membrane vesicles (Supattapone et al., 1988a). Such phosphorylation-induced decreases in IP_3-regulated Ca^{2+} release from intracellular stores may constitute a molecular mechanism whereby receptors acting through cyclic AMP (e.g., β-adrenergic receptors) modulate the physiological responses to those neurotransmitter receptors that induce IP_3 generation and intracellular Ca^{2+} release.

Interestingly, examination of the primary structure of the IP_3 receptor protein, deduced from the nucleotide sequence of cloned complementary DNA, has indicated that the protein is homologous to the so-called "ryanodine receptor" protein present in striated muscle sarcoplasmic reticulum (Furuichi et al., 1989; Mignery et al., 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, does not share sequence homology with the IP_3 receptor in those domains that contain possible phosphorylation sites for cyclic AMP-dependent protein kinase (Furuichi et al., 1989). The ryanodine receptor Ca^{2+} channel of striated muscle may thus be subject to regulatory mechanisms distinct from those of the IP_3 receptor.

C. Regulation of Interactions of Neurotransmitter Pathways

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 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 interaction that appears to be mediated, at least in part, by a

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protein phosphorylation pathway is the dopamine-glutamate interaction that occurs in the medium-sized spiny neurons of the neostriatum. It is generally accepted that dopamine, the neurotransmitter released from the nigrostriatal neurons (for examples, see Moore and Bloom, 1978), reduces the excitability of the medium-sized spiny neurons to glutamate, the neurotransmitter released from the corticostriatal fibers (Calabresi et al., 1987; Chiodo and Berger, 1986). Recent studies have elucidated a protein phosphorylation pathway that appears to be 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 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). These regions, which make up most of the so-called "extrapyramidal motor system," are organized in distinct, interconnected nuclei that funnel information 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, excitatory inputs from different parts of the cerebral cortex (Graybiel and Ragsdale, 1983; Nauta and Domesick, 1984). Evidence suggests that these input fibers are predominantly glutamatergic (Fonnum et al., 1981). Following activation of the corticostriatal synapses and information processing in the neostriatum, the nerve impulses are funneled out through the predominantly inhibitory, GABAergic and/or peptidergic pathways which terminate in the globus pallidus, the entopeduncular nucleus, and the pars reticulata of the substantia nigra (Fonnum and Walaas, 1979).

Major functional interactions in this neuronal system appear to take place at the corticostriatal synapses in the neostriatum. The efficacy of the glutamatergic transmission 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 of the medium-sized spiny neurons (Freund et al., 1984). In this synapse, dopamine, through cyclic AMP, induces 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 of particular importance that the dopamine D1 receptor, in addition to β- adrenergic receptors, serotonin and adenosine 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., 1979; Quik et al., 1978; Prémont et al., 1977, 1983; Minneman et al., 1978; Stoof and Kebabian, 1981, 1982).

Examination of rat, monkey, and human basal ganglia has demonstrated that these regions express a number of phosphoproteins that may be involved in the regulation of neuronal excitability by dopamine. The medium-sized spiny striatofugal neurons, in particular, contain many phosphoproteins that appear to be specific substrates for cyclic AMP-dependent protein kinase (Walaas et al., 1983b,c, 1989a; Ouimet et al., 1984b; Hemmings et al., 1987c). At the present time, *DARPP-32* is the best characterized of these proteins. Extensive evidence indicates that this protein, which was described briefly in section III, is involved in dopaminergic neurotransmission in the basal ganglia. DARPP-32 is enriched in those basal ganglion areas that are densely innervated by the mesotelencephalic dopaminergic fiber system (Walaas and Greengard, 1984; Ouimet et al., 1984b; 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 and White, 1987)). Moreover, anatomical studies have shown that the distribution of DARPP-32-containing neurons throughout the brain is in good agreement with the distribution of the D1 receptor (Aiso et al., 1987; Boyson et al., 1986). Recent studies have also shown that DARPP-32 is present in certain peripheral cells that contain dopamine D1 receptors, including parathyroid 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 actions of dopamine in these cells, and experimental evidence has been obtained that supports this hypothesis.

Under basal conditions, DARPP-32 is phosphorylated in intact cells predominantly on a serine residue which is a substrate for casein kinase II in vitro and in situ (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., 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 (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-34 in vitro prevents dephosphorylation of 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 (Girault et al., 1989a). If, as seems possible, casein kinase II in brain is regulated by neurotransmitters or neuromodulators, then such feedback between the two

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phosphorylation systems would provide an example of one class of receptor/receptor interaction, in this case between the dopamine receptor and the receptor for this unknown neurotransmitter.

Biochemical studies have demonstrated that DARPP-32 may achieve its effects through inhibition of protein 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 similar to a comparable domain in protein phosphatase inhibitor-1 (Williams et al., 1986; Aitken et al., 1982). Moreover, as observed with protein phosphatase inhibitor-1, DARPP-32 is a potent inhibitor of protein phosphatase-1 only when it is phosphorylated on this threonine residue (Hemmings et al., 1984a). Therefore, it would appear that DARPP-32 is involved in mediating or modulating transsynaptic effects of dopamine acting on D1 receptors by regulating the activity of protein phosphatase-1. In this way, dopamine would indirectly regulate the state of phosphorylation of substrates for protein phosphatase-1.

DARPP-32 phosphorylation provides a positive feedback mechanism for those phosphoproteins that are substrates for protein phosphatase-1 and that are phosphorylated by the dopamine D1-receptor/cyclic AMP/cyclic 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 been used by dopamine in the regulation of Na^+, K^+-ATPase activity in renal tubule cells, as discussed in 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, phospho-DARPP-32 formed in the presence of dopamine might prevent the dephosphorylation of substrate proteins phosphorylated by these other protein kinases. The increased phosphorylation and decreased dephosphorylation of these substrate proteins would be reflected in synergistic physiological actions of dopamine and these other neurotransmitters.

Another class of receptor-receptor interaction, mediated 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. Dephosphorylation of Thr-34 on DARPP-32 is catalyzed in vitro most efficiently by phosphatase-2B, the Ca^{2+}/calmodulin-dependent phosphatase specifically enriched in some of the cells in which DARPP-32 is located (Goto et al., 1986; Ouimet et al., 1984b). Activation of the NMDA type of glutamate receptor in striatal slices reversed the cyclic AMP-stimulated phosphorylation of DARPP-32, and this effect was achieved through 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, 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 through phosphatase-2B activation by Ca^{2+} (Halpain et al., 1990). Thus, the antagonistic effects of dopamine and glutamate on the excitability of striatal neurons are reflected in antagonistic effects of these neurotransmitters on the state of phosphorylation of DARPP-32.

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-dependent protein kinase (Walaas et al., 1983c, 1989a; Hemmings et al., 1989). Most or all of these proteins appear to be localized to neurons that contain dopamine receptors, and they would, therefore, be expected to be involved in the regulation of neuronal functions mediated by dopamine. Hypo- and hyperfunction of the dopaminergic system are associated with motor dysfunctions and pathological behavior, respectively (for examples, see Snyder, 1976; Creese and Snyder, 1978). Given the importance of dopaminergic neurotransmission in mammalian brain, further analysis of the characteristics of these proteins will be of great interest.

D. Regulation of Long-Term Potentiation

LTP is a phenomenon that has been used as a model for the early stages of memory formation and learning and that has attracted great attention. In this phenomenon, brief tetanic stimulation of afferent fibers results in a long-lasting increase in synaptic strength or efficacy, as first observed in the dentate gyrus of the hippocampal 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 phosphorylation (for reviews, see Malenka et al., 1989b; Nicoll et al., 1988). LTP appears to be composed of a number of different phenomena (for examples, see Swanson et al., 1982; Zalutsky and Nicoll, 1990), one of which 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 important 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 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 hippocampus), binding to two classes of glutamate receptors (Cotman and Iversen, 1987). The glutamate receptor respon-

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sible for normal excitatory postsynaptic potentials appears to be the so-called α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-selective glutamate receptor, 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 α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-selective glutamate receptor, activation of the NMDA receptor allows not only Na^+ but also Ca^{2+} to flow into the postsynaptic cells (for examples, see Dingledine, 1983). This Ca^{2+} influx is crucial for LTP to develop (for review, see Malenka et al., 1989b).

Ca^{2+}-sensitive enzymes that might be involved in the development and persistence of LTP include protein kinases, protein phosphatases, and/or proteases. The results of experiments in which relatively nonspecific protein kinase inhibitors such as H-7 have been injected 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 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 process of LTP. Increases in inositol phospholipid turnover have been associated with LTP, and protein kinase C becomes translocated to particulate fractions, and presumably activated, when LTP is induced in the 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 somewhat similarly to LTP (Malenka et al., 1986), whereas extracellular application of putative, but not very specifically (for examples, see Jefferson and Schulman, 1988), protein kinase C inhibitors such as sphingosine, polymyxin B, or H-7 blocks several components of LTP (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. However, evidence suggesting a postsynaptic localization 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 preparation), several features of LTP. Thus, a role for protein kinase C-catalyzed phosphorylation in the postsynaptic mechanisms involved in LTP appears probable.

Recent studies have also indicated a possible role for CaM kinase II in LTP. This enzyme is highly enriched in many of those nerve cells that can generate LTP in response to high frequency stimulation of afferent inputs (Ouimet et al., 1984a; Erondu and Kennedy, 1985). Moreover, 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 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 develop (Malenka et al., 1989b; Malinow et al., 1989). Thus, it seems possible that both types of Ca^{2+}-dependent protein kinases may be involved in the initial stages of LTP.

These protein kinases may also be involved in the maintenance of LTP. Sphingosine, a kinase inhibitor 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 the catalytic sites of protein kinase C and CaM kinase II (such as H-7) can block the initiation of LTP and also reverse the phenomenon if added later. Therefore, it has been proposed that proteolytic removal of the regulatory domain from the relevant protein kinase(s), and the resulting constitutive activation of one or both of these Ca^{2+}-dependent protein kinases, may be involved in the maintenance of LTP (Malinow et al., 1988, 1989; Reymann et al., 1988).

VI. Phosphoproteins and Clinical Disorders

The studies reviewed in the preceding sections have demonstrated that protein phosphorylation is involved 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 through perturbations of one or another protein phosphorylation system. For the same reason, one might also anticipate that abnormalities in protein phosphorylation could be involved in the etiology of a variety of clinical disorders. At present, such disorders include a subclass of diabetes, which has been shown to be attributable to a mutation 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 to transform cells by virtue of expressing protein tyrosine kinase activities (for review, see Bishop, 1982). Moreover, cystic fibrosis has been shown to be attributable to an inability of Cl^- 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 phosphorylation in Alzheimer's disease (Selkoe, 1989; Gandy et al., 1990a; see below).

In this section, we will summarize results of clinical studies correlating variant forms of synapsin II with alcoholism and discuss certain studies of protein phosphorylation relevant to cystic fibrosis. We will also de-

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scribe recent studies indicating that dopamine, a diuretic widely used clinically, induces natriuresis by a mechanism that involves a protein phosphorylation pathway. Finally, we will briefly discuss the involvement of protein phosphorylation in the pathogenesis of Alzheimer's disease.

A. Synapsin Variants and Alcoholism

The widespread involvement of protein phosphorylation in a variety of neuronal functions suggests that an analysis of neuronal protein phosphorylation systems in neuropsychiatric disorders might yield important information about molecular mechanisms involved in such diseases. Protein phosphorylation systems present in tissue from human brain appear to comprise many of the same protein kinases, phosphoproteins, and protein phosphatase regulators previously seen in animal brain (Routtenberg et al., 1981; Martinez-Millan and Rodnight, 1982; Walaas et al., 1989d). Moreover, methods for the detection of phosphoproteins in human cerebrospinal fluid have recently been developed, and, in fact, a phosphoprotein substrate for protein kinase C has been found to be present in cerebrospinal fluid from patients with paraneoplastic cerebellar degeneration (Gandy et 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 of 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 forms of synapsin II, a synaptic vesicle-associated protein discussed in section IV.A.2, may have some connection to alcoholism and possibly other neuropsychiatric disorders.

Synapsin II consists of two polypeptides, synapsin IIa and synapsin IIb (see section IV). Brains from all subhuman mammalian species studied to date have only one form of synapsin IIa and one form of synapsin IIb. In contrast, postmortem human brain samples have additional forms of synapsins IIa and IIb with higher apparent molecular weights (Perdahl et al., 1984). The forms designated synapsins IIa_1 and IIb_1 have the same apparent molecular masses as the nonhuman forms of synapsin IIa and IIb, respectively, and are referred to as the "normal" forms, and synapsins IIa_2, IIa_3, IIb_2, and IIb_3 are referred to as the "variant" forms. Within any single human brain, the same forms of synapsin II are present throughout all brain regions. Moreover, in each human brain, the presence or absence of synapsins IIa_1, IIa_2, and IIa_3 parallels the presence or absence of synapsins IIb_1, IIb_2, and IIb_3, respectively. Thus, an individual may have just one form of synapsin IIa and synapsin IIb (e.g., IIa_1 and IIb_1) or any two forms of synapsins IIa and IIb (e.g., IIa_1 and IIa_3 together with IIb_1 and IIb_3).

Variant forms of synapsin II have been examined in three studies of human postmortem brain tissue (Perdahl 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 increased occurrence of synapsin II variants among individuals 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 for alcoholism and that synapsin II variants may represent a specific genetic trait which may contribute to the polygenetic etiologies of several different clinical syndromes, including alcoholism. Additionally, synapsin II variants have been found in postmortem brain samples from infants and children who have died of a wide variety of accidents and medical illnesses, thus suggesting that 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 difficult to develop experimental models for the study of those variants.

B. Cystic Fibrosis and Cl^- Channel Regulation

Recent studies have shown that cystic fibrosis is due to a defect in ion channel function, in that Cl^- channels in the affected cells are unable to respond to activation in a physiological manner (Welsh, 1990). Given the importance of ion channel function in the CNS, a discussion of this disease seems warranted here.

Cystic fibrosis is a fatal, autosomal recessive genetic disease characterized by abnormalities in fluid and electrolyte transport in exocrine epithelia (Quinton, 1990). Both absorptive and secretory processes are affected by an underlying membrane defect in Cl^- permeability, and this defect results in tissue-specific symptoms. Although the defect is not fatal in and of itself, the effects in airway epithelia ultimately lead to irreversible and fatal secondary pulmonary infections. Cystic fibrosis is the most common fatal genetic disease in the United States and affects approximately 1 in 2000 Caucasians (Quinton, 1990).

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 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 Cl^- transport mechanisms. Cl^- secretion by the airway epithelium regulates the quantity and composition of the respiratory tract fluid; this Cl^- secretion is controlled by apical membrane Cl^- channels. A number of hormones and secretagogues that increase intracellular levels of cyclic AMP are known to increase Cl^- secretion by opening

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these Cl^- channels (Welsh, 1990). Certain secretagogues have also been found to increase diacylglycerol levels, indicating that protein kinase C also may regulate Cl^- channels, and, indeed, activators of protein kinase C were found to either stimulate or inhibit Cl^- secretion, depending on the physiological state of the cells (Li et al., 1989).

In airway epithelial cells from children with cystic fibrosis, Cl^- channels were found to be present, but their regulation was defective. Activation of apical membrane Cl^- channels by cyclic AMP-mediated stimuli was absent, despite normal agonist-induced increases in cellular cyclic AMP levels (Frizzell et al., 1986; Welsh, 1990). The molecular mechanism underlying these observations was examined in cell-free membrane patches. It was found that application of the purified C subunit of cyclic AMP-dependent protein kinase plus ATP opened Cl^- channels in patches from normal airway epithelial cells but failed to open such channels in patches from cystic fibrosis epithelial cells (Schoumacher et al., 1987; Li et al., 1988). Thus, the cystic fibrosis cells display an inability of the Cl^- channel, or a modulator thereof, to respond to cyclic AMP-dependent protein kinase, a response that is indispensable for normal regulation of Cl^- secretion.

In cell-free membrane patches from normal airway epithelal cells, protein kinase C had dual effects, activating Cl^- channels at low Ca^{2+} concentrations and inactivating the channels at high Ca^{2+} concentrations (Li et al., 1989). In membrane patches from cystic fibrosis cells, protein kinase C-induced inactivation was normal, but activation was defective. The data indicated that one or 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 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 respective protein kinases, or whether the proteins are phosphorylated in a normal way but are unable to respond with the conformational change necessary to modulate Cl^- permeability in a normal fashion.

C. Dopaminergic Regulation of Natriuresis

Na^+, K^+-ATPase, an integral membrane protein present in virtually all mammalian cells, regulates a number of vital functions, including intracellular electrolyte homeostasis, cell volume, membrane potential, and transport 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 the enzyme, in both renal tubule cells (Aperia et al., 1987) and in neostriatal neurons (Bertorello et al., 1990). The peripheral actions of dopamine (for examples, see Goldberg, 1972; Schmidt et al., 1986), which are critical for the clinical regulation of Na^+ and extracellular volume homeostasis and for the regulation of blood pressure, have made this catecholamine compound the diuretic drug of choice in certain clinical situations when renal function is compromised (Schwartz and Gewertz, 1988; Aperia et al., 1991). An understanding of the mechanism by which dopamine inhibits Na^+, K^+-ATPase is, therefore, of considerable importance.

Studies of proximal convoluted tubules from rat kidney showed that the dopamine-induced inhibition of Na^+, K^+-ATPase was mediated through both D1 and D2 dopamine receptors (Bertorello and Aperia, 1988). Such synergism is similar to the mechanisms necessary for full expression of the electrophysiological actions of dopamine in the CNS (Carlson et al., 1987). Recent work has shown that dopamine also inhibits the enzyme in permeabilized, intact nerve cells from neostriatum (Bertorello 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 tubules, dopamine acted through a synergistic effect on both D1 and D2 receptors.

Evidence obtained from studies in kidney cells points to direct phosphorylation of the ATPase and to modulation of protein phosphatase activity as possible mediators behind these effects. Thus, recent studies of a highly purified preparation of Na^+, K^+-ATPase from shark rectal gland have shown that both cyclic AMP-dependent protein kinase and protein kinase C can rapidly and stoichiometrically phosphorylate the α-1 subunit of the enzyme, while concomitantly inhibiting enzyme activity 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^+, K^+-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 both contain high levels of DARPP-32 (Ouimet et al., 1984b; Meister et al., 1989). Thus, cyclic AMP-regulated 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-induced regulation of Na^+, 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 form of this peptide retains potency as an inhibitor of protein phosphatase-1, whereas the dephosphoform is inactive in this respect (Hemmings et al., 1990). When introduced into saponin-permeabilized renal tubule cells from the medullary thick ascending loop of Henle, the phosphorylated but not the dephosphorylated peptide decreased Na^+, K^+-ATPase activity to the same extent as did

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optimal concentrations of D1 dopamine receptor agonists or dibutyryl cyclic AMP. This effect was associated with a decrease in the V_{max} and an increase in the K_m values of the Na^+, K^+-ATPase for K^+ (Aperia et al., 1991).

In summary, the results of these studies indicate that dopamine, acting through D1 dopamine receptors, may stimulate cyclic AMP-regulated phosphorylation and inhibition of the Na^+, K^+-ATPase in situ. The data further 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 renal tubule cells through both increased phosphorylation and decreased dephosphorylation of the Na^+ pump.

D. Protein Phosphorylation and Alzheimer's Disease

Alzheimer's disease, a progressive encephalopathy of 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 number of neurotransmitter deficiencies have been reported in this disease, particularly a pronounced destruction of 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 the quantitatively dominating glutamate transmitter systems in the brain has also been proposed as a factor in this disease (Hyman et al., 1987; Palmer and Gershon, 1990), as have deficiencies of serotonin and noradrenaline neurons (for examples, see Hardy et al., 1985). Pathologically, both limbic and association cortices, including the hippocampal formation, become involved, with large numbers of neurons ultimately degenerating. The disease is invariably characterized by accumulation of poorly soluble structures within and outside neurons and in surrounding cerebral vessels, together with an 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 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 these proteins (for reviews, see Selkoe, 1989; Gandy et al., 1990a). Similarly, recent evidence indicates that the extracellular deposits (the neuritic plaques) consist mainly of a distinct protein, termed the β-amyloid/A4 protein, which derives from a β-amyloid precursor protein localized in the cell membrane of a wide variety of cells and tissues. It appears that the processing of this precursor protein, which leads to the ultimate deposition of the β-amyloid protein in the extracellular plaques, may be regulated by protein phosphorylation systems. We will, therefore, in this section first describe some features of 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 β-amyloid precursor protein processing by a phosphorylation mechanism that might relate to future therapeutic interventions in the processes leading to Alzheimer's disease.

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 throughout neural cells. These proteins appear to be important in morphogenesis, in neuritic transport and extensions, in regulation of organelle interactions, and in 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 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. Neurofilament and microtubule protein phosphorylation will be discussed here.

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), 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 include second messenger-regulated enzymes such as cyclic AMP-dependent protein kinase (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-regulated protein kinases (section II. D). Immunohistochemical studies indicate that the neurofilament proteins present in neuronal somata are essentially dephosphorylated, whereas the axonal forms of the proteins become 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 neurofilaments. 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; Honchar et al., 1982; Carden et al., 1985; Bignami et al., 1986; Foster et al., 1987; Nixon et al., 1987; Matus, 1988a).

b. MICROTUBULE PROTEINS. Microtubules are present throughout nerve cells, both in association with postsynaptic membranes and in dendrites, somata, axons, and, less prominently, in presynaptic terminals (Olmstedt, 1986; Matus, 1988b; Gordon-Weeks et al., 1982). The

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major protein components of microtubules include α- and β-tubulin and MAPs, many of which appear to be phosphorylated.

Tubulin has been reported to be phosphorylated by both cyclic AMP-dependent protein kinase and CaM 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 enzymes (Nairn et al., 1985a; Schulman, 1988), recent in vitro studies have indicated that phosphorylation of tubulin increases its interaction with membranes (Hargreaves 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 regulation of in vivo tubulin phosphorylation in brain is not well understood.

MAP-2, a high molecular weight protein (280,000 to 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 that the protein can be phosphorylated on a large number of sites by a variety of other protein kinases, which include CaM kinase II, protein kinase C, and tyrosine-specific protein kinases (Islam and Burns, 1981; Theurkauf and Vallee, 1983; Akiyama et al., 1986; Tsuyama et al., 1986; Yamauchi and Fujisawa, 1982, 1988; Goldenring et al., 1985; Larson et al., 1985; Schulman, 1984; Walaas et al., 1983b,c; Walaas and Nairn, 1989). The protein is also phosphorylated on multiple sites in situ (Tsuyama et al., 1986), and evidence suggests that different types of protein phosphatases are responsible for the dephosphorylation of these phosphorylation sites (Tsuyama et al., 1986). Such phosphatase activities have not been extensively characterized, however.

Phosphorylation of MAP-2 by either cyclic AMP-dependent or Ca^{2+}-dependent protein kinases appears to induce disassembly of microtubules (Yamauchi and Fujisawa, 1983b) and to regulate their interaction with actin (Jameson et al., 1980; Selden and Pollard, 1983; Yamauchi and Fujisawa, 1988). The prominent expression of 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+} 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+} fluxes into the cells (Dingledine, 1983), induces a potent dephosphorylation of MAP-2 (Halpain and Greengard, 1990), presumably through activation of the Ca^{2+}/calmodulin-dependent protein phosphatase-2B which can dephosphorylate MAP-2 in vitro (Goto et al., 1985). In contrast, extracellular signals that increase the state of phosphorylation of MAP-2 in intact nerve cells have not yet been defined. The functional roles of the multiple protein kinases and phosphatases capable of regulating the different phosphorylation sites in MAP-2 also remain uncertain.

Tau factor is a group of four related MAPs (apparent 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 stimulate both nucleation and elongation of microtubules, and tau factor has also been found to interact with both actin and neurofilaments (Mitchison and Kirschner, 1988). Tau factor has been reported to be phosphorylated on multiple sites by both cyclic AMP-dependent protein kinase, CaM kinase II, and protein kinase C (Cleveland et al., 1977; Yamamoto et al., 1983, 1985; Hoshi et al., 1987). This phosphorylation appears to inhibit microtubule assembly, and tau factor may, therefore, play a role in microtubule function analogously to that of MAP-2 (Lindwall and Cole, 1984). Moreover, tau factor is a component of the intracellular neurofibrillary tangles characteristic of Alzheimer's disease.

2. Tau factor phosphorylation and neurofibrillary tangles. 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, trisomy 21, progressive supranuclear palsy, Hallervorden-Spatz disease, Guam Parkinson-dementia complex, and dementia pugilistica (Selkoe, 1989). These tangles are not fully characterized but appear, based on protein analysis and immunocytochemistry, to contain tau factor, together with other MAPs, ubiquitin, and other, unidentified proteins (for review, see Selkoe, 1989). The tau proteins present in neurofibrillary tangles appear to be phosphorylated in an unusual or aberrant manner (Grundke-Iqbal et al., 1986), and evidence from several laboratories implicates Ca^{2+}/calmodulin-dependent protein phosphorylation in the pathogenesis of these tangles.

Evidence for cytoskeletal protein phosphorylation 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 is dramatically enhanced if Alzheimer brain sections are preincubated with alkaline phosphatase, whereas normal brain sections do not demonstrate this phenomenon (Sternberger et al., 1985; Grundke-Iqbal et al., 1986). Originally, aberrant phosphorylation of the neurofilament proteins was believed to be responsible for this phenomenon (Sternberger et al., 1985). However, it has become clear that the antibodies to neurofilament protein that labeled paired helical filaments in the neurofibrillary tangles cross-react with phosphorylated epitopes on tau factor (Wood et al., 1986; Nukina et al., 1987;

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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).

Other evidence shows that tau proteins, extracted from neurofibrillary tangles, migrate in an aberrant manner during sodium dodecyl sulfate-polyacrylamide gel electrophoresis when compared to tau proteins from normal brain and that normal tau factor can be induced to assume the Alzheimer-type electrophoretic mobility by in vitro phosphorylation of tau protein with CaM kinase II (Baudier and Cole, 1987) but not with protein kinase C (Baudier et al., 1987). Finally, antigenic changes similar to those seen in neurofibrillary tangles have been 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 observations point to a component of CaM kinase II-catalyzed protein phosphorylation, particularly of tau proteins, possibly being involved in the pathogenesis of neurofibrillary tangles.

3. β-Amyloid precursor protein phosphorylation and neuritic plaques. In Alzheimer's disease, deposits of amyloid protein outside the cell and in the cerebral and meningeal vessels appear to consist mainly of the β/A4 amyloid protein (Selkoe, 1989). Such β/A4 accumulation 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., 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 processing leading to β/A4 protein accumulation is a constant feature of the disease.

Amyloidogenic isoforms of the amyloid precursor protein, 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 β/A4 portion of the amyloid precursor protein, which consists of approximately 40 amino acid residues, lies at the junction of the extracellular domain and this transmembrane domain, with 28 residues outside the cell and the rest embedded in the membrane (Selkoe, 1989). Present evidence indicates that the normal constitutive cleavage of the amyloid precursor protein takes place within the β/A4 domain, hence precluding generation of the amyloidogenic β/A4 protein (Sisodia et al., 1990; Esch et al., 1990). Failure of this normal cleavage represents a possible biochemical basis for cerebral amyloidosis.

Several possible mechanisms may contribute to failure of normal cleavage, including overexpression of the amyloid precursor protein gene and overloading of the normal proteolytic processing of the amyloid precursor protein or mutations within the amyloid precursor gene leading to diminished efficacy of the normal amyloid precursor protein degradative pathway in brain (Gandy et al., 1990a; Levy et al., 1990). Recent analysis has shown that amyloid precursor protein processing may be regulated by protein phosphorylation. Within the intracellular domains of the amyloid precursor protein, Thr-654/Ser-655 have been identified as candidate sites for rapid phosphorylation by protein kinase C and CaM kinase II (Gandy et al., 1988). Moreover, in pulse-chase studies in which PC12 cells were used, activation of protein kinase 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-terminal fragment of approximately 15 kDa (Buxbaum et al., 1990). Combination of phorbol ester and okadaic acid led to the generation of the 15-kDa fragment and 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 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 "normal" constitutive intra-β/A4 cleavage, whereas the 19-kDa COOH-terminal fragment represents processing via an alternative and potentially amyloidogenic pathway, perhaps by cleavage at or near the β/A4 NH_2 terminus (Buxbaum et al., 1990; Gandy et al., 1990a).

At present, the mechanisms behind the observed effects of manipulations of protein phosphorylation systems 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 kinase C-mediated phosphorylation in an intracellular domain homologous to that found in the amyloid precursor 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 phenomenon. Furthermore, protein phosphorylation may also be involved in the regulation of amyloid precursor protein expression, possibly via phosphorylation of transcription 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 cerebral amyloidosis and whether they constitute possible targets for antiamyloid therapy.

VII. Summary and Conclusion

Following the initial demonstration of phosphorylation of endogenous brain proteins (Johnson et al., 1971),

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two decades of work have shown that this biochemical mechanism represents one of the most important means by which extracellular signals are transduced into changes in neuronal functions. Evidence discussed in this review shows that neural cells contain a plethora of protein kinases, protein phosphatases, and phosphorylated proteins and that many of these systems appear essential for the regulation of cell functions as diverse as membrane excitability, neuronal secretory processes, cytoskeletal organization, neuronal morphology, and cellular metabolism. Moreover, there exists intricate functional relationships between many of the neuronal protein phosphorylation systems, which allow "cross-talk" 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., neurotransmitter release) and events lasting for hours and days (e.g., LTP). Our present knowledge concerning neuronal protein phosphorylation has also allowed studies to be initiated regarding the possible involvement of protein phosphorylation in various clinical disorders affecting signal transduction and brain function. It seems safe to predict that continued studies of neuronal protein phosphorylation systems will continue to improve our understanding of the anatomical, physiological, and pharmacological basis for nervous system function in both health and disease.

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