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# **CONTI-B97/88/4002-0087802.00/0**<br>
PHARMACOLOGICAL REVIEWS<br>
Copyright © 1988 by The American Society for Pharmacology and Experimental Therapeutics<br>  $\alpha_1$ -Adrenergic Receptor Subtypes, Inositol Phosphates,<br>
and Sources of **Pharmacology and Experimental Therapeutics<br>
Receptor Subtypes, Inositol Ph<br>
and Sources of Cell Ca<sup>2+\*</sup><br>
KENNETH P. MINNEMAN** and Sources of Cell Ca<sup>2+\*</sup><br><sup>KENNETH</sup> P. MINNEMAN<br>*Department of Pharmacology, Emory University School of Medicine, Atlanta, Georgia 30322*



**I. Introduction**<br> $\alpha_1$ -ADRENERGIC receptors are involved in a variety of **1. Introduction** u<br>  $\alpha_1$ -ADRENERGIC receptors are involved in a variety of  $\begin{bmatrix} 1 \\ t \\ t \end{bmatrix}$ <br>
portant physiological processes, including control of **important physiological processes, including control of**<br>
important physiological processes, including control of<br>
blood pressure, appetite, and mood. These receptors be-<br>
long to the class of cell-surface receptors whic  $\alpha_1$ -ADRENERGIC receptors are involved in a variety of<br>important physiological processes, including control of<br>blood pressure, appetite, and mood. These receptors be-<br>long to the class of cell-surface receptors which in  $\alpha_1$ -ADRENERGIC receptors are involved in a variet<br>important physiological processes, including control<br>blood pressure, appetite, and mood. These receptors<br>long to the class of cell-surface receptors which initi<br>signals important physiological processes, including control of<br>blood pressure, appetite, and mood. These receptors be-<br>long to the class of cell-surface receptors which initiate<br>signals in their target cells by increasing the co blood pressure, appetite, and mood. These receptors belong to the class of cell-surface receptors which initiate signals in their target cells by increasing the concentration of free cytosolic Ca<sup>2+</sup> and thereby affecting long to the class of cell-surface receptors which initiate signals in their target cells by increasing the concentration of free cytosolic  $Ca^{2+}$  and thereby affecting the metabolic or contractile state of the cell. Rece signals in their target cells by increasing the concentration of free cytosolic  $Ca^{2+}$  and thereby affecting the metabolic or contractile state of the cell. Recent advances in our understanding of membrane lipid biochemi ception of the cytosolic Ca<sup>2</sup> and thereby allecting the<br>metabolic or contractile state of the cell. Recent advances<br>in our understanding of membrane lipid biochemistry<br>have led to the conclusion that these receptors cont metabolic or contractile state of the cell. Recent advance<br>in our understanding of membrane lipid biochemisti<br>have led to the conclusion that these receptors contr<br>cytosolic Ca<sup>2+</sup> primarily by stimulating hydrolysis of<br>hi

uct of this hydrolysis, inositol 1,4,5-trisphospha<br>
[Ins(1,4,5)P<sub>3</sub>], has been shown to release  $Ca^{2+}$  seque  $\begin{array}{lll} \hline \end{array}$  (Instead of this hydrolysis, inositol 1,4,5-trisphosph [Ins(1,4,5)P<sub>3</sub>], has been shown to release Ca<sup>2+</sup> sequestered in intracellular stores, particularly the endoplasm uct of this hydrolysis, inositol  $1,4,5$ -trisphosphate [Ins(1,4,5)P<sub>3</sub>], has been shown to release Ca<sup>2+</sup> sequestered in intracellular stores, particularly the endoplasmic reticulum. reticulum.  $\alpha$  or this hydrotysis, inositot 1,4,5-trisphosphate  $\alpha$ s(1,4,5)P<sub>3</sub>], has been shown to release  $Ca^{2+}$  sequested in intracellular stores, particularly the endoplasmic ticulum.<br>Recent evidence suggests, however, that

*a* **b a Experience of the author's laboratory during the preparation** of this **responses**, while other tissues require influx of  $Ca^{2+}$  review was supported by NS 21325, DA 03413, and a grant from the through speci [Ins(1,4,5) $P_3$ ], has been shown to release Ca<sup>-1</sup> seques-<br>tered in intracellular stores, particularly the endoplasmic<br>reticulum.<br>Recent evidence suggests, however, that  $\alpha_1$ -adrenergic<br>receptors do not have the same p The existence of distinct subtypes of  $\alpha_1$ -adrenergic<br>receptors do not have the same properties in all tissues.<br>The existence of distinct subtypes of  $\alpha_1$ -adrenergic re-<br>ceptors has been supported by a variety of phar Feticulum.<br>Recent evidence suggests, however, that  $\alpha_1$ -adres<br>receptors do not have the same properties in all ti<br>The existence of distinct subtypes of  $\alpha_1$ -adrenerg<br>ceptors has been supported by a variety of pharma<br>i receptors do not have the same properties in all tissues.<br>The existence of distinct subtypes of  $\alpha_1$ -adrenergic receptors has been supported by a variety of pharmacological approaches. Interestingly, it has also become differences in the importance of extracellular  $Ca^{2+}$  in The existence of distinct subtypes of  $\alpha_1$ -adrenergic receptors has been supported by a variety of pharmacolog-<br>ical approaches. Interestingly, it has also become clear<br>from studies in smooth muscle that there are major reptors has been supported by a variety or pharmacolog-<br>ical approaches. Interestingly, it has also become clear<br>from studies in smooth muscle that there are major<br>differences in the importance of extracellular  $Ca^{2+}$  in ical approacnes. Interestingly, it has also become clear<br>from studies in smooth muscle that there are major<br>differences in the importance of extracellular  $Ca^{2+}$  in<br>responses to  $\alpha_1$ -adrenergic receptor stimulation. In from studies in smooth muscle that there are major<br>differences in the importance of extracellular  $Ca^{2+}$  in<br>responses to  $\alpha_1$ -adrenergic receptor stimulation. In some<br>tissues stored intracellular  $Ca^{2+}$  is sufficient differences in the importance of extracellular Ca<sup>-1</sup> in responses to  $\alpha_1$ -adrenergic receptor stimulation. In some tissues stored intracellular Ca<sup>2+</sup> is sufficient for normal responses, while other tissues require inf tissues stored intracellular  $Ca^{2+}$  is sufficient for normal

known  $\alpha_1$ -adrenergic receptor controlling Ins(1,4,5)P<sub>3</sub> the properties of each st formation and release of intracellular Ca<sup>2+</sup>, there is an- tor gene products (328). **EXECUTE:** MINN<br> **EXECUTE:** However and release of intracellular Ca<sup>2+</sup>, there is an-<br>
other pharmacologically distinct  $\alpha_1$ -adrenergic receptor MINNI<br>
known  $\alpha_1$ -adrenergic receptor controlling Ins(1,4,5)P<sub>3</sub><br>
formation and release of intracellular Ca<sup>2+</sup>, there is an-<br>
other pharmacologically distinct  $\alpha_1$ -adrenergic receptor<br>
subtype controlling influx of C known  $\alpha_1$ -adrenergic receptor controlling Ins(1,4,5)P<sub>3</sub> formation and release of intracellular Ca<sup>2+</sup>, there is another pharmacologically distinct  $\alpha_1$ -adrenergic receptor subtype controlling influx of Ca<sup>2+</sup> throug formation and release of intracellular  $Ca^{2+}$ , there is an-<br>other pharmacologically distinct  $\alpha_1$ -adrenergic receptor<br>subtype controlling influx of  $Ca^{2+}$  through specific mem-<br>brane channels. This subtype, which appe other pharmacologically distinct  $\alpha_1$ -adrenergic resubtype controlling influx of  $Ca^{2+}$  through specific<br>brane channels. This subtype, which appears to<br>dependent of inositol phospholipid metabolism, n<br>an example of a r btype controlling influx of  $Ca^{2+}$  through specific mem-<br>ane channels. This subtype, which appears to be in-<br>idependent of inositol phospholipid metabolism, may be<br>en example of a receptor-operated channel (34).<br>In this

brane channels. This subtype, which appears to be in-<br>dependent of inositol phospholipid metabolism, may be<br>enceptor and example of a receptor-operated channel (34).<br>In this section I have attempted to summarize the<br>post<br> an example or a receptor-operated channel (34).<br>
In this section I have attempted to summarize the po<br>
pharmacological properties of  $\alpha_1$ -adrenergic receptors L<br>
and the mechanism(s) by which they initiate signals in<br>
t In this section I have attempted to summarize the post-<br>pharmacological properties of  $\alpha_1$ -adrenergic receptors Land<br>the mechanism(s) by which they initiate signals in<br>target cells. I have concentrated most heavily on t and the mechanism(s) by which they initiate signals in rectarget cells. I have concentrated most heavily on the bepharmacological heterogeneity which has been observed ges between  $\alpha_1$ -adrenergic receptors in different pharmacological heterogeneity which has been observed gest<br>between  $\alpha_1$ -adrenergic receptors in different tissues and non<br>attempted to relate these pharmacological differences to also<br>the source of activator  $Ca^{2+}$  for between  $\alpha_1$ -adrenergic receptors in different tissues and not<br>attempted to relate these pharmacological differences to als<br>the source of activator Ca<sup>2+</sup> for tissue responses. Finally, bas<br>I have surveyed the possible attempted to relate these pharmacological differences<br>the source of activator Ca<sup>2+</sup> for tissue responses. Final<br>I have surveyed the possible alternative mechanisms,<br>addition to formation of Ins(1,4,5)P<sub>3</sub>, which might<br>im the source of activator C<br>I have surveyed the possed<br>dition to formation of<br>important in transduction<br>ergic receptor subtype.<br>H Advancenti I have surveyed the possible alternative mechanisms, in<br>addition to formation of  $Ins(1,4,5)P_3$ , which might be<br>important in transduction of signals by a novel  $\alpha_1$ -adre-<br>nergic receptor subtype.<br>II. Adrenergic Receptor

mergic receptor subtype.<br>
II. Adrenergic Receptor Subtypes<br>
In 1948, R. P. Ahlquist (3) began the modern era in<br>
adrenergic pharmacology by recognizing that responses<br>
to adrenergic stimuli could be divided into two major II. Adrenergic Receptor Subtypes<br>In 1948, R. P. Ahlquist (3) began the modern era in<br>adrenergic pharmacology by recognizing that responses<br>to adrenergic stimuli could be divided into two major<br>categories. He proposed that II. Adrenergic Receptor Subtypes<br>In 1948, R. P. Ahlquist (3) began the modern era in<br>adrenergic pharmacology by recognizing that responses<br>to adrenergic stimuli could be divided into two major<br>categories. He proposed that In 1948, R. P. Ahlquist (3) began the modern era in addrenergic pharmacology by recognizing that responses to adrenergic stimuli could be divided into two major receptor categories. He proposed that the two major receptor adrenergic pharmacology by recognizing that responses<br>to adrenergic stimuli could be divided into two major<br>categories. He proposed that the two major receptor<br>subtypes, which he named  $\alpha$  and  $\beta$ -, should be classified to adrenergic stimuli could be divided into two major categories. He proposed that the two major receptor subtypes, which he named  $\alpha$  and  $\beta$ -, should be classified on the basis of their pharmacological properties rath categories. He proposed that the two major receptor<br>subtypes, which he named  $\alpha$  and  $\beta$ -, should be classified<br>on the basis of their pharmacological properties rather<br>than on the type of tissue response caused by recep subtypes, which he named  $\alpha$  and  $\beta$ -, should be classified<br>on the basis of their pharmacological properties rather<br>than on the type of tissue response caused by receptor<br>stimulation. Each receptor subtype could be exci on the basis of their pharmacological properties rather<br>than on the type of tissue response caused by receptor<br>stimulation. Each receptor subtype could be excitatory<br>in some tissues and inhibitory in others, but it was th than on the type of tissue response caused by receptor<br>stimulation. Each receptor subtype could be excitatory<br>in some tissues and inhibitory in others, but it was the<br>ability of the receptors to recognize and respond to<br>ce stimulation. Each receptor subtype could be excitate<br>in some tissues and inhibitory in others, but it was a<br>ability of the receptors to recognize and respond<br>certain drugs which uniquely characterized each subty<br>It was thi in some tissues and inhibitory in others, but it was the ability of the receptors to recognize and respond to extrain drugs which uniquely characterized each subtype. It was this fundamental insight, that receptor classifi ability of the receptors to recognize and respond to<br>certain drugs which uniquely characterized each subtype.<br>It was this fundamental insight, that receptor classifi-<br>cation should be based on the drug specificities of the It was this fundamental insight, that receptor classification should be based on the drug specificities of the receptor recognition site, that laid the groundwork for the important receptor subclassification and selective tion should be based on the drug specificities of the epotype recognition site, that laid the groundwork for eimportant receptor subclassification and selecting development which has occurred subsequently. In the 1960s it receptor recognition site, that laid the groundwork f<br>the important receptor subclassification and selecti-<br>drug development which has occurred subsequently.<br>In the 1960s it became clear that  $\beta$ -adrenergic rece-<br>tors in

the important receptor subclassification and selective drug development which has occurred subsequently.<br>
In the 1960s it became clear that  $\beta$ -adrenergic receptors in different tissues showed different pharmacological A drug development which has occurred subsequently.<br>
In the 1960s it became clear that  $\beta$ -adrenergic recep-<br>
tors in different tissues showed different pharmacological<br>
properties. Lands and coworkers proposed that these<br> In the 1960s it became clear that  $\beta$ -adrenergic rece<br>tors in different tissues showed different pharmacologic<br>properties. Lands and coworkers proposed that the<br>receptors be divided into two subclasses called  $\beta_1$ - an<br> tors in different tissues showed different pharmacologic<br>properties. Lands and coworkers proposed that the<br>receptors be divided into two subclasses called  $\beta_1$ - and<br> $\beta_2$ -adrenergic receptors (195, 196).  $\beta_1$ -Adrener properties. Lands and coworkers proposed that these<br>receptors be divided into two subclasses called  $\beta_1$ - and<br> $\beta_2$ -adrenergic receptors (195, 196).  $\beta_1$ -Adrenergic recep-<br>tors were found predominantly in heart, whil  $\beta_2$ -adrenergic receptors (195, 196).  $\beta_1$ -Adrenergic receptors were found predominantly in heart, while  $\beta_2$ -adrenergic receptors were found predominantly in smooth muscle. Recent evidence from radioligand binding tors were found predominantly in heart, while  $\beta_2$ -adre-<br>nergic receptors were found predominantly in smooth<br>muscle. Recent evidence from radioligand binding assays<br>supports this subclassification and has made it clear mergic receptors were found predominantly in smooth<br>muscle. Recent evidence from radioligand binding assays<br>supports this subclassification and has made it clear that<br>these receptor subtypes can coexist in the same tissue muscie. Recent evidence from radiologiand binding assays<br>supports this subclassification and has made it clear that<br>these receptor subtypes can coexist in the same tissue<br>and on the same cells (248).  $\beta$ -Adrenergic recep these receptor subtypes can coexist in the same tissue<br>and on the same cells (248).  $\beta$ -Adrenergic receptor sub-<br>types show many similarities and only a few differences:<br>both  $\beta_1$  and  $\beta_2$ -adrenergic receptors stimul and on the same cells (248).  $\beta$ -Adrenergic receptor sub-<br>types show many similarities and only a few differences: that<br>both  $\beta_1$  and  $\beta_2$ -adrenergic receptors stimulate formation encor<br>of cyclic AMP as their primary types show many similarities and only a few differences: the both  $\beta_1$  and  $\beta_2$ -adrenergic receptors stimulate formation encof cyclic AMP as their primary mechanism for signal this initiation in cells; and very few dr both  $\beta_1$  and  $\beta_2$ -adrenergic receptors stimulate formation<br>of cyclic AMP as their primary mechanism for signal<br>initiation in cells; and very few drugs show more than a<br>20- to 50-fold difference in potency in binding initiation in cells; and very few drugs show more than a<br>20- to 50-fold difference in potency in binding to the two<br>different subtypes. However, the use of molecular biolog-<br>sucal techniques has demonstrated that the two r 20- to 50-fold difference in potency in binding to the two<br>different subtypes. However, the use of molecular biolog-<br>ical techniques has demonstrated that the two receptor<br>subtypes are not produced by alternative mRNA spli

the properties of each subtype are intrinsic to the recep-MAN<br>the properties of each sub<br>tor gene products (328).<br>In a similar vein, during

addition to formation of  $\text{Ins}(1,4,5)P_3$ , which might be exist on smooth muscle cells and activate contractile<br>important in transduction of signals by a novel  $\alpha_1$ -adre-<br>nergic receptor subtype.<br>II. Adrenergic Receptor IN<br>e properties of each subtype are intrinsic to the recep-<br>r gene products (328).<br>In a similar vein, during the 1970s it became clear that<br>adrenergic receptors in different tissues do not have the properties of each subtype are intrinsic to the receptor gene products (328).<br>In a similar vein, during the 1970s it became clear that  $\alpha$ -adrenergic receptors in different tissues do not have identical pharmacologic the properties of each subtype are intrinsic to the rece<br>tor gene products (328).<br>In a similar vein, during the 1970s it became clear th<br> $\alpha$ -adrenergic receptors in different tissues do not ha<br>identical pharmacological p tor gene products (328).<br>
In a similar vein, during the 1970s it became clear that<br>  $\alpha$ -adrenergic receptors in different tissues do not have<br>
identical pharmacological properties. Based on differ-<br>
ences in the potency In a similar vein, during the 1970s it became clear that  $\alpha$ -adrenergic receptors in different tissues do not have identical pharmacological properties. Based on differences in the potency of phenoxybenzamine in blocking  $\alpha$ -adrenergic receptors in different tissues do not have<br>identical pharmacological properties. Based on differ-<br>ences in the potency of phenoxybenzamine in blocking<br>presynaptic increases in norepinephrine release and<br>po identical pharmacological properties. Based on differences in the potency of phenoxybenzamine in blocking<br>presynaptic increases in norepinephrine release and<br>postsynaptic increases in contractility in cat spleen (70),<br>Lan ences in the potency of phenoxybenzamine in blocking<br>presynaptic increases in norepinephrine release and<br>postsynaptic increases in contractility in cat spleen (70),<br>Langer (197) proposed that postsynaptic  $\alpha$ -adrenergic<br> presynaptic increases in norepinephrine release and<br>postsynaptic increases in contractility in cat spleen (70),<br>Langer (197) proposed that postsynaptic  $\alpha$ -adrenergic<br>receptors be referred to as  $\alpha_1$ , and presynaptic r postsynaptic increases in contractinty in cat spieen ( $10$ ),<br>Langer (197) proposed that postsynaptic  $\alpha$ -adrenergic<br>receptors be referred to as  $\alpha_2$ . Berthelsen and Pettinger (23) sug-<br>gested that  $\alpha_2$ -adrenergic rec receptors be referred to as  $\alpha_1$ , and presynaptic receptors<br>be referred to as  $\alpha_2$ . Berthelsen and Pettinger (23) sug-<br>gested that  $\alpha_2$ -adrenergic receptors may have several<br>nonneuronal effects and proposed that the be referred to as  $\alpha_2$ . Berthelsen and Pettinger (23) suggested that  $\alpha_2$ -adrenergic receptors may have several nonneuronal effects and proposed that these receptors also be classified pharmacologically rather than on gested that  $\alpha_2$ -adrenergic receptors may have several<br>nonneuronal effects and proposed that these receptors<br>also be classified pharmacologically rather than on the<br>basis of their anatomical localization. The subsequent nonneuronal effects and proposed that these receptors<br>also be classified pharmacologically rather than on the<br>basis of their anatomical localization. The subsequent<br>realization that  $\alpha_2$ - as well as  $\alpha_1$ -adrenergic re also be classified pharmacologically rather than on the<br>basis of their anatomical localization. The subsequent<br>realization that  $\alpha_2$ - as well as  $\alpha_1$ -adrenergic receptors<br>exist on smooth muscle cells and activate cont basis of their anatomical localization. The subsequent<br>realization that  $\alpha_2$ - as well as  $\alpha_1$ -adrenergic receptors<br>exist on smooth muscle cells and activate contractile<br>responses (90, 96, 199, 322, 339, 344) supported realization that  $\alpha_2$ - as well as  $\alpha_1$ -adrenergic receptors exist on smooth muscle cells and activate contractile responses (90, 96, 199, 322, 339, 344) supported the importance of classifying these receptor subtypes exist on smooth muscle cells and activate contractile<br>responses (90, 96, 199, 322, 339, 344) supported the<br>importance of classifying these receptor subtypes on the<br>basis of their drug specificities, rather than by where<br>t responses (90, 96, 199, 322, 339, 344) supported the<br>importance of classifying these receptor subtypes on the<br>basis of their drug specificities, rather than by where<br>they are located or what type of response they subserve Importance or classirying these receptor subtypes on the basis of their drug specificities, rather than by where they are located or what type of response they subserve. It subsequently also became clear that  $\alpha_1$ -adren basis of their drug specificities, rather than by where<br>they are located or what type of response they subserve.<br>It subsequently also became clear that  $\alpha_1$ -adrenergic<br>receptors could exist on presynaptic nerve terminal they are located or what type of responently also became clear therefores could exist on presynaptic nerves in 190, 225, 327), particularly regulating to from sympathetic nerves in rat heart.<br>It is remarkable that, althou subsequently also became clear that  $\alpha_1$ -adrenergic<br>ceptors could exist on presynaptic nerve terminals (89,<br>0, 225, 327), particularly regulating transmitter release<br>om sympathetic nerves in rat heart.<br>It is remarkable receptors could exist on presynaptic nerve terminals<br>190, 225, 327), particularly regulating transmitter rel<br>from sympathetic nerves in rat heart.<br>It is remarkable that, although  $\alpha$ -adrenergic recept<br>were subclassified

150, 220, 327), particularly regulating transmitter release<br>from sympathetic nerves in rat heart.<br>It is remarkable that, although  $\alpha$ -adrenergic receptors<br>were subclassified almost a decade later than  $\beta$ -adrenergic<br>gic Trom sympathetic herves in rat heart.<br>It is remarkable that, although  $\alpha$ -adrenergic receptors<br>were subclassified almost a decade later than  $\beta$ -adrenergic<br>receptors, the  $\alpha$ -adrenergic receptor subtypes appear<br>to be m It is remarkable that, although  $\alpha$ -adrenergic receptors<br>were subclassified almost a decade later than  $\beta$ -adrener-<br>gic receptors, the  $\alpha$ -adrenergic receptor subtypes appear<br>to be much less closely related than  $\beta$ -a gic receptors, the  $\alpha$ -adrenergic receptor subtypes appear<br>to be much less closely related than  $\beta$ -adrenergic receptor<br>subtypes. Highly selective agonists and antagonists with<br>substantially different affinities for  $\alpha$ to be much less closely related than  $\beta$ -adrenergic receptory subtypes. Highly selective agonists and antagonists versibles abstantially different affinities for  $\alpha_1$ - and  $\alpha_2$ -adrene receptors were discovered within subtypes. Fightly selective agonists and antagonists with<br>substantially different affinities for  $\alpha_1$ - and  $\alpha_2$ -adrenergic<br>receptors were discovered within a few years of the<br>original subclassification (50, 323). Anta substantially different affinities for  $\alpha_1$ - and  $\alpha_2$ -adrenerg<br>receptors were discovered within a few years of the<br>original subclassification (50, 323). Antagonist selectiv<br>ties of two or three orders of magnitude bet receptors were discovered within a rew years of the<br>original subclassification (50, 323). Antagonist selectivi-<br>ties of two or three orders of magnitude between  $\alpha_1$ - and<br> $\alpha_2$ -adrenergic receptors are not uncommon, wh ties of two or three orders of magnitude between  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors are not uncommon, while selectivities of only one to two orders of magnitude are more commonly observed for  $\beta_1$ - and  $\beta_2$ -adren  $\alpha_2$ -adrenergic receptors are not uncommon, while sel<br>tivities of only one to two orders of magnitude are m<br>commonly observed for  $\beta_1$ - and  $\beta_2$ -adrenergic receptor<br>Although  $\beta_1$ - and  $\beta_2$ -adrenergic receptors a tivities of only one to two orders of magnitude are more<br>commonly observed for  $\beta_1$ - and  $\beta_2$ -adrenergic receptors.<br>Although  $\beta_1$ - and  $\beta_2$ -adrenergic receptors appear to share<br>a common signal transduction mechani commonly observed for  $\beta_1$ - and  $\beta_2$ -adrenergic receptors.<br>Although  $\beta_1$ - and  $\beta_2$ -adrenergic receptors appear to share<br>a common signal transduction mechanism, i.e., stimula-<br>tion of cyclic AMP formation,  $\alpha_1$ - Although  $\beta_1$ - and  $\beta_2$ -adrenergic receptors appear to share<br>a common signal transduction mechanism, i.e., stimula-<br>tion of cyclic AMP formation,  $\alpha_1$ - and  $\alpha_2$ -adrenergic<br>receptors use completely different mechan a common signal transduction mechanism, i.e., stimulation of cyclic AMP formation,  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors use completely different mechanisms for initiating signals in their target cells.  $\alpha_1$ -Adrenergi tion of cyclic AMP formation,  $\alpha_1$ - and  $\alpha_2$ -adrenergic<br>receptors use completely different mechanisms for initi-<br>ating signals in their target cells.  $\alpha_1$ -Adrenergic receptors<br>appear to control cytosolic Ca<sup>2+</sup> leve receptors use completely different mechanisms for initiating signals in their target cells.  $\alpha_1$ -Adrenergic receptors appear to control cytosolic Ca<sup>2+</sup> levels through effects on inositol phospholipid metabolism, while ating signals in their<br>appear to control cy<br>inositol phospholip<br>receptors inhibit ad<br>AMP levels (103).<br>These observatio pear to control cytosolic Ca<sup>2+</sup> levels through effects on<br>ositol phospholipid metabolism, while  $\alpha_2$ -adrenergic<br>ceptors inhibit adenylate cyclase and decrease cyclic<br>MP levels (103).<br>These observations raise the intere inositol phospholipid metabolism, while  $\alpha_2$ -adrenergic<br>receptors inhibit adenylate cyclase and decrease cyclic<br>AMP levels (103).<br>These observations raise the interesting possibility<br>that each major  $\alpha$ -adrenergic rece

receptors inhibit adenylate cyclase and decrease cyclic<br>AMP levels (103).<br>These observations raise the interesting possibility<br>that each major  $\alpha$ -adrenergic receptor subtype might<br>encompass a family of more closely rela AMP levels (103).<br>These observations raise the interesting possibility<br>that each major  $\alpha$ -adrenergic receptor subtype might<br>encompass a family of more closely related subtypes. In<br>this article I will discuss the evidenc that each major  $\alpha$ -adrenergic receptor subtype might<br>encompass a family of more closely related subtypes. In<br>this article I will discuss the evidence for the existence<br>of subtypes of  $\alpha_1$ -adrenergic receptors. It is i encompass a family of more closely related subtypes. In<br>this article I will discuss the evidence for the existence<br>of subtypes of  $\alpha_1$ -adrenergic receptors. It is interesting<br>to note, however, that several lines of evid this article I will discuss the evidence for the existence of subtypes of  $\alpha_1$ -adrenergic receptors. It is interestint to note, however, that several lines of evidence no suggest that there are pharmacologically distinc or subtypes of  $\alpha_1$ -adrenergic receptors. It is interesting<br>to note, however, that several lines of evidence now<br>suggest that there are pharmacologically distinct sub-<br>types of  $\alpha_2$ -adrenergic receptors. Differences i

 $\alpha_1$ -ADRENERGIC RECE<br>adrenergic receptors have been shown to accelerate Na<sup>+</sup>/ il<br>H<sup>+</sup> exchange in addition to inhibiting adenylate cyclase cativity (158). Finally, cloning of the gene for the  $\alpha_2$ - d  $\alpha_1$ -ADRENERGIC RECE<br>adrenergic receptors have been shown to accelerate Na<sup>+</sup>/ il<br>H<sup>+</sup> exchange in addition to inhibiting adenylate cyclase c<br>activity (158). Finally, cloning of the gene for the  $\alpha_2$ - d<br>adrenergic rec adrenergic receptors have been shown to accelerate Na<sup>+</sup>/ ile :<br>H<sup>+</sup> exchange in addition to inhibiting adenylate cyclase certactivity (158). Finally, cloning of the gene for the  $\alpha_2$ - dianadrenergic receptor in human p attenergic receptors have been shown to accelerate iva  $H^+$  exchange in addition to inhibiting adenylate cyclase activity (158). Finally, cloning of the gene for the  $\alpha_2$ -adrenergic receptor in human platelets has reve activity (158). Finally, cloning of the gene for the  $\alpha_2$ - diated adrenergic receptor in human platelets has revealed two dow related genes which hybridize under low stringency conditions, possibly coding for additional related genes which hybridize under low stringency conditions, possibly coding for additional  $\alpha_2$ -adrenergic receptor subtypes (189). It will be interesting, therefore, to ceptors in different tissues. examine more closely the properties of α-adrenergic receptors in different tissues.<br> **III.**  $\alpha_1$ -Adrenergic Receptors<br>  $\alpha_1$ -Adrenergic receptors are generally defined as receptors which are potently blocked by the co

**III.**  $\alpha_1$ -**Adrenergic Receptors**<br> $\alpha_1$ -**Adrenergic receptors are generally defined as recep**ceptors in different tissues.<br>  $III. \alpha_1$ -Adrenergic Receptors<br>  $\alpha_1$ -Adrenergic receptors are generally defined as recep-<br>
tors which are potently blocked by the competitive an-<br>
tagonists phentolamine and prazosin, irrev III.  $\alpha_1$ -Adrenergic Receptors<br>  $\alpha_1$ -Adrenergic receptors are generally defined as recep-<br>
tors which are potently blocked by the competitive an-<br>
tagonists phentolamine and prazosin, irreversibly<br>
blocked by the alky  $\alpha_1$ -Adrenergic receptors are generally defined as receptors  $\alpha_1$ -Adrenergic receptors are generally defined as receptors which are potently blocked by the competitive antagonists phentolamine and prazosin, irreversib  $\alpha_1$ -Adrenergic receptors are generally defined as receptors which are potently blocked by the competitive antagonists phentolamine and prazosin, irreversibly tivelends by the alkylating agent phenoxybenzamine, and ince tors which are potently blocked by the competitive an-<br>tagonists phentolamine and prazosin, irreversibly t<br>blocked by the alkylating agent phenoxybenzamine, and is<br>selectively stimulated by the agonists phenylephrine and tagonists phentolamine and prazosin, irreversibly<br>blocked by the alkylating agent phenoxybenzamine, and<br>selectively stimulated by the agonists phenylephrine and<br>methoxamine. In addition, a wide variety of other drugs<br>are a blocked by the alkylating agent phenoxybenzamine, and<br>selectively stimulated by the agonists phenylephrine and<br>methoxamine. In addition, a wide variety of other drugs<br>are available to distinguish these receptors from other methoxamine. In addition, a wide variety of other drugs<br>are available to distinguish these receptors from other<br>adrenergic receptor subtypes, including both competitive<br>antagonists, alkylating agents, and agonists. Example methoxamine. In addition, a wide variety of other drugs are available to distinguish these receptors from other adrenergic receptor subtypes, including both competitive antagonists, alkylating agents, and agonists. Example are avail<br>adrenerg<br>antagoni<br>of such<br>ble 1.<br> $\alpha_1$ -Adı antagonists, alkylating agents, and agonists. Example<br>of such drugs mentioned in this review are given in ta<br>ble 1.<br> $\alpha_1$ -Adrenergic receptors are found in almost all mam-<br>malian tissues, but serve a particularly importa

ble 1. agoing  $\alpha_1$ -Adrenergic receptors are found in almost all mam-<br>malian tissues, but serve a particularly important func-<br>tion in smooth muscle. Norepinephrine released from bloc<br>sympathetic nerves acts on  $\alpha_1$ -ad  $\alpha_1$ -Adrenergic receptors are found in almost all mam-<br>malian tissues, but serve a particularly important func-<br>tion in smooth muscle. Norepinephrine released from<br>sympathetic nerves acts on  $\alpha_1$ -adrenergic receptors malian tissues, but serve a particularly important function in smooth muscle. Norepinephrine released from bisympathetic nerves acts on  $\alpha_1$ -adrenergic receptors to increase cytosolic Ca<sup>2+</sup> and promote smooth muscle co tion in smooth muscle. Norepinephrine released from blood<br>sympathetic nerves acts on  $\alpha_1$ -adrenergic receptors to nation<br>increase cytosolic Ca<sup>2+</sup> and promote smooth muscle concrisis,<br>traction, and this appears to be on sympathetic nerves acts on  $\alpha_1$ -adrenergic receptors to<br>increase cytosolic Ca<sup>2+</sup> and promote smooth muscle con-<br>traction, and this appears to be one of the primary<br>mechanisms by which the sympathetic nervous system<br>con traction, and this appears to be one of the primary<br>mechanisms by which the sympathetic nervous system<br>controls total peripheral resistance  $(44)$ .  $\alpha_1$ -Adrenergic<br>receptors are also probably very important in the centr mechanisms by which the sympathetic nervous system<br>controls total peripheral resistance  $(44)$ .  $\alpha_1$ -Adrenergic<br>receptors are also probably very important in the central<br>nervous system. While their precise function is s controls total peripheral resistance  $(44)$ .  $\alpha_1$ -Adrenergic<br>receptors are also probably very important in the central<br>nervous system. While their precise function is still<br>uncertain, there is a high density of this sub receptors are also probably very important in the central<br>nervous system. While their precise function is still<br>uncertain, there is a high density of this subtype in most<br>brain regions (167), and specific agonists and anta mervous system. While their precise idirction is still<br>uncertain, there is a high density of this subtype in most<br>brain regions (167), and specific agonists and antagonists<br>have marked effects on membrane currents in neuro

**PECEPTOR SUBTAPLE 1**<br> *Berthelsen and Pettinger (23), Starke (322), and Timmermans and van*<br> *Berthelsen and Pettinger (23), Starke (322), and Timmermans and van*<br> *Zwieten (344) for references].* Iip *ZABLE 1*<br>*Drugs useful in classifying α-adrenergic receptor subtypes [see*<br>*Berthelsen and Pettinger (23), Starke (322), and Timmermans and van*<br>*Zwieten (344) for references]*.

	LWIEVEIL (J44) JUT TEJETEIKESJ.		
	$\alpha_1$ selective	$\alpha_2$ selective	Nonselective
Antagonists	Prazosin	Yohimbine	Phentolamine
	BE 2254	<b>Rauwolacine</b>	Dihydroergot-
	<b>WB 4101</b>	Idazoxan	amine
	Indoramin	Piperoxan	
Agonists	<b>Phenyl-</b>	Clonidine	Norepinephrine
	ephrine	UK 14.304	Epinephrine
	Methox- amine	Guanabenz <b>BHT 920</b>	
	Cirazoline		
	6-Fluorono- repine- phrine		
Alkylating agents	<b>Phenoxy-</b>		<b>EEDO</b>
	benzamine Dibenamine		Benextramine

EPTOR SUBTYPES<br>
ile status of nonvascular smooth muscles (44), and under<br>
certain physiological conditions it is responsible for me-<br>
diating the effects of catecholamines on glycogen break-EPTOR SUBTYPES<br>ile status of nonvascular smooth muscles (44), and und<br>certain physiological conditions it is responsible for n<br>diating the effects of catecholamines on glycogen break-<br>down in liver (154).  $\alpha_1$ -ADRENERGIC RECEPTOR SUBTYPES<br>to accelerate Na<sup>+</sup>/ ile status of nonvascular smooth muscles (44), and under<br>adenylate cyclase certain physiological conditions it is responsible for me-<br>gene for the  $\alpha_2$ - diating t is status of nonvascular smooth muscles (44), and under<br>rtain physiological conditions it is responsible for me-<br>ating the effects of catecholamines on glycogen break-<br>wn in liver (154).<br>An intriguing question about  $\alpha_1$ 

function which has been receiving much recent attention<br>function which has been receiving much recent attention<br>is the possibility that this subtype may be involved in<br>some of the effects of catecholamines on the heart. down in liver (154).<br>An intriguing question about  $\alpha_1$ -adrenergic receptor<br>function which has been receiving much recent attention<br>is the possibility that this subtype may be involved in<br>some of the effects of catechola Although these effects are generally mediated by  $\beta$ -ad-<br>some of the effects of catecholamines on the heart.<br>Although these effects are generally mediated by  $\beta$ -ad-<br>renergic receptors, it is now clear that  $\alpha_1$ -adren is the possibility that this subtype may be involved in some of the effects of catecholamines on the heart.<br>Although these effects are generally mediated by  $\beta$ -adenergic receptors, it is now clear that  $\alpha_1$ -adrenergic Some of the enects of catecholamines on the heart.<br>Although these effects are generally mediated by  $\beta$ -ad-<br>renergic receptors, it is now clear that  $\alpha_1$ -adrenergic<br>receptors exist in this tissue in some species in a d renergic receptors, it is now clear that  $\alpha_1$ -adrenergic<br>receptors exist in this tissue in some species in a density<br>similar to or even greater than that of  $\beta$ -adrenergic<br>receptors. Stimulation of these receptors caus receptors exist in this tissue in some species in a density<br>similar to or even greater than that of  $\beta$ -adrenergic<br>receptors. Stimulation of these receptors causes a rela-<br>tively slow positive inotropic response in many similar to or even greater than that of  $\beta$ -adrenergic<br>receptors. Stimulation of these receptors causes a rela-<br>tively slow positive inotropic response in many species,<br>including man (18, 40, 317, 362), as well as a posi receptors. Stimulation of these receptors causes a relatively slow positive inotropic response in many species, including man (18, 40, 317, 362), as well as a positive chronotropic response in rat heart (104, 347). Althoug tively slow positive inotropic response in many speci<br>including man (18, 40, 317, 362), as well as a positic<br>chronotropic response in rat heart (104, 347). Althou<br>the functional role of these receptors is obscure, th<br>may f including man (18, 40, 317, 362), as well as a positive<br>chronotropic response in rat heart (104, 347). Although<br>the functional role of these receptors is obscure, they<br>may function as a reserve mechanism for cardiac stimu ronotropic response in rat heart (104, 347). Although<br>e functional role of these receptors is obscure, they<br>ay function as a reserve mechanism for cardiac stimu-<br>ion under various stressful or pathological conditions.<br>It

ble 1. agonists and antagonists selective for this receptor type<br> $\alpha_1$ -Adrenergic receptors are found in almost all mam-<br>malian tissues, but serve a particularly important func-<br>tions, including relieving nasal congestio the functional role of these receptors is obscure, they may function as a reserve mechanism for cardiac stimulation under various stressful or pathological conditions.<br>It is clear that  $\alpha_1$ -adrenergic receptors play a v hagonists and are interesting to tradition under various stressful or pathological conditions.<br>It is clear that  $\alpha_1$ -adrenergic receptors play a variety<br>of important roles in mammalian physiology. Similarly,<br>agonists an of important roles in mammalian physiology. Similarly, of important roles in mammalian physiology. Similar agonists and antagonists selective for this receptor ty have found widespread use in various clinical applicions, including relieving nasal congestion, reducing look bloo agonists and antagonists selective for this receptor type<br>have found widespread use in various clinical applica-<br>tions, including relieving nasal congestion, reducing local<br>blood flow, inducing mydriasis for ophthalamic ex nave round wheespread use in various clinical applicions, including relieving nasal congestion, reducing loblood flow, inducing mydriasis for ophthalamic exametions, and in treatment of hypertension, hypertens crisis, pheo crisis, pheochromocytoma, and paroxysmal atrial tachy-<br> **IV. Signal Transduction through Inositol<br>
Phospholipid Metabolism** 

## **IV. Signal Transduction through Inositol**

 $\alpha_1$ -Adrenergic receptors are among those receptors IV. Signal Transduction through Inositol<br>
Phospholipid Metabolism<br>  $\alpha_1$ -Adrenergic receptors are among those receptors<br>
which utilize changes in intracellular free Ca<sup>2+</sup> as their<br>
primary signal transduction mechanism. **Phospholipid Metabolism**<br> $\alpha_1$ -Adrenergic receptors are among those receptors<br>which utilize changes in intracellular free  $Ca^{2+}$  as their<br>primary signal transduction mechanism. Recent rapid<br>progress in this field has l  $\alpha_1$ -Adrenergic receptors are among those receptors<br>which utilize changes in intracellular free Ca<sup>2+</sup> as their<br>primary signal transduction mechanism. Recent rapid<br>progress in this field has led to a detailed understand primary signal transduction mechanism. Recent rapid<br>progress in this field has led to a detailed understanding<br>of the mechanisms by which these receptors control the primary signal transduction mechanism. Recent rapid<br>progress in this field has led to a detailed understanding<br>of the mechanisms by which these receptors control the<br>mobilization of stored intracellular  $Ca^{2+}$ . Like othe progress in this field has led to a detailed understanding<br>of the mechanisms by which these receptors control the<br>mobilization of stored intracellular  $Ca^{2+}$ . Like other<br>" $Ca^{2+}$ -mobilizing" receptors, activation of  $\alpha_$ of the mechanisms by which these receptors control the mobilization of stored intracellular  $Ca^{2+}$ . Like other " $Ca^{2+}$ -mobilizing" receptors, activation of  $\alpha_1$ -adrenergic receptors increases the hydrolysis of a speci "Ca<sup>2+</sup>-mobilizing" receptors, activation of  $\alpha_1$ -adrenergic<br>receptors increases the hydrolysis of a specific membrane<br>lipid to release diffusible second messenger substances<br>into the cell cytosol.<br>For many years, numer receptors increases the hydrolysis of a specific membrane<br>lipid to release diffusible second messenger substances<br>into the cell cytosol.<br>For many years, numerous reports linked stimulation<br>of  $\alpha$ -adrenergic receptors to lipid to release diffusible second messenger substances

lipid to release diffusible second messenger substances<br>into the cell cytosol.<br>For many years, numerous reports linked stimulation<br>of  $\alpha$ -adrenergic receptors to increases in turnover of the<br>membrane lipid phosphatidylin into the cell cytosol.<br>
For many years, numerous reports linked stimulation<br>
of  $\alpha$ -adrenergic receptors to increases in turnover of the<br>
membrane lipid phosphatidylinositol (145, 172). Michell<br>
(237) proposed that all r membrane lipid phosphatidylinositol (145, 172). Michell (237) proposed that all receptors which increase cytosolic  $Ca^{2+}$  levels also increase turnover of phosphatidylinositol, and proposed that this effect might be invo of  $\alpha$ -adrenergic receptors to increases in turnover of the<br>membrane lipid phosphatidylinositol (145, 172). Michell<br>(237) proposed that all receptors which increase cytosolic<br>Ca<sup>2+</sup> levels also increase turnover of phosp membrane lipid phosphatidylinositol (145, 172). Michell (237) proposed that all receptors which increase cytosolic  $Ca^{2+}$  levels also increase turnover of phosphatidylinositol, and proposed that this effect might be invo (237) proposed that all receptors which increase cytosolic  $Ca^{2+}$  levels also increase turnover of phosphatidylinositol, and proposed that this effect might be involved in the opening of  $Ca^{2+}$  gates. This hypothesis wa Ca<sup>-1</sup> levels also increase turnover of phosphatidylinositol, and proposed that this effect might be involved in the opening of  $Ca^{2+}$  gates. This hypothesis was strongly supported by the results of Fain and Berridge (10 to, and proposed that this effect might be involved in<br>the opening of  $Ca^{2+}$  gates. This hypothesis was strongly<br>supported by the results of Fain and Berridge (102) who<br>showed that phosphatidylinositol breakdown appeared the opening of Ca<sup>2</sup> gates. This hypothesis was strongly supported by the results of Fain and Berridge (102) who showed that phosphatidylinositol breakdown appeared to be intimately involved in the stimulation of fluid sec supported by the results of Fain and Berridge (102) who<br>showed that phosphatidylinositol breakdown appeared<br>to be intimately involved in the stimulation of fluid<br>secretion by serotonin in an insect salivary gland. Their<br>re to be intimately involved in the stimulation of fluid secretion by serotonin in an insect salivary gland. Their results made it clear that breakdown of phosphatidylinositol was probably an important pathway for the for-<br>m secretion by serotonin in an insect sailwary giand. I heir<br>results made it clear that breakdown of phosphatidyli-<br>nositol was probably an important pathway for the for-<br>mation of second messengers involved in control of c

90 MINNE postulated that this was the major mechanism of signal transduction for  $\alpha_1$ -adrenergic receptors. 90<br>postulated that this was the major mech<br>transduction for  $\alpha_1$ -adrenergic receptors.<br>Phosphatidylinositol is unique among

MINN<br>stulated that this was the major mechanism of signal<br>ansduction for  $\alpha_1$ -adrenergic receptors.<br>Phosphatidylinositol is unique among membrane lip-<br>in that it also occurs in two more highly phosphorylpostulated that this was the major mechanism of s<br>transduction for  $\alpha_1$ -adrenergic receptors.<br>Phosphatidylinositol is unique among membrane<br>ids in that it also occurs in two more highly phosph<br>ated forms, i.e., phosphat transduction for  $\alpha_1$ -adrenergic receptors.<br>
Phosphatidylinositol is unique among membrane lip-<br>
ids in that it also occurs in two more highly phosphoryl-<br>
ated forms, i.e., phosphatidylinositol-4-monophosphate<br>
(PIP) a transduction for  $\alpha_1$ -adrenergic receptors.<br>
Phosphatidylinositol is unique among membrane lip-<br>
ids in that it also occurs in two more highly phosphoryl-<br>
ated forms, i.e., phosphatidylinositol-4-monophosphate<br>
(PIP) a Further work, particularly by Berridge and colleagues,<br>
Further work, phosphatidylinositol-4-monophosphat<br>
(PIP) and phosphatidylinositol-4,5-bisphosphate (PIP<sub>2</sub>)<br>
Further work, particularly by Berridge and colleagues<br>
m ated forms, i.e., phosphatidylinositol-4-monophosple (PIP) and phosphatidylinositol-4,5-bisphosphate (PI<br>Further work, particularly by Berridge and colleage made it clear that stimulation of  $Ca^{2+}$ -mobilizing retors caus (PIP) and phosphatidylinositol-4,5-bisphosphate (PIP<sub>2</sub>). tion<br>Further work, particularly by Berridge and colleagues, bisp<br>made it clear that stimulation of  $Ca^{2+}$ -mobilizing recep-cyc<br>tors causes activation of a membran made it clear that stimulation of  $Ca^{2+}$ -mobilizing receptors causes activation of a membrane-bound phospholipase C to catalyze the breakdown primarily of PIP<sub>2</sub>, and release diacylglycerol and  $\text{Ins}(1,4,5)P_3$  (21). The made it clear that stimulation of  $Ca^{2+}$ -mobilizing recep-cycl<br>tors causes activation of a membrane-bound phospholi-pase<br>pase C to catalyze the breakdown primarily of PIP<sub>2</sub>, and<br>release diacylglycerol and Ins(1,4,5)P<sub>3</sub> tors causes activation of a membrane-bound phospholi-<br>pase C to catalyze the breakdown primarily of  $\text{PIP}_2$ , and<br>release diacylglycerol and  $\text{Ins}(1,4,5)P_3$  (21). The forma-<br>intion of  $\text{Ins}(1,4,5)P_3$  appears to link re pase C to catalyze the breakdown primarily of PIP;<br>release diacylglycerol and  $\text{Ins}(1,4,5)P_3$  (21). The form of  $\text{Ins}(1,4,5)P_3$  appears to link receptor activativelease of intracellular  $\text{Ca}^{2+}$ , since this compounds release diacylglycerol and  $\text{Ins}(1,4,5)P_3$  (21). The formation of  $\text{Ins}(1,4,5)P_3$  appears to link receptor activation to release of intracellular  $\text{Ca}^{2+}$ , since this compound was soon shown to cause release of  $\text{Ca$ tion of  $\text{Ins}(1,4,5)P_3$  appears to link receptor activation to release of intracellular  $\text{Ca}^{2+}$ , since this compound was soon shown to cause release of  $\text{Ca}^{2+}$  from nonmitochondrial intracellular stores in a vari soon shown to cause release of  $Ca^{2+}$  from nonmitochondrial intracellular stores in a variety of cell types (174, 329). Interestingly, the diacylglycerol released also appears to serve a second messenger function; this c soon shown to cause release of  $Ca^{2+}$  from nonmitoch drial intracellular stores in a variety of cell types (1<br>329). Interestingly, the diacylglycerol released also a pears to serve a second messenger function; this co<br>po drial intracellular stores in a variety of cell types (174, P-<br>329). Interestingly, the diacylglycerol released also ap-<br>pears to serve a second messenger function; this com-<br>pound activates protein kinase C by reducing i 329). Interestingly, the diacylglycerol released also ap<br>pears to serve a second messenger function; this com<br>pound activates protein kinase C by reducing its require<br>ment for Ca<sup>2+</sup> (261). Thus agonist-induced hydrolysis pears to serve a second messenger function; this com-<br>pound activates protein kinase C by reducing its require-<br>ment for  $Ca^{2+}$  (261). Thus agonist-induced hydrolysis of<br> $\text{PIP}_2$  generates two intracellular messengers,<br> pound activates protein kinase C by reducing its require-<br>ment for Ca<sup>2+</sup> (261). Thus agonist-induced hydrolysis of<br>PIP<sub>2</sub> generates two intracellular messengers, an<br>Ins(1,4,5)P<sub>3</sub>, which mobilizes stored intracellular Ca ment for  $Ca^{2+}$  (261). Thus agon<br>PIP<sub>2</sub> generates two inti<br>Ins(1,4,5)P<sub>3</sub>, which mobilizes s<br>and diacylglycerol, which activ<br>specific cellular proteins (20).<br>There is strong evidence tha  $P_2$  generates two intracellular messengers,<br>s(1,4,5) $P_3$ , which mobilizes stored intracellular Ca<sup>2+</sup>,<br>d diacylglycerol, which activates phosphorylation of<br>ecific cellular proteins (20).<br>There is strong evidence that

and diacylgiverol, which activates phosphorylation of  $\alpha$ <br>specific cellular proteins (20). There is strong evidence that  $\alpha_1$ -adrenergic receptor his<br>activation causes hydrolysis of inositol phospholipids in almost all incre is strong evidence that  $\alpha_1$ -addeneity<br>activation causes hydrolysis of inositol phosphamost all tissues where this phenomenon<br>looked for. The use of lithium to inhibit brinositol monophosphates by myo-inositolmo.<br> activation causes hydrotysis of mositor phosphonpids in<br>almost all tissues where this phenomenon has been yet<br>inositol monophosphates by myo-inositolmonophospha-<br>tases (22, 127) has made it relatively easy to examine into<br> looked for. The use of lithium to inhibit breakdown<br>inositol monophosphates by myo-inositolmonophospl<br>tases (22, 127) has made it relatively easy to exami<br>accumulation of [<sup>3</sup>H]inositol phosphates in response<br>receptor act mositor inonophosphates by myo-mositonionophospha-<br>tases (22, 127) has made it relatively easy to examine<br>accumulation of [<sup>3</sup>H]inositol phosphates in response to<br>receptor activation. Increased accumulation of [<sup>3</sup>H]ino-<br> tases (22, 127) has made it relatively easy to examined accumulation of [<sup>3</sup>H]inositol phosphates in response receptor activation. Increased accumulation of [<sup>3</sup>H]insitol phosphates in response to  $\alpha_1$ -adrenergic recepa accumulation of  $[^{3}H]$ inositol phosphates in response to<br>receptor activation. Increased accumulation of  $[^{3}H]$ ino-<br>sitol phosphates in response to  $\alpha_1$ -adrenergic receptor<br>activation in the presence of lithium has b receptor activation. Increased accumulation of  $[^{3}H]$ ino-<br>sitol phosphates in response to  $\alpha_1$ -adrenergic receptor<br>activation in the presence of lithium has been demon-<br>strated in parotid (22), brain (22, 42, 247, 306 sitol phosphates in response to  $\alpha_1$ -aurenergic receptor<br>activation in the presence of lithium has been demon-<br>strated in parotid (22), brain (22, 42, 247, 306), liver<br>(275), cultured neuronal and glial cells (122, 269) activation in the presence of itinum has been demon-<br>strated in parotid (22), brain (22, 42, 247, 306), liver<br>(275), cultured neuronal and glial cells (122, 269), cardiac<br>myocytes (43), smooth muscle (110, 360), and kidne (275), cultured neuronal and glial cells (122, 269), cardiac<br>myocytes (43), smooth muscle (110, 360), and kidney<br>mediated alterations in adenylate cyclase activity, it<br>(259) as well as other tissues. Although these report myocytes (43), smooth muscle (110, 360), and kidney (259) as well as other tissues. Although these reports indicate strong correlations between activation of  $\alpha_1$ -adrenergic receptors and increased inositol phospholipid myocytes (45), smooth muscle (110, 300), and kidney<br>(259) as well as other tissues. Although these reports<br>indicate strong correlations between activation of  $\alpha_1$ -<br>adrenergic receptors and increased inositol phospholipi mucate strong correlations between activation of  $u_1$ -<br>adrenergic receptors and increased inositol phospholipid<br>hydrolysis, it is important to remember that what was<br>measured in most of these experiments was only producadrenergic receptors and increased mosttof phosphonpid<br>hydrolysis, it is important to remember that what was<br>measured in most of these experiments was only produc-<br>tion of total [<sup>3</sup>H]inositol phosphates in the presence of mydrotysis, it is important to remember that what was<br>measured in most of these experiments was only produc-<br>tion of total [<sup>3</sup>H]inositol phosphates in the presence of<br>lithium. Individual inositol phosphate species have n tion of total [<sup>3</sup>H]inositol phosphates in the presence of olithium. Individual inositol phosphate species have not cusually been separated or quantified. It is often assumed what the increase in inositol phosphates obser the PIP<sub>2</sub> hydrolysis and formation of Ins(1,4,5)P<sub>3</sub>. How-<br>that the increase in inositol phosphates observed follow-<br>ing  $\alpha_1$ -adrenergic receptor stimulation is due primarily<br>to PIP<sub>2</sub> hydrolysis and formation of Ins(1 that the increase in inositol phosphates observed following  $\alpha_1$ -adrenergic receptor stimulation is due primarily cyto  $\text{PIP}_2$  hydrolysis and formation of  $\text{Ins}(1,4,5)P_3$ . However, this has actually been shown in onl ing  $\alpha_1$ -adrenergic receptor stimulation is due primarily cyclase activity through G proteins was markedly af-<br>to PIP<sub>2</sub> hydrolysis and formation of Ins(1,4,5)P<sub>3</sub>. How-<br>ever, this has actually been shown in only a few ever, this has actually been shown in only a few instances.<br>In most cases the source of the inositol phosphates which<br>accumulate in the presence of lithium has not yet been<br>clearly identified.<br>Although there is widespread er, this has actually been shown in only a few instances. This most cases the source of the inositol phosphates which compulate in the presence of lithium has not yet been GT early identified. diss<br>although there is wides

In most cases the source of the inositol phosphates will accumulate in the presence of lithium has not yet b<br>clearly identified.<br>Although there is widespread agreement that the<br>products of  $\text{PIP}_2$  hydrolysis,  $\text{Ins}(1,4,$ accumulate in the presence of lithium has not yet b<br>clearly identified.<br>Although there is widespread agreement that the t<br>products of  $\text{PIP}_2$  hydrolysis,  $\text{Ins}(1,4,5)\text{P}_3$  and diacylgl<br>erol, play important roles in mob clearly identified.<br>
Although there is widespread agreement that the two<br>
products of  $\text{PIP}_2$  hydrolysis,  $\text{Ins}(1,4,5)P_3$  and diacylglyc-<br>
erol, play important roles in mobilizing stored intracel-<br>
lular Ca<sup>2+</sup> and act Although there is widespread agreement that the two<br>products of  $\text{PIP}_2$  hydrolysis,  $\text{Ins}(1,4,5)P_3$  and diacylglyc-<br>erol, play important roles in mobilizing stored intracel-<br>lular Ca<sup>2+</sup> and activating protein kinase C

Ins(1,4,5)P<sub>3</sub>, which mobilizes stored intracellular Ca<sup>2+</sup>, sitol trisphosphate formed following receptor stimulation<br>and diacylglycerol, which activates phosphorylation of (235). Ins(1,3,4)P<sub>3</sub> appears to be formed by d MAN<br>in the actions of  $Ca^{2+}$ -mobilizing receptors. The situation<br>has recently become more interesting with the realization<br>that inositol phosphate metabolism is extremely com-MAN<br>in the actions of  $Ca^{2+}$ -mobilizing receptors. The situation<br>has recently become more interesting with the realization<br>that inositol phosphate metabolism is extremely com-<br>plex, and other inositol phosphates have bee in the actions of  $Ca^{2+}$ -mobilizing receptors. The situation<br>has recently become more interesting with the realization<br>that inositol phosphate metabolism is extremely com-<br>plex, and other inositol phosphates have been id has recently become more interesting with the realization<br>that inositol phosphate metabolism is extremely com-<br>plex, and other inositol phosphates have been identified<br>which may perform important second messenger func-<br>ti tions. Inositol 1-monophosphate [Ins(1)P], inositol 1,4 that inositol phosphate metabolism is extremely complex, and other inositol phosphates have been identified which may perform important second messenger functions. Inositol 1-monophosphate [Ins(1)P], inositol 1,4-bisphosp plex, and other mositor phosphates have been identify<br>which may perform important second messenger f<br>tions. Inositol 1-monophosphate  $[Ins(1,9P]$ , inositol<br>bisphosphate  $[Ins(1,4)P_2]$ , and  $Ins(1,4,5)P_3$  all exis<br>cyclic forms which may perform important second messenger functions. Inositol 1-monophosphate [Ins(1,9)P], inositol 1,4-<br>bisphosphate [Ins(1,4)P<sub>2</sub>], and Ins(1,4,5)P<sub>3</sub> all exist in<br>cyclic forms which are also made directly by phospho bisphosphate  $\lfloor \text{ins}(1,4)\rfloor r_2$ , and  $\lfloor \text{ins}(1,4,5)\rfloor r_3$  and exist in cyclic forms which are also made directly by phospholipase C attack on phospholipid precursors (221), and in some cases they may be as potent as the cyclic forms which are also made directly by phosphon-<br>pase C attack on phospholipid precursors (221), and in<br>some cases they may be as potent as the noncyclic forms<br>in activating  $Ca^{2+}$  mobilization. In addition,  $\text{Ins$ some cases they may be as potent as the noncyclic forms<br>in activating  $Ca^{2+}$  mobilization. In addition,  $Ins(1,4,5)P_3$ <br>is rapidly phosphorylated in many tissues to form inositol<br>1,3,4,5-tetrakisphosphate  $[Ins(1,3,4,5)P_4]$ in activating Ca<sup>2+</sup> mobilization. In addition, Ins(1,4,5)P<sub>3</sub> is rapidly phosphorylated in many tissues to form inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P<sub>4</sub>] (14, 155). The rapid formation of this compound raises is rapidly phosphorylated in many tissues to form inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P<sub>4</sub>] (14, 155). The rapid formation of this compound raises the interesting possibility that it might also play a second m 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P<sub>4</sub>] (14, 155). The rapid formation of this compound raises the interesting possibility that it might also play a second messenger role, and it has been suggested that  $\text{Ins}(1,3,4,5$ rapid formation of this compound raises the interesting<br>possibility that it might also play a second messenger<br>role, and it has been suggested that  $\text{Ins}(1,3,4,5)P_4$  is<br>involved in opening cell-surface  $\text{Ca}^{2+}$  channe possibility that it might also play a second messenge<br>role, and it has been suggested that  $\text{Ins}(1,3,4,5)P_4$  involved in opening cell-surface  $\text{Ca}^{2+}$  channels (156). Th<br>existence of this compound explains the previou role, and it has been suggested that  $Ins(1,3,4,5)P_4$  is<br>involved in opening cell-surface  $Ca^{2+}$  channels (156). The<br>existence of this compound explains the previously puz-<br>zling fact that inositol 1,3,4-trisphosphate [In mvoived in opening cen-suriace Ca channels (150). The existence of this compound explains the previously puzzling fact that inositol 1,3,4-trisphosphate [Ins(1,3,4)P<sub>3</sub>], and not Ins(1,4,5)P<sub>3</sub>, is in many cases the prima zing fact that mositol 1,3,4-trisphosphate [Ins(1,3,4) $F_3$ ],<br>and not Ins(1,4,5) $P_3$ , is in many cases the primary ino-<br>sitol trisphosphate formed following receptor stimulation<br>(235). Ins(1,3,4) $P_3$  appears to be forme sitol trisphosphate formed following receptor stimulation (235). Ins(1,3,4) $P_3$  appears to be formed by dephosphorylation of Ins(1,3,4,5) $P_4$  (93). Interestingly, even more highly phosphorylated forms of inositol also e (235). Ins(1,3,4) $P_3$  appears to be formed by dephosphorylation of  $Ins(1,3,4,5)P_4$  (93). Interestingly, even more highly phosphorylated forms of inositol also exist in animal cells (12, 137), although no functional role rylation of  $\text{Ins}(1,3,4,5)P_4$  (93). Interestingly, even more highly phosphorylated forms of inositol also exist in animal cells (12, 137), although no functional role has yet been proposed for these compounds. It is like highly phosphorylated forms of inositol also exist in<br>animal cells (12, 137), although no functional role has<br>yet been proposed for these compounds. It is likely that<br>a further understanding of the complicated metabolic<br>pa animal cells (12, 137), although no functional role heat by the mechanisms of these compounds. It is likely the further understanding of the complicated metabol pathways of these compounds will lead to further insigh into duction. For andersaming of the completed measures of these compounds will lead to further instead of the mechanisms of receptor-mediated signal to the nucleotide<br>Regulatory Proteins  $R$  is ms of receptor-mediate<br> **Regulatory Proteins**<br> **Regulatory Proteins**<br> **Regulatory Proteins** 

## V. Involvement of Guanine Nucleotide<br>Regulatory Proteins<br>The mechanism by which  $\alpha_1$ -adrenergic receptor stim-

V. Involvement of Guanine Nucleotide<br>Regulatory Proteins<br>The mechanism by which  $\alpha_1$ -adrenergic receptor stitulation activates PIP<sub>2</sub> breakdown is not yet fully und<br>stood. However, in a manner analogous to recepte **Stoch and Structure Community Community Community Regulatory Proteins**<br>The mechanism by which  $\alpha_1$ -adrenergic receptor stim-<br>ulation activates  $\text{PIP}_2$  breakdown is not yet fully under-<br>stood. However, in a manner ana I he mechanism by which  $\alpha_1$ -adrenergic receptor sum-<br>ulation activates  $\text{PIP}_2$  breakdown is not yet fully under-<br>stood. However, in a manner analogous to receptor-<br>mediated alterations in adenylate cyclase activity, ulation activates  $\text{PIP}_2$  breakdown is not yet fully understood. However, in a manner analogous to receptor-<br>mediated alterations in adenylate cyclase activity, it<br>seems likely that, in at least some cases, a guanine<br>nu stood. However, in a manner a<br>mediated alterations in adenyla<br>seems likely that, in at least s<br>nucleotide regulatory protein (G<br>activation of phospholipase C.<br>The first evidence for involver ediated alterations in adenylate cyclase activity, it<br>
ems likely that, in at least some cases, a guanine<br>
icleotide regulatory protein (G protein) is involved in<br>
itivation of phospholipase C.<br>
The first evidence for inv

seems likely that, in at least some cases, a guanine<br>nucleotide regulatory protein (G protein) is involved in<br>activation of phospholipase C.<br>The first evidence for involvement of a G protein in<br>the actions of  $\alpha_1$ -adren nucleotide regulatory protein (G protein) is involved in<br>activation of phospholipase C.<br>The first evidence for involvement of a G protein in<br>the actions of  $\alpha_1$ -adrenergic receptors came from studies<br>of the effects of g activation of phospholipase C.<br>The first evidence for involvement of a G protein in<br>the actions of  $\alpha_1$ -adrenergic receptors came from studies<br>of the effects of guanine nucleotides on the affinity<br>constants of agonists The first evidence for involvement of a G protein in<br>the actions of  $\alpha_1$ -adrenergic receptors came from studies<br>of the effects of guanine nucleotides on the affinity<br>constants of agonists in radioligand binding studies. or the errects or guanne nucleotides on the arminty<br>constants of agonists in radioligand binding studies. It<br>was well established that the binding affinity of agonists<br>(but not antagonists) for receptors regulating adenyla was well established that the binding affinity of agonists<br>(but not antagonists) for receptors regulating adenylate<br>cyclase activity through G proteins was markedly af-<br>fected by GTP and its nonhydrolyzable analogs (207).<br> (but not antagonists) for receptors regulating adenylate cyclase activity through G proteins was markedly affected by GTP and its nonhydrolyzable analogs (207).<br>This is due to formation of a stable high affinity ternary complex of agonist/receptor/G protein in the absence of GTP discolution of a stable high affinity ternary<br>discomplex of agonist/receptor/G protein in the absence of<br>GTP. This complex is destabilized by GTP to promote<br>dissociation of the G protein, leaving only the relatively<br>low af complex of agonist/receptor/G protein in the absence of GTP. This complex is destabilized by GTP to promote<br>dissociation of the G protein, leaving only the relatively<br>low affinity agonist/receptor complex. Since it was<br>tho GTP. This complex is destabilized by GTP to promote dissociation of the G protein, leaving only the relatively low affinity agonist/receptor complex. Since it was thought that only adenylate cyclase-linked receptors partic dissociation of the G protein, leaving only the relativel<br>low affinity agonist/receptor complex. Since it wa<br>thought that only adenylate cyclase-linked receptors par<br>ticipated in such a GTP-modulated equilibrium, it wa<br>sur low affinity agonist/receptor complex. Since it was<br>thought that only adenylate cyclase-linked receptors par-<br>ticipated in such a GTP-modulated equilibrium, it was<br>surprising when Goodhardt et al. (123) (fig. 1) and Sna-<br>v



PHARMACOLOGICAL REVIEW!

PHARMACOLOGICAL REVIEY

**a**spet



**potency of epinephrine in inhibiting specific [3H]prazosin binding to**<br> **potency of epinephrine in inhibiting specific [3H]prazosin binding to**<br> **potency of epinephrine in inhibiting specific [3H]prazosin binding to**<br> **r rate 10 CEPINEPHRINE) (M)**<br>FIG. 1. Effect of the nonhydrolyzable GTP analog GppNHp on the<br>potency of epinephrine in inhibiting specific [<sup>3</sup>H]prazosin binding to<br>rat liver plasma membranes.  $\bullet$ , assays carried out in the FIG. 1. Effect of the nonhydrolyzable GTP analog GppNHp on t<br>potency of epinephrine in inhibiting specific [<sup>3</sup>H]prazosin binding<br>rat liver plasma membranes.  $\bullet$ , assays carried out in the absence<br>GppNHp; O, assays carrie potency of epinephrine in inhibiting specific [<sup>3</sup>H]prazosin binding to rat liver plasma membranes.  $\bullet$ , assays carried out in the absence of GppNHp; O, assays carried out in the presence of 0.1 mMGppNHp. Note the presenc **for** epinephrine in control tissues. **C**, assays carried out in the absence of GppNHp; O, assays carried out in the presence of 0.1 mMGppNHp. Note the presence of both high and low affinity binding components for epinephr **is to convert all receptors of the all receptors of 0.1 mMGppNHp.** It like Note the presence of both high and low affinity binding components still for epinephrine in control tissues. The effect of the guanine nucleotide Note the presence of both high and for epinephrine in control tissues. This to convert all receptors to the application of the sum Goodhardt et al.  $(123)$  with permission.

For epinephrine in control tissues. The effect of the guanine nucleotide<br>is to convert all receptors to the apparent low affinity state. From<br>Goodhardt et al. (123) with permission.<br>also modulated the affinity constants o Goodhardt et al. (123) with permission.<br>also modulated the affinity constants of agonists at  $\alpha_1$ -<br>adrenergic receptors. This observation was subsequently<br>confirmed by others (38, 66, 215) and was the first<br>evidence tha also modulated the affinity constants of agonists at  $\alpha_1$ -<br>adrenergic receptors. This observation was subsequently<br>confirmed by others (38, 66, 215) and was the first<br>evidence that  $\alpha_1$ -adrenergic receptors could inte adrenergic receptors. This observation was subsequently<br>confirmed by others (38, 66, 215) and was the first<br>evidence that  $\alpha_1$ -adrenergic receptors could interact with<br>G proteins.<br>More direct evidence that G proteins ar renergic receptors. This observation was subsequently photon firmed by others (38, 66, 215) and was the first showed inclease that  $\alpha_1$ -adrenergic receptors could interact with slice proteins. More direct evidence that

confirmed by others  $(38, 66, 215)$  and was the firevidence that  $\alpha_1$ -adrenergic receptors could interact with G proteins.<br>
More direct evidence that G proteins are involved interactions in phospholipase C activity came evidence that  $\alpha_1$ -adrenergic receptors could interact with<br>
G proteins.<br>
More direct evidence that G proteins are involved in<br>
receptor-mediated alterations in phospholipase C activ-<br>
ity came from Gomperts (119) who s G proteins.<br>
More direct evidence that G proteins are involved in  $\frac{2}{2}$ <br>
receptor-mediated alterations in phospholipase C activ-<br>
ity came from Gomperts (119) who showed that guanine<br>
inucleotides stimulated a Ca<sup>2+</sup>more direct evidence that G proteins are involved in 2).<br>
receptor-mediated alterations in phospholipase C activ-<br>
ity came from Gomperts (119) who showed that guanine<br>
nucleotides stimulated a Ca<sup>2+</sup>-dependent secretion ity came from Gomperts (119) who showed that guanine<br>nucleotides stimulated a  $Ca^{2+}$ -dependent secretion of<br>histamine from permeabilized mast cells. Stable analogs<br>of GTP have been shown to activate  $PIP_2$  breakdown in<br>p nucleotides stimulated a  $Ca^{2+}$ -dependent secretion of not inhistamine from permeabilized mast cells. Stable analogs ers (se of GTP have been shown to activate  $\text{PIP}_2$  breakdown in partial permeabilized pancreatic acin histamine from permeabilized mast cells. Stable anal<br>of GTP have been shown to activate  $\text{PIP}_2$  breakdown<br>permeabilized pancreatic acinar cells (236) and neut<br>phils (39), and also in membrane preparations fr<br>neutrophil of GTP have been shown to activate  $\text{PIP}_2$  breakdown in permeabilized pancreatic acinar cells (236) and neutro-<br>phils (39), and also in membrane preparations from<br>neutrophil (64), liver (363), brain (121), turkey erythr permeabilized pancreatic acinar cells (236) and neutro-<br>phils (39), and also in membrane preparations from<br>neutrophil (64), liver (363), brain (121), turkey erythro-<br>cytes (132), and other tissues (209). These results sup phils (39), and also in membrane preparations from Homewort<br>point (64), liver (363), brain (121), turkey erythroweves (132), and other tissues (209). These results support<br>the concept that G proteins regulate the activity heutrophil (04), liver (303), brain (121), turkey erythro-<br>cytes (132), and other tissues (209). These results support<br>the concept that G proteins regulate the activity of<br>phospholipase C. In addition, direct activation of the concept that G proteins regulate the activity of phospholipase C. In addition, direct activation of  $PIP_2$  hydrolysis in membrane preparations has now been observed in response to activation of variety of receptors, i phospholipase C. In addition, direct activation of  $\text{PIP}_2$ <br>hydrolysis in membrane preparations has now been ob-<br>served in response to activation of variety of receptors,<br>including serotonergic (210), muscarinic choliner hydrolysis in membrane preparations has now been observed in response to activation of variety of receptors, including serotonergic (210), muscarinic cholinergic (134),  $\alpha_1$ -adrenergic, vasopressin, and angiotensin (348 served in response to activation of variety of receptors,<br>including serotonergic (210), muscarinic cholinergic V<br>(134),  $\alpha_1$ -adrenergic, vasopressin, and angiotensin (348). As<br>a expected, this activation is dependent on *G* protein. 34),  $\alpha_1$ -adrenergic, vasopressin, and angiotensin (348).<br>
sexpected, this activation is dependent on the presence<br>
guanine nucleotides, supporting the involvement of a<br>
protein.<br>
The identity and properties of the G pr As expected, this activation is dependent on the presence<br>of guanine nucleotides, supporting the involvement of a<br>G protein.<br>The identity and properties of the G protein(s) in-<br>volved are not certain. Pertussis toxin, whi

of guanine nucleotides, supporting the involvement of a G protein.<br>The identity and properties of the G protein(s) involved are not certain. Pertussis toxin, which inactivates the  $G_i$  protein which is responsible for rec The identity and properties of the G protein(s) in-<br>volved are not certain. Pertussis toxin, which inactivates of other mechanisms may be involved in signal transduc-<br>the G<sub>i</sub> protein which is responsible for receptor-med The identity and properties of the G protein(s) in-<br>volved are not certain. Pertussis toxin, which inactivates of<br>the G<sub>i</sub> protein which is responsible for receptor-mediated<br>inhibition of adenylate cyclase (207), blocks a volved are not certain. Pertussis toxin, which inactivates of<br>the  $G_i$  protein which is responsible for receptor-mediated<br>inhibition of adenylate cyclase (207), blocks activation<br>of inositol phospholipid breakdown stimula the G<sub>i</sub> protein which is responsible for receptor-mediated the inhibition of adenylate cyclase (207), blocks activation of inositol phospholipid breakdown stimulated by some in receptor types (39, 257, 274), and blocks s inhibition of adenylate cyclase (207), blocks activation<br>of inositol phospholipid breakdown stimulated by some<br>receptor types (39, 257, 274), and blocks some of the<br>effects of  $\alpha_1$ -adrenergic receptor stimulation in car of inositol phospholipid breakdown stimulated by son<br>receptor types (39, 257, 274), and blocks some of the<br>ffects of  $\alpha_1$ -adrenergic receptor stimulation in cardia<br>myocytes cocultured with sympathetic neurons (324<br>Since receptor types (39, 257, 274), and blocks some of the effects of  $\alpha_1$ -adrenergic receptor stimulation in cardiac myocytes cocultured with sympathetic neurons (324). Since pertussis toxin is thought to selectively ADP-ri

ential engineers and the G protein involved in these<br>
enylate cyclase (114), the G protein involved in these<br>
receptor-mediated alterations in inositol phospholipid EPTOR SUBTYPES 91<br>enylate cyclase (114), the G protein involved in these<br>receptor-mediated alterations in inositol phospholipid<br>hydrolysis may be similar to G<sub>i</sub>. However, in most sys-EPTOR SUBTYPES 91<br>enylate cyclase (114), the G protein involved in these<br>receptor-mediated alterations in inositol phospholipid<br>hydrolysis may be similar to  $G_i$ . However, in most sys-<br>tems, pretreatment with pertussis to enylate cyclase  $(114)$ , the G protein involved in these receptor-mediated alterations in inositol phospholipid hydrolysis may be similar to  $G_i$ . However, in most systems, pretreatment with pertussis toxin has no effect enylate cyclase (114), the G protein involved in the receptor-mediated alterations in inositol phospholip hydrolysis may be similar to  $G_i$ . However, in most stems, pretreatment with pertussis toxin has no effect receptor receptor-mediated alterations in inositol phospholipid<br>hydrolysis may be similar to  $G_i$ . However, in most sys-<br>tems, pretreatment with pertussis toxin has no effect on<br>receptor-mediated activation of phosphoinositide bre hydrolysis may be similar to  $G_i$ . However, in most systems, pretreatment with pertussis toxin has no effect on receptor-mediated activation of phosphoinositide break-<br>down (46, 134, 209, 236). Why pertussis toxin should tems, pretreatment with pertussis toxin has no effect on<br>receptor-mediated activation of phosphoinositide break-<br>down (46, 134, 209, 236). Why pertussis toxin should<br>block receptor-mediated inositol phospholipid hydrolysis receptor-mediated activation of phosphoinositide break-<br>down (46, 134, 209, 236). Why pertussis toxin should<br>block receptor-mediated inositol phospholipid hydrolysis<br>in some systems but not others is not yet clear. Possibl down (46, 134, 209, 236). Why pertussis toxin shou<br>block receptor-mediated inositol phospholipid hydrolys<br>in some systems but not others is not yet clear. Possib<br>two different G proteins are involved in activation<br>phosphol block receptor-mediated inositol phospholipid hydrolysis<br>in some systems but not others is not yet clear. Possibly<br>two different G proteins are involved in activation of<br>phospholipase C by different receptors. Alternativel in some systems but not others is not yet clear. Possibly<br>two different G proteins are involved in activation of<br>phospholipase C by different receptors. Alternatively,<br>alterations in inositol phospholipid hydrolysis could two different G proteins are involved in activation of phospholipase C by different receptors. Alternatively, alterations in inositol phospholipid hydrolysis could, in some cases, come subsequently to another signal which cyclase). alterations in inositol phospholipid hydrolysis could, in<br>some cases, come subsequently to another signal which<br>requires an intact  $G_i$  protein (i.e., inhibition of adenylate<br>cyclase).<br>Free cytosolic  $Ca^{2+}$  is also invol some cases, come subsequently to another signal which<br>requires an intact  $G_i$  protein (i.e., inhibition of adenylate<br>cyclase).<br>Free cytosolic  $Ca^{2+}$  is also involved in maintaining<br>phospholipase C activity and  $PIP_2$  hyd

requires an intact  $G_i$  protein (i.e., inhibition of adeny cyclase).<br>
Free cytosolic  $Ca^{2+}$  is also involved in maintain<br>
phospholipase C activity and  $PIP_2$  hydrolysis. Althought to release intracel-<br>
formation of  $Ins(1$ cyclase).<br>
Free cytosolic Ca<sup>2+</sup> is also involved in maintaining<br>
phospholipase C activity and PIP<sub>2</sub> hydrolysis. Although<br>
formation of Ins(1,4,5)P<sub>3</sub> is thought to release intracel-<br>
lular Ca<sup>2+</sup>, the activation of PIP<sub></sub> Free cytosolic Ca<sup>2+</sup> is also involved in maintaining<br>phospholipase C activity and  $PIP_2$  hydrolysis. Although<br>formation of Ins(1,4,5) $P_3$  is thought to release intracel-<br>lular Ca<sup>2+</sup>, the activation of  $PIP_2$  hydrolysis Free cytosolic Ca<sup>2+</sup> is also involved in maintaining<br>phospholipase C activity and PIP<sub>2</sub> hydrolysias Although<br>formation of Ins(1,4,5)P<sub>3</sub> is thought to release intracel-<br>lular Ca<sup>2+</sup>, the activation of PIP<sub>2</sub> hydrolysis stimulation is blocked by chelation of  $Ca^{2+}$  (120, 169, lular Ca<sup>2+</sup>, the activation of PIP<sub>2</sub> hydrolysis by receptostimulation is blocked by chelation of Ca<sup>2+</sup> (120, 161<br>184, 188), suggesting that activation of the enzyme is<br>dependent on at least a minimal concentration of C stimulation is blocked by chelation of  $Ca^{2+}$  (120, 1<br>184, 188), suggesting that activation of the enzym-<br>dependent on at least a minimal concentration of C<br>inside cells, although there is no evidence that this pi<br>ess is 184, 188), suggesting that activation of the enzyme is<br>dependent on at least a minimal concentration of  $Ca^{2+}$ <br>inside cells, although there is no evidence that this proc-<br>ess is under the *control* of  $Ca^{2+}$ . In membran dependent on at least a minimal concentration of  $Ca^{2+}$ <br>inside cells, although there is no evidence that this proc-<br>ess is under the *control* of  $Ca^{2+}$ . In membrane prepara-<br>tions,  $Ca^{2+}$  has been shown to increase th inside cells, although there is no evidence that this process is under the *control* of  $Ca^{2+}$ . In membrane prepara-<br>tions,  $Ca^{2+}$  has been shown to increase the activity of<br>phospholipase C (121, 144), and depolarizatio ess is under the *control* of  $Ca^{2+}$ . In membrane prep<br>tions,  $Ca^{2+}$  has been shown to increase the activit<br>phospholipase C (121, 144), and depolarization has<br>shown to increase phosphoinositide hydrolysis in h<br>slices in tions,  $Ca^{2+}$  has been shown to increase the activity of phospholipase C (121, 144), and depolarization has been shown to increase phosphoinositide hydrolysis in brain slices in a manner sensitive to inhibition by dihydr phospholipase C (121, 144), and depolarization has b<br>shown to increase phosphoinositide hydrolysis in br<br>slices in a manner sensitive to inhibition by dihydrop<br>idine-type  $Ca^{2+}$  entry blockers (124, 185, 220, 291) (<br>2). shown to increase phosphoinositide hydrolysis in brain slices in a manner sensitive to inhibition by dihydropyridine-type  $Ca^{2+}$  entry blockers (124, 185, 220, 291) (fig. 2). Although such effects might be caused by a ca slices in a manner sensitive to inhibition by dihydropyridine-type  $Ca^{2+}$  entry blockers (124, 185, 220, 291) (fig.<br>2). Although such effects might be caused by a calcium-<br>dependent release of neurotransmitters which sti idine-type Ca<sup>2+</sup> entry blockers (124, 185, 220, 291) (f 2). Although such effects might be caused by a calcium dependent release of neurotransmitters which stimula inositol phospholipid metabolism, such release is usua n 2). Although such effects might be caused by a calcium-<br>dependent release of neurotransmitters which stimulate<br>inositol phospholipid metabolism, such release is usually<br>not inhibited by dihydropyridine-type  $Ca^{2+}$  entry dependent release of neurotransmitters which stin<br>inositol phospholipid metabolism, such release is u<br>not inhibited by dihydropyridine-type  $Ca^{2+}$  entry l<br>ers (see below). Such data may be explained at<br>partially by the e inositol phospholipid metabolism, such release is usually<br>not inhibited by dihydropyridine-type  $Ca^{2+}$  entry block-<br>ers (see below). Such data may be explained at least<br>partially by the existence of two types of phosphat not immoted by dinydropyridine-type Ca<sup>-</sup> entry biock-<br>ers (see below). Such data may be explained at least<br>partially by the existence of two types of phosphatidyli-<br>nositol-specific phospholipase C enzymes as shown by<br>Hof partially by the existence of two types of phosphatidyli-<br>nositol-specific phospholipase C enzymes as shown by<br>Hoffman and Majerus (144), although these enzymes<br>were isolated from cytosolic, not membrane, compart-<br>ments. T nositol-specific phospholipase C enzymes as shown by<br>Hoffman and Majerus (144), although these enzymes<br>were isolated from cytosolic, not membrane, compart-<br>ments. The relationship of receptor-, G protein-, and<br>Ca<sup>2+</sup>-acti Hoffman and Majerus (144), although these enzymes<br>were isolated from cytosolic, not membrane, compart-<br>ments. The relationship of receptor-, G protein-, and<br> $Ca^{2+}$ -activated phospholipase C activity is not yet clear.<br>The were isolated from cytosolic, not membra<br>ments. The relationship of receptor-,  $G_1$ <br> $Ca^{2+}$ -activated phospholipase C activity is<br>The involvement of  $Ca^{2+}$  in inositol phot<br>drolysis is discussed in more detail below.<br>MI  $A^2$ <sup>+</sup>-activated phospholipase C activity is not yet clear<br>
the involvement of  $Ca^{2+}$  in inositol phospholipid hy<br>
rolysis is discussed in more detail below.<br> **VI. Alternate Signal Transduction Mechanisms**<br>
Although  $\$ the involvement of  $Ca^{2+}$  in inositol phospholipid hy-<br>olysis is discussed in more detail below.<br>VI. Alternate Signal Transduction Mechanisms<br>Although  $\alpha_1$ -adrenergic receptor activation increases<br>ositol phospholipid h

drolysis is discussed in more detail below.<br>
VI. Alternate Signal Transduction Mechanisms<br>
Although  $\alpha_1$ -adrenergic receptor activation increases<br>
inositol phospholipid hydrolysis in every tissue so far<br>
studied (see ab VI. Alternate Signal Transduction Mechanisms<br>Although  $\alpha_1$ -adrenergic receptor activation increases<br>inositol phospholipid hydrolysis in every tissue so far<br>studied (see above), this may not be the only mechanism<br>through VI. Alternate Signal Transduction Mechanisms<br>Although  $\alpha_1$ -adrenergic receptor activation increases<br>inositol phospholipid hydrolysis in every tissue so far<br>studied (see above), this may not be the only mechanism<br>through Although  $\alpha_1$ -adrenergic receptor activation increases<br>inositol phospholipid hydrolysis in every tissue so far<br>studied (see above), this may not be the only mechanism<br>through which these receptors initiate signals in th inositol phospholipid hydrolysis in every tissue so far studied (see above), this may not be the only mechanism<br>through which these receptors initiate signals in their<br>target cells. Increasing evidence suggests that a variety<br>of other mechanisms may be involved in signal trans rough which these receptors initiate signals in their<br>rget cells. Increasing evidence suggests that a variety<br>other mechanisms may be involved in signal transduc-<br>on by  $\alpha_1$ -adrenergic receptors in some tissues.<br>This ph target cells. Increasing evidence suggests that a variet of other mechanisms may be involved in signal transdution by  $\alpha_1$ -adrenergic receptors in some tissues.<br>This phenomenon has been most extensively studie in liver.

of other mechanisms may be involved in signal transduction by  $\alpha_1$ -adrenergic receptors in some tissues.<br>This phenomenon has been most extensively studied in liver. Activation of  $\alpha_1$ -adrenergic receptors in hepatocyt tion by  $\alpha_1$ -adrenergic receptors in some tissues.<br>This phenomenon has been most extensively studied<br>in liver. Activation of  $\alpha_1$ -adrenergic receptors in hepa-<br>tocytes causes an increase in inositol phosphates which<br>r This phenomenon has been most extensively studied<br>in liver. Activation of  $\alpha_1$ -adrenergic receptors in hepa-<br>tocytes causes an increase in inositol phosphates which<br>requires extracellular Ca<sup>2+</sup> but an increase in cycli in liver. Activation of  $\alpha_1$ -adrenergic receptors in her<br>tocytes causes an increase in inositol phosphates whi<br>requires extracellular Ca<sup>2+</sup> but an increase in cyclic AN<br>which is independent of extracellular Ca<sup>2+</sup> (251 requires extracellular  $Ca^{2+}$  but an increase in cyclic AMP<br>which is independent of extracellular  $Ca^{2+}$  (251). The<br>effects of  $\alpha_1$ -adrenergic agonists, vasopressin, and angio-<br>tensin II on metabolic responses in hepa

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FIG. 2. Doee response relationship for the calcium channel agonist<br>Bay K 8644 in increasing [<sup>3</sup>H]inositol phosphate (<sup>3</sup>H-IP) accumulation<br>in slices of rat cerebral cortex in the presence and absence of calcium. <sup>1</sup><br>
FIG. 2. Dose response relationship for the calcium channel agonist<br>
Bay K 8644 in increasing [<sup>3</sup>H]inositol phosphate (<sup>3</sup>H-IP) accumulation<br>
in slices of rat cerebral cortex in the presence and absence of calcium.<br>
N FIG. 2. Dose response relationship for the calcium channel agonist<br>Bay K 8644 in increasing [<sup>3</sup>H]inositol phosphate (<sup>3</sup>H-IP) accumulation<br>in slices of rat cerebral cortex in the presence and absence of calcium.<br>Note tha FIG. 2. Dose response relationship for the calcium channel agonist<br>Bay K 8644 in increasing [<sup>3</sup>H]inositol phosphate (<sup>3</sup>H-IP) accumulation<br>in alices of rat cerebral cortex in the presence and absence of calcium.<br>Note tha in alices of rat cerebral cortex in the presence and absence of calculate Note that the activation of [<sup>3</sup>H] inositol phosphate accumulation caby this compound is dependent on the presence of  $Ca^{2+}$  in the e cellular med

Note that the activation of ['H]inositol phosphate accumulation caused<br>by this compound is dependent on the presence of  $Ca^{2+}$  in the extra-<br>cellular medium. From Kendall and Nahorski (185) with permission.<br>thought to be dellular medium. From Kendall and Nahorski (185) with permission.<br>thought to be due to changes in phosphatidylinositol<br>metabolism and increasing cytosolic Ca<sup>2+</sup> levels (214)<br>However, the responses to  $\alpha_1$ -adrenergic re valuation from 1990 and thought to be due to changes in phosphatidylinositol<br>metabolism and increasing cytosolic Ca<sup>2+</sup> levels (214).<br>However, the responses to  $\alpha_1$ -adrenergic receptor acti-<br>vation persist in calcium-depleted hepatocytes where metabolism and increasing cytosolic Ca<sup>2+</sup> levels (214)<br>However, the responses to  $\alpha_1$ -adrenergic receptor activation persist in calcium-depleted hepatocytes where the<br>effects of vasopressin and angiotensin are abolishe However, the responses to  $\alpha_1$ -adrenergic receptor activation persist in calcium-depleted hepatocytes where the effects of vasopressin and angiotensin are abolished (113, 187). Measurement of Ca<sup>2+</sup> fluxes with ion-sele vation persist in calcium-depleted hepatocytes where the<br>ffects of vasopressin and angiotensin are abolished (113<br>187). Measurement of Ca<sup>2+</sup> fluxes with ion-selective electrodes showed marked differences between  $\alpha_1$ -a effects of vasopressin and angiotensin are abolished (113,<br>187). Measurement of Ca<sup>2+</sup> fluxes with ion-selective electrodes showed marked differences between  $\alpha_1$ -adrenergic<br>receptor stimulation and peptide receptor sti 187). Measurement of Ca<sup>2+</sup> fluxes with ion-selective electrodes showed marked differences between  $\alpha_1$ -adrenergic receptor stimulation.<br>The effects of  $\alpha_1$ -adrenergic receptor stimulation were characterized by a net trodes showed marked differences between  $\alpha_1$ -adrenerg<br>receptor stimulation and peptide receptor stimulation<br>The effects of  $\alpha_1$ -adrenergic receptor stimulation we<br>characterized by a net Ca<sup>2+</sup> efflux, and no reupta<br>o receptor stimulation and peptide receptor stimulation.<br>The effects of  $\alpha_1$ -adrenergic receptor stimulation were<br>characterized by a net  $Ca^{2+}$  efflux, and no reuptake<br>occurred until agonist was removed. Conversely, angi The effects of  $\alpha_1$ -adrenergic receptor stimulation were<br>characterized by a net Ca<sup>2+</sup> efflux, and no reuptake<br>occurred until agonist was removed. Conversely, angio-<br>tensin and vasopressin caused a relatively small amou characterized by a net  $Ca^{2+}$  efflux, and no reupts<br>occurred until agonist was removed. Conversely, ang<br>tensin and vasopressin caused a relatively small amou<br>of  $Ca^{2+}$  efflux, a large  $Ca^{2+}$  influx, and a subseque<br>slow occurred until agonist was removed. Conversely, angio-<br>tensin and vasopressin caused a relatively small amount<br>of  $Ca^{2+}$  efflux, a large  $Ca^{2+}$  influx, and a subsequent<br>slower efflux (4). These receptors mobilize  $Ca^{2+}$ tensin and vasopressin caused a relatively small amount<br>of  $Ca^{2+}$  efflux, a large  $Ca^{2+}$  influx, and a subsequent<br>slower efflux (4). These results suggest that the mecha-<br>nisms by which these receptors mobilize  $Ca^{2+}$  of Ca<sup>2+</sup> efflux, a large Ca<sup>2+</sup> influx, and a subsequent slower efflux (4). These results suggest that the mechanisms by which these receptors mobilize Ca<sup>2+</sup> are substantially different. Thyroid deficiency reduces the e misms by which these receptors mobilize  $Ca^{2+}$  are substantially different. Thyroid deficiency reduces the ef-<br>fects of vasopressin and angiotensin II but not of  $\alpha_1$ -<br>adrenergic receptor agonists (68), while insulin r stantially different. Thyroid deficiency reduces the ef-<br>fects of vasopressin and angiotensin II but not of  $\alpha_1$ -<br>adrenergic receptor agonists (68), while insulin reduces<br>the effects of  $\alpha_1$ -adrenergic receptor agonis fects of vasopressin and angiotensin II but not of a<br>adrenergic receptor agonists (68), while insulin reduct<br>the effects of  $\alpha_1$ -adrenergic receptor agonists but not<br>the peptides (79). Curiously, effects of  $\alpha_1$ -adren adrenergic receptor agonists (68), while insulin reduces<br>the effects of  $\alpha_1$ -adrenergic receptor agonists but not of<br>the peptides (79). Curiously, effects of  $\alpha_1$ -adrenergic re-<br>ceptor agonists become completely depen the effects of  $\alpha_1$ -adrenergic receptor agonists but not of<br>the peptides (79). Curiously, effects of  $\alpha_1$ -adrenergic re-<br>ceptor agonists become completely dependent on exter-<br>nal Ca<sup>2+</sup> in livers from adrenalectomized the peptides (79). Curiously, effects of  $\alpha_1$ -adrener<br>ceptor agonists become completely dependent on<br>nal Ca<sup>2+</sup> in livers from adrenalectomized rats (57<br>Apparently corticosteroids are required for the<br>independent effect ceptor agonists become completely dependent on exter-<br>nal Ca<sup>2+</sup> in livers from adrenalectomized rats (57, 113). a<br>Apparently corticosteroids are required for the Ca<sup>2+</sup>- p<br>independent effects. Garcia-Sainz and Hernandeznal Ca<sup>2+</sup> in livers from adrenalectomized rats (57, 113). <br>Apparently corticosteroids are required for the Ca<sup>2+</sup>-<br>independent effects. Garcia-Sainz and Hernandez-Soto-<br>mayor (113) proposed that there are two mechanisms Apparently corticosteroids are required for the Ca<sup>2+</sup>- proj<br>independent effects. Garcia-Sainz and Hernandez-Soto- cept<br>mayor (113) proposed that there are two mechanisms for rele<br>the metabolic effects of  $\alpha_1$ -adrenergi

insulin, and modulated by glucocorticoids (presumably related to the cyclic AMP response); the other dependent MAN<br>insulin, and modulated by glucocorticoids (presumably<br>related to the cyclic AMP response); the other dependent<br>on external Ca<sup>2+</sup>, insensitive to insulin, and modulated MAN<br>insulin, and modulated by glucocorticoids (presumably<br>related to the cyclic AMP response); the other dependent<br>on external  $Ca^{2+}$ , insensitive to insulin, and modulated<br>by thyroid hormones (presumably related to the insulin, and modulated by glucocorticoids (presumably related to the cyclic AMP response); the other dependent on external  $Ca^{2+}$ , insensitive to insulin, and modulated by thyroid hormones (presumably related to the inos insulin, and modulat<br>related to the cyclic A<br>on external  $Ca^{2+}$ , insulty thyroid hormones<br>phosphate response).<br>Similarly, in slices External Ca<sup>2+</sup>, insensitive to insulin, and modulated<br>thyroid hormones (presumably related to the inositol<br>losphate response).<br>Similarly, in slices of rat brain,  $\alpha_1$ -adrenergic receptor<br>tivation also increases the acc

by thyroid hormones (presumably related to the inositol<br>phosphate response).<br>Similarly, in slices of rat brain,  $\alpha_1$ -adrenergic receptor<br>activation also increases the accumulation of both ino-<br>sitol phosphates (see abov by thyroid hormones (presumably related to the inositol<br>phosphate response).<br>Similarly, in slices of rat brain,  $\alpha_1$ -adrenergic receptor<br>activation also increases the accumulation of both ino-<br>sitol phosphates (see abov phosphate response).<br>
Similarly, in slices of rat brain,  $\alpha_1$ -adrenergic reactivation also increases the accumulation of both<br>
sitol phosphates (see above) and cyclic AMP (76<br>
302, 307). As in liver, the  $\alpha_1$ -adrenerg Similarly, in slices of rat brain,  $\alpha_1$ -adrenergic receptor<br>activation also increases the accumulation of both ino-<br>sitol phosphates (see above) and cyclic AMP (76, 168,<br>302, 307). As in liver, the  $\alpha_1$ -adrenergic rec activation also increases the accumulation of both ino-<br>sitol phosphates (see above) and cyclic AMP (76, 168,<br>302, 307). As in liver, the  $\alpha_1$ -adrenergic receptor-stimu-<br>lated increases in inositol phosphate accumulatio sitol phosphates (see above) and cyclic AMP (76, 168, 302, 307). As in liver, the  $\alpha_1$ -adrenergic receptor-stimulated increases in inositol phosphate accumulation are blocked by chelation of extracellular  $Ca^{2+}$ , while 302, 307). As in liver, the  $\alpha_1$ -adrenergic receptor-stimu-<br>lated increases in inositol phosphate accumulation are<br>blocked by chelation of extracellular Ca<sup>2+</sup>, while  $\alpha_1$ -<br>adrenergic receptor-stimulated increases in lated increases in inositol phosphate accumulation are<br>blocked by chelation of extracellular  $Ca^{2+}$ , while  $\alpha_1$ -<br>adrenergic receptor-stimulated increases in basal cyclic<br>AMP accumulation are unaffected by this procedur blocked by chelation of extracellular  $Ca^{2+}$ , while  $\alpha_1$ -<br>adrenergic receptor-stimulated increases in basal cyclic<br>AMP accumulation are unaffected by this procedure<br>(169). In brain, however, another unusual phenomenon<br> adrenergic receptor-stimulated increases in basal cy<br>AMP accumulation are unaffected by this proced<br>(169). In brain, however, another unusual phenomer<br>is observed. Although the increases in basal cyclic Al<br>accumulation ca AMP accumulation are unaffected by this procedure (169). In brain, however, another unusual phenomenon is observed. Although the increases in basal cyclic AMP accumulation caused by  $\alpha_1$ -adrenergic receptor stimulation is observed. Although the increases in basal cyclic AMP accumulation caused by  $\alpha_1$ -adrenergic receptor stimulation are relatively small, stimulation of this receptor type can greatly potentiate the increases in cyclic accumulation caused by  $\alpha_1$ -adrenergic receptor stimulaaccumulation caused by  $\alpha_1$ -adrenergic receptor stimulation are relatively small, stimulation of this receptor ty can greatly potentiate the increases in cyclic AMP acumulation caused by activation of other receptors. S tion are relatively small, stimulation of this receptor type<br>can greatly potentiate the increases in cyclic AMP ac-<br>cumulation caused by activation of other receptors. Sim-<br>ilar potentiative effects can be observed between can greatly potentiate the increases in cyclic AMP ac-<br>cumulation caused by activation of other receptors. Sim-<br>ilar potentiative effects can be observed between hista-<br>mine H<sub>1</sub> receptors and other receptor types. For exa cumulation caused by activation of other receptors. Similar potentiative effects can be observed between histamine  $H_1$  receptors and other receptor types. For example, norepinephrine causes a much greater increase in cy mine  $H_1$  receptors and other receptor types. For example, norepinephrine causes a much greater increase in cyclic AMP levels in slices of rat cerebral cortex than does either the specific  $\beta$ -adrenergic receptor agonis mine  $H_1$  receptors and other receptor types. For example,<br>norepinephrine causes a much greater increase in cyclic<br>AMP levels in slices of rat cerebral cortex than does<br>either the specific  $\beta$ -adrenergic receptor agonis fluoronorepinephrine (73). Addition of 6-fluoronorepi-AMP levels in slices of rat cerebral cortex than does<br>either the specific  $\beta$ -adrenergic receptor agonist isopro-<br>terenol or the specific  $\alpha_1$ -adrenergic receptor agonist 6-<br>fluoronorepinephrine (73). Addition of 6-flu either the specific  $\beta$ -adrenergic receptor agonist isopro-<br>terenol or the specific  $\alpha_1$ -adrenergic receptor agonist 6-<br>fluoronorepinephrine (73). Addition of 6-fluoronorepi-<br>nephrine in the presence of isoproterenol c terenol or the specific  $\alpha_1$ -adrenergic receptor agonist 6-<br>fluoronorepinephrine (73). Addition of 6-fluoronorepi-<br>nephrine in the presence of isoproterenol causes a much<br>greater than additive increase in cyclic AMP lev fluoronorepinephrine (73). Addition of 6-fluoronorepinephrine in the presence of isoproterenol causes a much greater than additive increase in cyclic AMP levels. This interaction between  $\alpha_1$ - and  $\beta$ -adrenergic recept mephrine in the presence of isoproterenol causes a much<br>greater than additive increase in cyclic AMP levels. This<br>interaction between  $\alpha_1$ - and  $\beta$ -adrenergic receptors has<br>been well studied in many different brain reg greater than additive increase in cyclic AMP levels. This<br>interaction between  $\alpha_1$ - and  $\beta$ -adrenergic receptors has<br>been well studied in many different brain regions (74,<br>171, 201) and appears to be greatest in the ol interaction between  $\alpha_1$ - and  $\beta$ -adrenergic receptors has<br>been well studied in many different brain regions (74,<br>171, 201) and appears to be greatest in the olfactory bulb<br>(325). Similar potentiative interactions of been well studied in many different brain regions (74, 171, 201) and appears to be greatest in the olfactory bulb (325). Similar potentiative interactions of  $\alpha_1$ -adrenergic receptor activation are observed with adenosi 171, 201) and appears to be gr (325). Similar potentiative in receptor activation are observed 170, 171, 302) and vasoactive (218, 219) receptor activation. The mechanism by which  $c$ 25). Similar potentiative interactions of  $\alpha_1$ -adrenergic ceptor activation are observed with adenosine (168<br>0, 171, 302) and vasoactive intestinal peptide (VIP)<br>18, 219) receptor activation.<br>The mechanism by which  $\alpha_$ 

receptor activation are observed with adenosine (168, 170, 171, 302) and vasoactive intestinal peptide (VIP) (218, 219) receptor activation.<br>
The mechanism by which  $\alpha_1$ -adrenergic receptor activation potentiates cyclic 170, 171, 302) and vasoactive intestinal peptide (VI<br>
(218, 219) receptor activation.<br>
The mechanism by which  $\alpha_1$ -adrenergic receptor activation<br>
vation potentiates cyclic AMP responses to activation<br>
other receptor ty (218, 219) receptor activation.<br>The mechanism by which  $\alpha_1$ -adrenergic receptor activation potentiates cyclic AMP responses to activation of other receptor types in brain is still unclear. The potentiative interactions The mechanism by which  $\alpha_1$ -adrenergic receptor activation potentiates cyclic AMP responses to activation of other receptor types in brain is still unclear. The potentiative interactions are generally lost when the tiss vation potentiates cyclic AMP responses to activation of<br>other receptor types in brain is still unclear. The poten-<br>tiative interactions are generally lost when the tissue is<br>homogenized and/or membranes are prepared. This other receptor types in brain is still unclear. The potentiative interactions are generally lost when the tissue is<br>homogenized and/or membranes are prepared. This suggests that the potentiative response does not involve<br>d tiative interactions are generally lost when the tissue is<br>homogenized and/or membranes are prepared. This sug-<br>gests that the potentiative response does not involve<br>direct interactions between receptors and/or G proteins, homogenized and/or membranes are prepared. This suggests that the potentiative response does not involve direct interactions between receptors and/or G proteins, but may require involvement of some diffusible second messen gests that the potentiative response does not involve direct interactions between receptors and/or G proteins, but may require involvement of some diffusible second messenger substances. If brain tissue is homogenized in a direct interactions between receptors and/or G proteins,<br>but may require involvement of some diffusible second<br>messenger substances. If brain tissue is homogenized in<br>an isotonic physiological salt solution (Krebs-Ringer b but may require involvement of some diffusible second<br>messenger substances. If brain tissue is homogenized in<br>an isotonic physiological salt solution (Krebs-Ringer bi-<br>carbonate buffer), potentiative interactions can still messenger substances. If brain tissue is homogenized in<br>an isotonic physiological salt solution (Krebs-Ringer bi-<br>carbonate buffer), potentiative interactions can still be<br>observed although their magnitude is reduced (59, an isotonic physiological salt solution (Krebs-Ringer hearbonate buffer), potentiative interactions can still be observed although their magnitude is reduced (59, 7 150). It has been shown that this homogenization predure carbonate buffer), potentiative interactions can still b<br>observed although their magnitude is reduced (59, 7<br>150). It has been shown that this homogenization pro<br>cedure results in resealed "sac-like" entities which main<br>ta observed although their magnitude is reduced (59, 72, 150). It has been shown that this homogenization procedure results in resealed "sac-like" entities which maintain the metabolic integrity and second messenger interacti 150). It has been shown that this homogenization pro-<br>cedure results in resealed "sac-like" entities which main-<br>tain the metabolic integrity and second messenger inter-<br>actions of intact cells (72). Several hypotheses ha cedure results in resealed "sac-like" entities which maintain the metabolic integrity and second messenger inter-<br>actions of intact cells (72). Several hypotheses have been<br>proposed to explain these potentiative interacti tain the metabolic integrity and second messenger inter-<br>actions of intact cells (72). Several hypotheses have been<br>proposed to explain these potentiative interactions. Re-<br>ceptor-mediated increases in intracellular  $Ca^{2+$ actions of intact cells (72). Several hypotheses have been<br>proposed to explain these potentiative interactions. Re-<br>ceptor-mediated increases in intracellular Ca<sup>2+</sup> (310),<br>release of adenosine (74), activation of protein proposed to explain these potentiative interactions. Receptor-mediated increases in intracellular  $Ca^{2+}$  (310), release of adenosine (74), activation of protein kinase C (148), and activation of phospholipase  $A_2$  (98,

 $\alpha_1$ -ADRENERGIC RECEPT<br>troversial (75, 169), and the complexity of brain slices been<br>makes it difficult to identify the exact events involved in tiva<br>this interaction. It is interesting, however, that adrenal- acti troversial (75, 169), and the complexity of brain slimakes it difficult to identify the exact events involved<br>this interaction. It is interesting, however, that adrer<br>ectomy increases the  $\alpha_1$ -adrenergic potentiation of troversial (75, 169), and the complexity of brain slices be<br>makes it difficult to identify the exact events involved in<br>this interaction. It is interesting, however, that adrenal-<br>ectomy increases the  $\alpha_1$ -adrenergic po troversial (75, 169), and the complexity of brain slices that this interaction. It is interesting, however, that adrenaleretomy increases the  $\alpha_1$ -adrenergic potentiation of cyclic that adrenaleretomy increases the  $\alpha_$ makes it difficult to identify the exact events involved in<br>this interaction. It is interesting, however, that adrenal-<br>ectomy increases the  $\alpha_1$ -adrenergic potentiation of cyclic<br>AMP accumulation in brain slices (249, this interaction. It is interesting, however, that adrenal-<br>ectomy increases the  $\alpha_1$ -adrenergic potentiation of cyclic<br>AMP accumulation in brain slices (249, 250), while stress<br>or administration of ACTH decreases this ectomy increases the  $\alpha_1$ -adrenergic potentiation of cyclic<br>AMP accumulation in brain slices (249, 250), while stress<br>or administration of ACTH decreases this response (99,<br>183, 326). Thus this response in the brain is AMP accumulation in brain slices (249, 250), while<br>or administration of ACTH decreases this respons<br>183, 326). Thus this response in the brain is like<br>independent responses in the liver in that it is mod<br>by corticosteroid administration of ACTH decreases this response (99, 3, 326). Thus this response in the brain is like Ca<sup>2+</sup>-<br>dependent responses in the liver in that it is modulated<br>corticosteroids, although in opposite directions.<br>Simil

independent responses in the liver in that it is modulated<br>by corticosteroids, although in opposite directions.<br>Similar  $\alpha_1$ -mediated potentiation of cyclic AMP re-<br>disponses to activation of other receptor types is obs by corticosteroids, although in opposite directions.<br>Similar  $\alpha_1$ -mediated potentiation of cyclic AMP responses to activation of other receptor types is observe<br>in rat pineal, which lends itself better to examination of Similar  $\alpha_1$ -mediated potentiation of cyclic AMP responses to activation of other receptor types is observed<br>in rat pineal, which lends itself better to examination of<br>the molecular mechanisms underlying this phenomenon sponses to activation of other receptor types is observ<br>in rat pineal, which lends itself better to examination<br>the molecular mechanisms underlying this phenomeno<br>Klein et al. (186) showed that activation of  $\alpha_1$ -adrene in rat pineal, which lends itself better to examination<br>the molecular mechanisms underlying this phenomence<br>Klein et al. (186) showed that activation of  $\alpha_1$ -adrenerg<br>receptors greatly increased the magnitude of the ind the molecular mechanisms underlying this phenomenon<br>Klein et al. (186) showed that activation of  $\alpha_1$ -adrenerg<br>receptors greatly increased the magnitude of the indu<br>tion of pineal enzyme activity normally observed follo Klein et al. (186) showed that activation of  $\alpha_1$ -adrenergic (3.<br>receptors greatly increased the magnitude of the induc-<br>tion of pineal enzyme activity normally observed follow-<br>ing activation of  $\beta$ -adrenergic recepto receptors greatly increased the magnitude of the induction of pineal enzyme activity normally observed following activation of  $\beta$ -adrenergic receptors. Subsequently, this group showed that, similar to previous work in b tion of pineal enzyme activity normally observed following activation of  $\beta$ -adrenergic receptors. Subsequently, this group showed that, similar to previous work in brain slices, activation of  $\alpha_1$ -adrenergic receptors ing activation of  $\beta$ -adrenergic receptors. Subsequently, leadsing this group showed that, similar to previous work in brain resolutions, activation of  $\alpha_1$ -adrenergic receptors potentiated can the increase in cyclic A this group showed that, similar to previous work in brain resilices, activation of  $\alpha_1$ -adrenergic receptors potentiated can the increase in cyclic AMP accumulation caused by  $\beta$ - eradrenergic receptor activation in th slices, activation of  $\alpha_1$ -adrenergic receptors potentiated cause<br>the increase in cyclic AMP accumulation caused by  $\beta$ -<br>adrenergic receptor activation in the pineal by more than<br>10-fold (349). Similar results were obt the increase in cyclic AMP accumulation caused by  $\beta$ -<br>adrenergic receptor activation in the pineal by more than<br>10-fold (349). Similar results were obtained when cyclic<br>GMP accumulation was studied (349). These effects adrenergic receptor activation in the pineal by more than<br>10-fold (349). Similar results were obtained when cyclic<br>GMP accumulation was studied (349). These effects may<br>be related to inositol phospholipid hydrolysis and a 10-fold (349). Similar results were obtained when cyclic  $\Gamma$  GMP accumulation was studied (349). These effects may to related to inositol phospholipid hydrolysis and activation of protein kinase C, since phorbol esters w GMP accumulation was studied (349). These effects may<br>be related to inositol phospholipid hydrolysis and acti-<br>vation of protein kinase C, since phorbol esters were<br>found to mimic both the potentiative effects on enzyme<br>in be related to inositol phospholipid hydrolysis and activation of protein kinase C, since phorbol esters were found to mimic both the potentiative effects on enzyme induction (371) and cyclic AMP accumulation (333). Suppea vation of protein kinase C, since phorbol esters were<br>found to mimic both the potentiative effects on enzyme<br>induction (371) and cyclic AMP accumulation (333). S<br>However, these potentiative effects appear to require<br>influ found to mimic both the potentiative effects on enzym<br>induction (371) and cyclic AMP accumulation (333<br>However, these potentiative effects appear to requirinflux of  $Ca^{2+}$  from the extracellular fluid (331). Althoug<br> $\alpha_$ induction (371) and cyclic AMP accumulation (333).<br>
However, these potentiative effects appear to require F<br>
influx of Ca<sup>2+</sup> from the extracellular fluid (331). Although<br>  $\alpha_1$ -adrenergic receptor activation clearly inc However, these potentiative effects appear to require<br>influx of  $Ca^{2+}$  from the extracellular fluid (331). Although<br> $\alpha_1$ -adrenergic receptor activation clearly increases intra-<br>cellular  $Ca^{2+}$  in these cells, this inc  $\alpha_1$ -adrenergic receptor activation clearly increases intra-<br>cellular Ca<sup>2+</sup> in these cells, this increase is sustained<br>rather than transient and appears to be totally dependent<br>on influx (332). This is inconsistent wit  $\alpha_1$ -adrenergic receptor activation clearly increases intra-<br>cellular Ca<sup>2+</sup> in these cells, this increase is sustained<br>rather than transient and appears to be totally dependent<br>on influx (332). This is inconsistent wit rather than transient and appears to be totally dependent rather than transient and appears to be totally dependent<br>on influx (332). This is inconsistent with a primary effect<br>of Ins(1,4,5)P<sub>3</sub> on mobilization of intracellular Ca<sup>2+</sup> in<br>these cells. In fact, although inositol ph on influx (332). This is inconsistent with a primary effect<br>of Ins(1,4,5)P<sub>3</sub> on mobilization of intracellular Ca<sup>2+</sup> in<br>these cells. In fact, although inositol phosphates are<br>formed following  $\alpha_1$ -adrenergic receptor a of Ins(1,4,5)P<sub>3</sub> on mobilization of intracellular Ca<sup>2+</sup> in<br>these cells. In fact, although inositol phosphates are<br>formed following  $\alpha_1$ -adrenergic receptor activation (133),<br>these seem to be mainly Ins(1,4)P<sub>2</sub> and In these cells. In fact, although inositol phosphates are formed following  $\alpha_1$ -adrenergic receptor activation (133) these seem to be mainly  $\text{Ins}(1,4)\text{P}_2$  and  $\text{Ins}(1)\text{P}$ ; littl  $\text{Ins}(1,4,5)\text{P}_3$  can be observed (332 formed following  $\alpha_1$ -adrenergic receptor activation (133),<br>these seem to be mainly  $\text{Ins}(1,4)\text{P}_2$  and  $\text{Ins}(1)\text{P}$ ; little<br> $\text{Ins}(1,4,5)\text{P}_3$  can be observed (332, 370). This observation<br>might be explained if phosph these seem to be mainly  $\text{Ins}(1,4)\text{P}_2$  and  $\text{Ins}(1)\text{P}$ ; little  $\text{Ins}(1,4,5)\text{P}_3$  can be observed (332, 370). This observation might be explained if phospholipase C was only transiently stimulated following receptor a Ins(1,4,5) $P_3$  can be observed (332, 370). This observation<br>might be explained if phospholipase C was only tran-<br>siently stimulated following receptor activation, as is<br>observed with substance P in rat parotid acinar cel might be explained if phospholipase C was only tran-<br>siently stimulated following receptor activation, as is<br>observed with substance P in rat parotid acinar cells<br>(234a). In this case, a rapid desensitization to substance siently stimulated following receptor activation, as is<br>observed with substance P in rat parotid acinar cells<br>(234a). In this case, a rapid desensitization to substance<br>P occurs, yet the  $\text{Ins}(1,4,5)P_3$  released is suffi observed with substance P in rat parotid acinar cells (234a). In this case, a rapid desensitization to substance P occurs, yet the  $\text{Ins}(1,4,5)P_3$  released is sufficient to release intracellular  $\text{Ca}^{2+}$ . However, a c (234a). In this case, a rapid desensitization to substance P occurs, yet the  $\text{Ins}(1,4,5)P_3$  released is sufficient to release intracellular  $\text{Ca}^{2+}$ . However, a continued buildup of inositol mono- and bis-phosphates

of inositol mono- and bis-phosphates over time during<br>receptor activation argues against such a rapid desensi-<br>tization.<br>One possible link between  $\alpha_1$ -adrenergic receptor ac-<br>tivation and increases in cyclic AMP accumu receptor activation argues against such a rapid desensi-<br>tization.<br>One possible link between  $\alpha_1$ -adrenergic receptor ac-<br>tivation and increases in cyclic AMP accumulation is<br>arachidonic acid. Partington et al. (268) re tization.<br>
One possible link between  $\alpha_1$ -adrenergic receptor activation and increases in cyclic AMP accumulation is<br>
arachidonic acid. Partington et al. (268) reported tha<br>
inhibitors of cyclooxygenase, such as aspirin One possible link between  $\alpha_1$ -adrenergic receptor activation and increases in cyclic AMP accumulation is arachidonic acid. Partington et al. (268) reported that inhibitors of cyclooxygenase, such as aspirin and indomet tivation and increases in cyclic AMP accumulation is<br>arachidonic acid. Partington et al. (268) reported that<br>inhibitors of cyclooxygenase, such as aspirin and indo-<br>methacin, partially blocked the effects of  $\alpha_1$ -adrene arachidonic acid. Partington et al. (268) reported that<br>inhibitors of cyclooxygenase, such as aspirin and indo-<br>methacin, partially blocked the effects of  $\alpha_1$ -adrenergic<br>receptor activation on cyclic AMP accumulation i inhibitors of cyclooxygenase, such as aspirin and indo-<br>methacin, partially blocked the effects of  $\alpha_1$ -adrenergic<br>receptor activation on cyclic AMP accumulation in brain<br>slices. Similar results have been reported by Sc methacin, partially blocked the effects of  $\alpha_1$ -adrenergic<br>receptor activation on cyclic AMP accumulation in brain<br>slices. Similar results have been reported by Schaad et<br>al. (304), although others (98, 169) found no ef

troversial (75, 169), and the complexity of brain slices been shown that  $\alpha_1$ -adrenergic receptor stimulation ac-<br>makes it difficult to identify the exact events involved in tivates phospholipase  $A_2$  as well as phosph 183, 326). Thus this response in the brain is like  $Ca^{2+}$ - showed that  $\alpha_1$ -adrenergic receptor-mediated activation independent responses in the liver in that it is modulated of phospholipases  $A_2$  and C can be differ EPTOR SUBTYPES 93<br>been shown that  $\alpha_1$ -adrenergic receptor stimulation ac-<br>tivates phospholipase  $A_2$  as well as phospholipase C EPTOR SUBTYPES 93<br>been shown that  $\alpha_1$ -adrenergic receptor stimulation ac-<br>tivates phospholipase  $A_2$  as well as phospholipase C<br>activity in several cell types. In clonal cell lines from EPTOR SUBTYPES 93<br>been shown that  $\alpha_1$ -adrenergic receptor stimulation ac-<br>tivates phospholipase  $A_2$  as well as phospholipase C<br>activity in several cell types. In clonal cell lines from<br>thyroid (46) and kidney (318) a been shown that  $\alpha_1$ -adrenergic receptor stimulation activates phospholipase  $A_2$  as well as phospholipase C activity in several cell types. In clonal cell lines from thyroid (46) and kidney (318) and in primary cultur been shown that  $\alpha_1$ -adrenergic receptor stimulation activates phospholipase  $A_2$  as well as phospholipase C activity in several cell types. In clonal cell lines from thyroid (46) and kidney (318) and in primary cultur tivates phospholipase  $A_2$  as well as phospholipase C<br>activity in several cell types. In clonal cell lines from<br>thyroid (46) and kidney (318) and in primary cultures of<br>rat pineal (142),  $\alpha_1$ -adrenergic receptor stimul activity in several cell types. In clonal cell lines from<br>thyroid (46) and kidney (318) and in primary cultures of<br>rat pineal (142),  $\alpha_1$ -adrenergic receptor stimulation in-<br>creases release of arachidonic acid. Burch et thyroid (46) and kidney (318) and in primary cultures of<br>rat pineal (142),  $\alpha_1$ -adrenergic receptor stimulation in-<br>creases release of arachidonic acid. Burch et al. (46)<br>showed that  $\alpha_1$ -adrenergic receptor-mediated rat pineal (142),  $\alpha_1$ -adrenergic receptor stimulation in-<br>creases release of arachidonic acid. Burch et al. (46)<br>showed that  $\alpha_1$ -adrenergic receptor-mediated activation<br>of phospholipases  $A_2$  and C can be different creases release of arachidonic acid. Burch et al. (46)<br>showed that  $\alpha_1$ -adrenergic receptor-mediated activation<br>of phospholipases  $A_2$  and C can be differentiated by<br>pertussis toxin pretreatment (fig. 3), neomycin, and showed that  $\alpha_1$ -adrenergic receptor-mediated activat<br>of phospholipases  $A_2$  and C can be differentiated<br>pertussis toxin pretreatment (fig. 3), neomycin, and<br>ducing extracellular Ca<sup>2+</sup>. These authors suggested t<br>diffe of phospholipases  $A_2$  and C can be differentiated<br>pertussis toxin pretreatment (fig. 3), neomycin, and<br>ducing extracellular  $Ca^{2+}$ . These authors suggested<br>different G proteins might be involved in the recep<br>mediated a pertussis toxin pretreatment (fig. 3), neomycin, and reducing extracellular  $Ca^{2+}$ . These authors suggested that different G proteins might be involved in the receptor-<br>mediated activation of these two different phosphol ducing extracellular  $Ca^{2+}$ . These authors suggested that<br>different G proteins might be involved in the receptor-<br>mediated activation of these two different phospholi-<br>pases. Similar results were obtained by Slivka and I different G proteins might be involved in the receptor-<br>mediated activation of these two different phospholi-<br>pases. Similar results were obtained by Slivka and Insel<br>(318). Ho and Klein (142) presented evidence that in-<br> mediated activation of these two different phospholi-<br>pases. Similar results were obtained by Slivka and Insel<br>(318). Ho and Klein (142) presented evidence that in-<br>creased cytosolic Ca<sup>2+</sup> and activation of protein kinas pases. Similar results were obtained by Slivka and Insel<br>(318). Ho and Klein (142) presented evidence that in-<br>creased cytosolic Ca<sup>2+</sup> and activation of protein kinase C<br>may be involved in  $\alpha_1$ -adrenergic receptor-medi (318). Ho and Klein (142) presented evidence that in-<br>creased cytosolic Ca<sup>2+</sup> and activation of protein kinase C<br>may be involved in  $\alpha_1$ -adrenergic receptor-mediated re-<br>lease of arachidonic acid in pinealocytes. There may be involved in  $\alpha_1$ -adrenergic receptor-mediated re-<br>lease of arachidonic acid in pinealocytes. Therefore some<br>responses to  $\alpha_1$ -adrenergic receptor activation may be<br>caused by arachidonic acid release, possibly v may be involved in  $\alpha_1$ -adrenergic receptor-mediated re-<br>lease of arachidonic acid in pinealocytes. Therefore some<br>responses to  $\alpha_1$ -adrenergic receptor activation may be<br>caused by arachidonic acid release, possibly v lease of arachidonic acid in pinealocytes. Therefore some<br>responses to  $\alpha_1$ -adrenergic receptor activation may be<br>caused by arachidonic acid release, possibly via a differ-<br>ent mechanism than stimulation of inositol pho responses to  $\alpha_1$ -adrenergic receptor activation may be caused by arachidonic acid release, possibly via a different mechanism than stimulation of inositol phosphate formation. Conversely, stimulation of arachidonic aci ent mechanism than stimulation of inositol phosphate<br>formation. Conversely, stimulation of arachidonic acid<br>release may be secondary to activation of other signal<br>transduction mechanisms, such as influx of  $Ca^{2+}$  or ac-<br> tivation of protein kinase C. release may be secondary to activation of other signal transduction mechanisms, such as influx of  $Ca^{2+}$  or activation of protein kinase C.<br>There may also be multiple signal transduction mechanisms for  $\alpha_1$ -adrenergic

release may be secondary to activation of other signal<br>transduction mechanisms, such as influx of  $Ca^{2+}$  or ac-<br>tivation of protein kinase C.<br>There may also be multiple signal transduction mech-<br>anisms for  $\alpha_1$ -adrener tivation of protein kinase C.<br>There may also be multiple signal transduction mechanisms for  $\alpha_1$ -adrenergic receptor activation in the heart<br>Stimulation of these receptors increases inositol phos-<br>phate formation in car There may also be multiple signal transduction mechanisms for  $\alpha_1$ -adrenergic receptor activation in the heart Stimulation of these receptors increases inositol phose phate formation in cardiomyocytes (43), but also act anisms for  $\alpha_1$ -adrenergic receptor activation in the hea<br>Stimulation of these receptors increases inositol ph<br>phate formation in cardiomyocytes (43), but also a<br>vates cyclic AMP degradation (47) apparently by a<br>vating Stimulation of these receptors increases inositol phos-<br>phate formation in cardiomyocytes (43), but also acti-<br>vates cyclic AMP degradation (47) apparently by acti-<br>vating a cyclic nucleotide phosphodiesterase.  $\alpha_1$ -Adr phate formation in cardiomyocytes (43), but also accurates cyclic AMP degradation (47) apparently by accurating a cyclic nucleotide phosphodiesterase.  $\alpha_1$ -Adimergic receptor activation also increases cell hypertrop and vates cyclic AMP degradation  $(47)$  apparently by a<br>vating a cyclic nucleotide phosphodiesterase.  $\alpha_1$ -Ad<br>nergic receptor activation also increases cell hypertrop<br>and spontaneous contractile activity in cultured card<br>my vating a cyclic nucleotide phosphodiesterase.  $\alpha_1$ -Adrenergic receptor activation also increases cell hypertrophy<br>and spontaneous contractile activity in cultured cardio-<br>myocytes (315). The hypertrophy and increased sp (324) showed that  $\alpha_1$ -adrenergic receptor stimulation and spontaneous contractile activity in cultured cardio-<br>myocytes (315). The hypertrophy and increased sponta-<br>neous activity can be induced independently under dif-<br>ferent experimental conditions (315). Steinberg et al.<br> myocytes (315). The hypertrophy and increased spontaneous activity can be induced independently under different experimental conditions (315). Steinberg et al. (324) showed that  $\alpha_1$ -adrenergic receptor stimulation caus neous activity can be induced independently under dif-<br>ferent experimental conditions (315). Steinberg et al.<br>(324) showed that  $\alpha_1$ -adrenergic receptor stimulation<br>caused both positive and negative effects on the rate blic Ca<sup>2+</sup> and activation of protein kinase C<br>
ved in  $\alpha_1$ -adrenergic receptor-mediated re-<br>
idonic acid in pinealoxytes. Therefore some<br>  $\alpha_1$ -adrenergic receptor activation may be<br>
chidonic acid release, possibly vi



This treatment had no effect on receptor-stimulated [<sup>3</sup>H]inositol phos-Pertussis toxin, ng/ml<br>
FIG. 3. Inhibition of  $\alpha_1$ -adrenergic receptor-stimulated arachidon<br>
acid release by pertussis toxin pretreatment of FRTL5 thyroid cell<br>
This treatment had no effect on receptor-stimulated [<sup>3</sup>H] FIG. 3. Inhibition of  $\alpha_1$ -adrenergic receptor-stimulated arachidonic<br>acid release by pertussis toxin pretreatment of FRTL5 thyroid cells.<br>This treatment had no effect on receptor-stimulated [<sup>3</sup>H]inositol phos-<br>phate a From the interaction of an example receptor-stimulated and methods and relation of FRTL5 thyroid cell<br>This treatment had no effect on receptor-stimulated [<sup>3</sup>H]inositol pho<br>phate accumulation in these cells, suggesting inv

94<br>and that only the negative chronotropic effect was po<br>blocked by treatment with pertussis toxin. It should be cy 94<br>
and that only the negative chronotropic effect was pea<br>
blocked by treatment with pertussis toxin. It should be cyt<br>
noted that pertussis toxin pretreatment does not block and MINNEMA<br>and that only the negative chronotropic effect was per<br>blocked by treatment with pertussis toxin. It should be cyt<br>noted that pertussis toxin pretreatment does not block and<br> $\alpha_1$ -adrenergic receptor-mediated inc and that only the negative chronotropic effect was<br>blocked by treatment with pertussis toxin. It should be<br>noted that pertussis toxin pretreatment does not block<br> $\alpha_1$ -adrenergic receptor-mediated increases in inositol<br>p and that only the negative chronotropic effect was<br>blocked by treatment with pertussis toxin. It should be<br>noted that pertussis toxin pretreatment does not block<br> $\alpha_1$ -adrenergic receptor-mediated increases in inositol<br>p blocked by treatment with pertussis toxin. It should be cytomoted that pertussis toxin pretreatment does not block and  $\alpha_1$ -adrenergic receptor-mediated increases in inositol som phosphates (43) or cyclic AMP degradatio noted that pertussis toxin p<br> $\alpha_1$ -adrenergic receptor-mediphosphates (43) or cyclic AM<br>diomyocytes, or the positive<br>strips of rat ventricle (31).<br>Clearly, activation of  $\alpha_1$ -ad -adrenergic receptor-mediated increases in inositol soicesphates (43) or cyclic AMP degradation (47) in car-<br>hypnyocytes, or the positive chronotropic response in vertips of rat ventricle (31).<br>Clearly, activation of  $\alpha_$ 

phosphates (43) or cyclic AMP degradation (47) in car-<br>diomyocytes, or the positive chronotropic response in vers<br>strips of rat ventricle (31). to to<br>clearly, activation of  $\alpha_1$ -adrenergic receptors has many som<br>diverse diomyocytes, or the positive chronotropic response in vertips of rat ventricle (31).<br>
Clearly, activation of  $\alpha_1$ -adrenergic receptors has many solverse effects on cellular metabolism in addition to a<br>
activating PIP<sub>2</sub> strips of rat ventricle (31). to to<br>clearly, activation of  $\alpha_1$ -adrenergic receptors has many som<br>diverse effects on cellular metabolism in addition to activation<br>activating PIP<sub>2</sub> breakdown. These include activation of Clearly, activation of  $\alpha_1$ -adrenergic receptors has many<br>diverse effects on cellular metabolism in addition to<br>activating  $PIP_2$  breakdown. These include activation of t<br>calcium influx, increasing cyclic AMP and cyclic diverse effects on cellular metabolism in addition<br>activating  $\text{PIP}_2$  breakdown. These include activation<br>calcium influx, increasing cyclic AMP and cyclic GM<br>levels and responsiveness to other hormones, activati<br>arachid activating  $\text{PIP}_2$  breakdown. These include activation of the calcium influx, increasing cyclic AMP and cyclic GMP clevels and responsiveness to other hormones, activating arachidonic acid release, increasing cyclic AMP levels and responsiveness to other hormones, activating<br>arachidonic acid release, increasing cyclic AMP degra-<br>dation, and complex effects on cell growth. Many of<br>these effects may occur secondary to the consequences<br>of levels and responsiveness to other hormones, actively arachidonic acid release, increasing cyclic AMP d dation, and complex effects on cell growth. Man these effects may occur secondary to the conseque of  $\text{PIP}_2$  hydrol arachidonic acid release, increasing cyclic AMP degra-<br>dation, and complex effects on cell growth. Many of<br>these effects may occur secondary to the consequences<br>of  $\text{PIP}_2$  hydrolysis [release of Ins(1,4,5)P<sub>3</sub>, phosphor dation, and complex effects on cell growth. Many<br>these effects may occur secondary to the consequen<br>of  $\text{PIP}_2$  hydrolysis [release of  $\text{Ins}(1,4,5)P_3$ , phosphory<br>tion to  $\text{Ins}(1,3,4,5)P_4$ , release of stored intracellul these effects may occur secondary to the consequences  $\frac{1}{2}$ <br>of PIP<sub>2</sub> hydrolysis [release of Ins(1,4,5)P<sub>3</sub>, phosphoryla-<br>tion to Ins(1,3,4,5)P<sub>4</sub>, release of stored intracellular Ca<sup>2+</sup>,<br>and/or activation of protein of PIP<sub>2</sub> hydrolysis [release of Ins(1,4,5)P<sub>3</sub>, phosphoryla-<br>tion to Ins(1,3,4,5)P<sub>4</sub>, release of stored intracellular Ca<sup>2+</sup>, on<br>and/or activation of protein kinase C]. However, increas-<br>ing evidence suggests that some tion to  $\text{Ins}(1,3,4,5)P_4$ , release of stored intracellular Ca<sup>2-</sup><br>and/or activation of protein kinase C]. However, increasing evidence suggests that some of these alternate effect<br>are unrelated to receptor-mediated PIP<sub>2</sub> and/or activation of protein kinase C]. However, increasing evidence suggests that some of these alternate effects are unrelated to receptor-mediated PIP<sub>2</sub> hydrolysis and may represent distinct signal transduction mechan ing evidence suggests that some of these<br>are unrelated to receptor-mediated PI<br>may represent distinct signal transduc<br>The possible relationship of these event<br>receptor subtypes is discussed below.<br>NH. Origin of Increased C between the increased  $\frac{1}{2}$   $\frac{1}{2}$   $\frac{1}{2}$   $\frac{1}{2}$   $\frac{1}{2}$   $\frac{1}{2}$  or  $\frac{1}{2}$  or  $\frac{1}{2}$  persent distinct signal transduction mechanis basible relationship of these events to  $\alpha_1$ -adrenes or subtypes Example relationship of these events to  $\alpha_1$ -adrenergic<br>
Ceptor subtypes is discussed below.<br>
VII. Origin of Increased Cytosolic Ca<sup>2+</sup><br>
It is clear that many, if not all, of the cellular effects<br>  $\alpha_1$ -adrenergic rece

receptor subtypes is discussed below.<br>
VII. Origin of Increased Cytosolic Ca<sup>2+</sup><br>
It is clear that many, if not all, of the cellular effects<br>
of  $\alpha_1$ -adrenergic receptor activation are caused by in-<br>
creases in free ion VII. Origin of Increased Cytosolic Ca<sup>2+</sup><br>It is clear that many, if not all, of the cellular effects<br>of  $\alpha_1$ -adrenergic receptor activation are caused by in-<br>creases in free ionized intracellular Ca<sup>2+</sup>. Such increases<br> VII. Origin of Increased Cytosonc Ca<sup>-1</sup><br>It is clear that many, if not all, of the cellular effects<br>of  $\alpha_1$ -adrenergic receptor activation are caused by in-<br>creases in free ionized intracellular Ca<sup>2+</sup>. Such increases<br>c It is clear that many, if not all, of the cellular effects<br>of  $\alpha_1$ -adrenergic receptor activation are caused by in-<br>creases in free ionized intracellular  $Ca^{2+}$ . Such increases<br>could be caused by release from intracell of  $\alpha_1$ -adrenergic receptor activation are caused by increases in free ionized intracellular Ca<sup>2+</sup>. Such increases could be caused by release from intracellular organelles and/or influx from the extracellular fluid. Th creases in free ionized intracellular  $Ca^{2+}$ . Such increases<br>could be caused by release from intracellular organelles<br>and/or influx from the extracellular fluid. The recent<br>advances in our understanding of inositol phosp could be caused by release from intracellular organelles nels, GOCs). These classes undoubtedly have some over-<br>and/or influx from the extracellular fluid. The recent lap. For example, the permeability of VOCs can also be and/or influx from the extracellular fluid. The recent<br>advances in our understanding of inositol phospholipid<br>metabolism and the role of  $\text{Ins}(1,4,5)P_3$  in releasing  $\text{Ca}^{2+}$ <br>from the endoplasmic or sarcoplasmic retic advances in our understanding of inositol phospholipid<br>metabolism and the role of  $\text{Ins}(1,4,5)P_3$  in releasing  $\text{Ca}^{2+}$ <br>from the endoplasmic or sarcoplasmic reticulum have<br>focused attention on pools of intracellular metabolism and the role of  $\text{Ins}(1,4,5)P_3$  in releasing C<br>from the endoplasmic or sarcoplasmic reticulum h<br>focused attention on pools of intracellular Ca<sup>2+</sup> (28<br>However, in many cases  $\alpha_1$ -adrenergic receptor-media<br>in from the endoplasmic or sarcoplasmic reticulum hafocused attention on pools of intracellular  $Ca^{2+}$  (28 However, in many cases  $\alpha_1$ -adrenergic receptor-mediat increases in cytosolic  $Ca^{2+}$  are partly or wholely depere focused attention on pools of intracellular Ca<sup>2+</sup> (280).<br>However, in many cases  $\alpha_1$ -adrenergic receptor-mediated<br>increases in cytosolic Ca<sup>2+</sup> are partly or wholely depend-<br>ent on influx from the extracellular fluid. However, in many cases  $\alpha_1$ -adrenergic receptor-mediated<br>increases in cytosolic Ca<sup>2+</sup> are partly or wholely depend-<br>ent on influx from the extracellular fluid. The mecha-<br>nism(s) by which receptor activation is linked increases in cytosolic Ca<sup>2+</sup> are partly or wholely<br>ent on influx from the extracellular fluid. The<br>nism(s) by which receptor activation is linked<br>influx, and its relationship to inositol phospho<br>tabolism, is currently re nism(s) by which receptor activation is linked to  $Ca^{2+}$ <br>influx, and its relationship to inositol phospholipid me-<br>tabolism, is currently receiving much attention.<br>A. *Intracellular*  $Ca^{2+}$ <br>There are several pools of st flux, and its relationship to inositol phospholipid me-<br>bolism, is currently receiving much attention.<br>Intracellular  $Ca^{2+}$ <br>There are several pools of stored intracellular  $Ca^{2+}$ <br>nich might be released following recepto

tabolism, is currently receiving much attention.<br>A. Intracellular  $Ca^{2+}$ <br>There are several pools of stored intracellular  $Ca^{2+}$ <br>which might be released following receptor activation<br>The three major subcellular regions i A. Intracellular  $Ca^{2+}$  VC<br>There are several pools of stored intracellular  $Ca^{2+}$  medicing which might be released following receptor activation. Ca<br>The three major subcellular regions in which  $Ca^{2+}$  is distored in mo A. Intracellular  $Ca^{2+}$ <br>There are several pools of stored intracellular  $Ca^{2+}$ <br>which might be released following receptor activation.<br>The three major subcellular regions in which  $Ca^{2+}$  is<br>stored in most cells are the There are several pools of stored intracellular Ca<br>which might be released following receptor activation<br>The three major subcellular regions in which  $Ca^{2+}$ <br>stored in most cells are the endoplasmic or sarcoplasm<br>reticulu which might be released following receptor activation.<br>The three major subcellular regions in which  $Ca^{2+}$  is<br>stored in most cells are the endoplasmic or sarcoplasmic<br>reticulum, the mitochondria, and the inner plasma mem The three major subcellular regions in which  $Ca^{2+}$  is<br>stored in most cells are the endoplasmic or sarcoplasmic<br>reticulum, the mitochondria, and the inner plasma mem-<br>brane (77, 285). The endoplasmic and sarcoplasmic restored in most cells are the endoplasmic or sarcoplasm<br>reticulum, the mitochondria, and the inner plasma men<br>brane (77, 285). The endoplasmic and sarcoplasmic re<br>ticulum and the mitochondria actively sequester Ca<br>with ener reticulum, the mitochondria, and the inner plasma mem-<br>brane (77, 285). The endoplasmic and sarcoplasmic re-<br>ior channel activation, the time course of inactivation,<br>ticulum and the mitochondria actively sequester  $Ca^{2+}$ brane (77, 285). The endoplasmic and sarcoplasmic reduction and the mitochondria actively sequester  $Ca^2$  with energy-requiring pumps, while the plasma membrane appears to contain molecules with a high affinit for binding ticulum and the mitochondria actively sequester  $Ca^{2+}$  swith energy-requiring pumps, while the plasma mem-<br>brane appears to contain molecules with a high affinity stor binding  $Ca^{2+}$ , although these have not yet been id with energy-requiring pumps, while the plasma mem-<br>brane appears to contain molecules with a high affinity<br>for binding  $Ca^{2+}$ , although these have not yet been iden-<br>tified. The endoplasmic or sarcoplasmic reticulum serv brane appears to contain molecules with a high affinity ative for binding  $Ca^{2+}$ , although these have not yet been iden-<br>tified. The endoplasmic or sarcoplasmic reticulum serves type<br>as the major source of activator  $Ca^{2$ for binding Ca<sup>-1</sup>, although these have not yet been identified. The endoplasmic or sarcoplasmic reticulum serves to as the major source of activator  $Ca^{2+}$  in many cells (35, n 192, 285). It is this pool which appears t

MAN<br>pears to function to stabilize the concentration of free<br>cytosolic  $Ca^{2+}$ , by sequestering it when free  $Ca^{2+}$  is high MAN<br>pears to function to stabilize the concentration of free<br>cytosolic Ca<sup>2+</sup>, by sequestering it when free Ca<sup>2+</sup> is high<br>and leaking it out when free Ca<sup>2+</sup> is low (285). There is mand pears to function to stabilize the concentration of free cytosolic  $Ca^{2+}$ , by sequestering it when free  $Ca^{2+}$  is high and leaking it out when free  $Ca^{2+}$  is low (285). There is some evidence from liver that this pears to function to stabilize the concentration of free cytosolic  $Ca^{2+}$ , by sequestering it when free  $Ca^{2+}$  is high and leaking it out when free  $Ca^{2+}$  is low (285). There is some evidence from liver that this pool pears to function to stabilize the concentration of f<br>cytosolic  $Ca^{2+}$ , by sequestering it when free  $Ca^{2+}$  is hi<br>and leaking it out when free  $Ca^{2+}$  is low (285). There<br>some evidence from liver that this pool is also and leaking it out when free  $Ca^{2+}$  is low (285). There is<br>some evidence from liver that this pool is also regulated<br>by receptor activation (29, 175), although this is contro-<br>versial (285). The identity and function of and leaking it out when free  $Ca^{2+}$  is low (285). There is<br>some evidence from liver that this pool is also regulated<br>by receptor activation (29, 175), although this is contro-<br>versial (285). The identity and function of some evidence from liver that this pool is also regulated<br>by receptor activation (29, 175), although this is contro-<br>versial (285). The identity and function of  $Ca^{2+}$  bound<br>to the inner plasma membrane are less clear. T by receptor activation (29, 175), although this is controversial (285). The identity and function of  $Ca^{2+}$  bound to the inner plasma membrane are less clear. There is some evidence that this pool can be released by rece versial (285). The identity and function of  $Ca^{2+}$  bound<br>to the inner plasma membrane are less clear. There is<br>some evidence that this pool can be released by receptor<br>activation (85), and it has been suggested that rele to the inner plasma membr<br>some evidence that this pool<br>activation (85), and it has be<br>this small pool might trigge<br>coplasmic reticulum (203).<br>R. Extracellular  $Ca^{2+}$ **activation (85), and it**<br>this small pool might<br>coplasmic reticulum (2<br>*B. Extracellular*  $Ca^{2+}$ <br>There are also many is small pool might trigger  $Ca^{2+}$  release from the sar-<br>plasmic reticulum (203).<br>*Extracellular*  $Ca^{2+}$ <br>There are also many different types of channels in the<br>asma membrane through which extracellular  $Ca^{2+}$ 

coplasmic reticulum (203).<br>
B. Extracellular  $Ca^{2+}$ <br>
There are also many different types of channels in the<br>
plasma membrane through which extracellular  $Ca^{2+}$ <br>
might enter the cell. These channels can be subdivided B. Extracellular  $Ca^{2+}$ <br>There are also many different types of channels in the<br>plasma membrane through which extracellular  $Ca^{2+}$ <br>might enter the cell. These channels can be subdivided<br>on the basis of their selective pe B. Extraceutuar Ca<sup>-1</sup><br>There are also many different types of channels in the<br>plasma membrane through which extracellular Ca<sup>2+</sup><br>might enter the cell. These channels can be subdivided<br>on the basis of their selective perme There are also many different types of channels in the plasma membrane through which extracellular  $Ca^{2+}$  might enter the cell. These channels can be subdivided on the basis of their selective permeability to particular plasma membrane through which extracellular  $Ca^{2+}$  might enter the cell. These channels can be subdivided on the basis of their selective permeability to particular ions such as  $Ca^{2+}$ , and also by the stimulus which pr might enter the cell. These channels can be subdivided<br>on the basis of their selective permeability to particular<br>ions such as  $Ca^{2+}$ , and also by the stimulus which pri-<br>marily controls channel permeability (34, 41, 234 on the basis of their selective permeability to particular<br>ions such as  $Ca^{2+}$ , and also by the stimulus which pri-<br>marily controls channel permeability  $(34, 41, 234)$ . Thus<br>there are channels which open in response to ions such as Ca<sup>2+</sup>, and also by the stimulus which pri-<br>marily controls channel permeability (34, 41, 234). Thus<br>there are channels which open in response to changes in<br>(a) trans-membrane voltage (voltage-operated channel marily controls channel permeability  $(34, 41, 234)$ . Thus<br>there are channels which open in response to changes in<br> $(a)$  trans-membrane voltage (voltage-operated channels,<br> $VOCs$ ),  $(b)$  ligand occupation of a binding site o there are channels which open in response to changes in (*a*) trans-membrane voltage (voltage-operated channels, VOCs), (*b*) ligand occupation of a binding site on the channel complex (receptor-operated channels, ROCs), ( ( $a$ ) trans-membrane voltage (voltage-operated channels,<br>VOCs),  $(b)$  ligand occupation of a binding site on the<br>channel complex (receptor-operated channels, ROCs),<br> $(c)$  increases in the concentration of a second messenger VOCs),  $(b)$  ligand occupation of a binding site on the channel complex (receptor-operated channels, ROCs),  $(c)$  increases in the concentration of a second messenger such as cyclic nucleotides or inositol phosphates inside channel complex (receptor-operated channels, ROC;<br>(c) increases in the concentration of a second messeng<br>such as cyclic nucleotides or inositol phosphates insisthe cell (second messenger-operated channels, SMOC;<br>and more r (c) increases in the concentration of a second messeng<br>such as cyclic nucleotides or inositol phosphates inside<br>the cell (second messenger-operated channels, SMOCs<br>and more recently  $(d)$  activation of G proteins by recept such as cyclic nucleotides or inositol phosphates insid<br>the cell (second messenger-operated channels, SMOCs)<br>and more recently (*d*) activation of G proteins by recep<br>tors or exogenous compounds (G protein-operated chan<br>ne the cell (second messenger-operated channels, SMOCs),<br>and more recently (*d*) activation of G proteins by recep-<br>tors or exogenous compounds (G protein-operated chan-<br>nels, GOCs). These classes undoubtedly have some over-<br> and more recently  $(d)$  activation of G proteins by receptors or exogenous compounds (G protein-operated channels, GOCs). These classes undoubtedly have some overlap. For example, the permeability of VOCs can also be alter (234). delays. These classes undoubtedly have some over-<br>  $\alpha$ . For example, the permeability of VOCs can also be<br>  $\alpha$  class of channels which are permeable to<br>  $\beta$  within each class of channels which are permeable to<br>  $\beta$  pa might enter the cell. These channels can be subdivided<br>on the basis of their selective permeability to particular<br>on such as Ca<sup>2+</sup>, and also by the stimulus which pri-<br>marily controls channel permeability (34, 41, 234).

lap. For example, the permeability of VOCs can also be altered by changes in second messenger concentration (234).<br>
Within each class of channels which are permeable to a particular ion and opened by a particular stimulus altered by changes in second messenger concentration (234).<br>
Within each class of channels which are permeable to<br>
a particular ion and opened by a particular stimulus,<br>
there are also subclasses. Dihydropyridine-type  $Ca^{$ (234). Within each class of channels which are permeable to a particular ion and opened by a particular stimulus there are also subclasses. Dihydropyridine-type  $Ca^{2+}$  entry blockers inhibit the slow inward  $Ca^{2+}$  curre Within each class of channels which are permeable to<br>a particular ion and opened by a particular stimulus,<br>there are also subclasses. Dihydropyridine-type  $Ca^{2+}$  en-<br>try blockers inhibit the slow inward  $Ca^{2+}$  current a a particular ion and opened by a particular stimulus,<br>there are also subclasses. Dihydropyridine-type  $Ca^{2+}$  en-<br>try blockers inhibit the slow inward  $Ca^{2+}$  current acti-<br>vated by depolarization of myocardial cells and there are also subclasses. Dihydropyridine-type  $Ca^{2+}$  entry blockers inhibit the slow inward  $Ca^{2+}$  current activated by depolarization of myocardial cells and other tissues (106, 162). However, they usually have littl vated by depolarization of myocardial cells and other tissues (106, 162). However, they usually have little or no effect on depolarization-evoked transmitter release caused by opening of voltage-operated  $Ca^{2+}$  channels tissues (106, 162). However, they usually have little no effect on depolarization-evoked transmitter rele caused by opening of voltage-operated  $Ca^{2+}$  channels presynaptic nerve terminals (108, 109, 125, 256, 3). Voltage mo effect on depolarization-evoked transmitter release<br>caused by opening of voltage-operated  $Ca^{2+}$  channels in<br>presynaptic nerve terminals (108, 109, 125, 256, 312).<br>Voltage-clamp and single channel conductance measurecaused by opening of voltage-operated  $Ca^{2+}$  channels in<br>presynaptic nerve terminals (108, 109, 125, 256, 312).<br>Voltage-clamp and single channel conductance measure-<br>ments have suggested the existence of multiple types o presynaptic nerve terminals (108, 109, 125, 256, 312).<br>Voltage-clamp and single channel conductance measure-<br>ments have suggested the existence of multiple types of<br> $Ca^{2+}$  conductances (15, 111, 213, 330). Recently, thre voltage-clamp and single channel conductance measure-<br>ments have suggested the existence of multiple types of<br>Ca<sup>2+</sup> conductances (15, 111, 213, 330). Recently, three<br>distinct types of Ca<sup>2+</sup> channels have been identified  $Ca^{2+}$  conductances (15, 111, 213, 330). Recently, thre distinct types of  $Ca^{2+}$  channels have been identified is several cell types. These channels can be distinguishe on the basis of the strength of depolarization req distinct types of  $Ca^{2+}$  channels have been identified in several cell types. These channels can be distinguished on the basis of the strength of depolarization required for channel activation, the time course of inactiv several cell types. These channels can be distinguished<br>on the basis of the strength of depolarization required<br>for channel activation, the time course of inactivation,<br>and the sensitivity to dihydropyridine-type Ca<sup>2+</sup> ch on the basis of the strength of depolarization required<br>for channel activation, the time course of inactivation,<br>and the sensitivity to dihydropyridine-type  $Ca^{2+}$  channel<br>agonists and antagonists. "L type" channels requ for channel activation, the time course of inactive and the sensitivity to dihydropyridine-type  $Ca^{2+}$  class and antagonists. "L type" channels requisively strong depolarizations for activation, inactively, are at least and the sensitivity to dihydropyridine-type  $Ca^{2+}$  channel agonists and antagonists. "L type" channels require reatively strong depolarizations for activation, inactivated by  $Cae^{2+}$  entry blockers, and potentiated by agonists and antagonists. "L type" channels require relatively strong depolarizations for activation, inactivate<br>slowly, are at least partially blocked by dihydropyridine-<br>type Ca<sup>2+</sup> entry blockers, and potentiated by Ca atively strong depolarizations for activation, inactivate<br>slowly, are at least partially blocked by dihydropyridine-<br>type  $Ca^{2+}$  entry blockers, and potentiated by  $Ca^{2+}$  chan-<br>nel agonists. "T type" channels are activa slowly, are at least partially blocked by dihydropyridine-<br>type  $Ca^{2+}$  entry blockers, and potentiated by  $Ca^{2+}$  chan-<br>nel agonists. "T type" channels are activated by a smaller<br>depolarization, inactivate rapidly, and a type  $Ca^{2+}$  entry blockers, and potentiated by  $Ca^{2+}$  channel agonists. "T type" channels are activated by a smaller depolarization, inactivate rapidly, and are insensitive to dihydropyridines. "N type" channels also re

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 $\alpha_1$ -ADRENERGIC RECEPT<br>intermediate time course, and are also insensitive to bety<br>dihydropyridines (108, 109, 263). These channels can crea  $\alpha_1$ -ADRENERGIC RECEPT<br>intermediate time course, and are also insensitive to bet<br>dihydropyridines (108, 109, 263). These channels can crealso be distinguished by their sensitivities to blockade by inv a<sub>1</sub>-ADRENERGIC RECEPT<br>intermediate time course, and are also insensitive to bett<br>dihydropyridines (108, 109, 263). These channels can crea<br>also be distinguished by their sensitivities to blockade by inve<br>cadmium (N and L intermediate time course, and are also insensitive to between dihydropyridines (108, 109, 263). These channels can creas also be distinguished by their sensitivities to blockade by involced mium (N and L more sensitive th intermediate time course, and are also insensitive to betweedihydropyridines (108, 109, 263). These channels can creases also be distinguished by their sensitivities to blockade by involve cadmium (N and L more sensitive dihydropyridines (108, 109, 263). These channels ca<br>also be distinguished by their sensitivities to blockade b<br>cadmium (N and L more sensitive than T), nickel ("<br>more sensitive than N or L), and omega-conotoxin (1<br>and L mo also be distinguished by their sensitivities to blockade cadmium (N and L more sensitive than T), nickel more sensitive than N or L), and omega-conotoxin and L more sensitive than T) (108, 223). Undoubted more subtypes wil more sensitive than N or L), and omega-conotoxin (N and L more sensitive than T) (108, 223). Undoubtedly, more subtypes will be described as single channel recording techniques are increasingly applied to this area.

and L more sensitive than T) (108, 223). Undoubtedly, middle more subtypes will be described as single channel recordsom<br>ing techniques are increasingly applied to this area. The maddition to these voltage-operated  $Ca^{2+}$ more subtypes will be described as single channel recording techniques are increasingly applied to this area.<br>In addition to these voltage-operated  $Ca^{2+}$  channels, it has been suggested for some time that there may be r ing techniques are increasingly applied to this area.<br>In addition to these voltage-operated  $Ca^{2+}$  channels<br>has been suggested for some time that there may<br>receptor-operated  $Ca^{2+}$  channels  $(34, 351)$ . The imperfor thi In addition to these voltage-operated  $Ca^{2+}$  channels has been suggested for some time that there may receptor-operated  $Ca^{2+}$  channels (34, 351). The imptor this suggestion came from observations that contion of smooth has been suggested for some time that there may be by<br>receptor-operated  $Ca^{2+}$  channels  $(34, 351)$ . The impetus difor this suggestion came from observations that contraction of smooth muscle could be elicited by transmi receptor-operated Ca<sup>2+</sup> channels (34, 351). The impetus<br>for this suggestion came from observations that contrac-<br>tion of smooth muscle could be elicited by transmitter-<br>receptor interactions even in muscles which were alr for this suggestion came from observations that contration of smooth muscle could be elicited by transmitte receptor interactions even in muscles which were alreadepolarized with high potassium solutions (34, 100, 321 Also tion of smooth muscle could be elicited by transmitter-<br>receptor interactions even in muscles which were already<br>depolarized with high potassium solutions  $(34, 100, 321)$ .<br>Also, norepinephrine can still produce changes i depolarized with high potassium solutions (34, 100, 321). der<br>Also, norepinephrine can still produce changes in mem-<br>brane permeability in potassium-depolarized smooth ver<br>muscle (163, 217). It was also shown that contract Also, norepinephrine can still produce changes in mem-<br>brane permeability in potassium-depolarized smooth ve<br>muscle (163, 217). It was also shown that contraction of cause<br>some smooth muscles can be caused by transmitters brane permeability in potassium-depolarized smooth ver<br>muscle (163, 217). It was also shown that contraction of case<br>some smooth muscles can be caused by transmitters and che<br>hormones in concentrations which do not appear muscle (163, 217). It was also shown that contraction some smooth muscles can be caused by transmitters  $\epsilon$  hormones in concentrations which do not appear to call membrane depolarization (97, 135). Thus there has lower a some smooth muscles can be caused by transmitters and<br>hormones in concentrations which do not appear to cause<br>membrane depolarization (97, 135). Thus there has long<br>been a major distinction between "electromechanical<br>coupl hormones in concentrations which do not appear to calculation (97, 135). Thus there has loven a major distinction between "electromechanical coupling" (contraction elicited by changes in membre potential) and "pharmacomech membrane depolarization (97, 135). Thus there has lo<br>been a major distinction between "electromechanic<br>coupling" (contraction elicited by changes in membra<br>potential) and "pharmacomechanical coupling" (contra<br>tion elicited been a major distinction between "electromechanical b<br>coupling" (contraction elicited by changes in membrane<br>potential) and "pharmacomechanical coupling" (contrac-cion elicited by receptor stimulation). Almost by defini-<br>t potential) and "pharmacomechanical coupling" (contraction elicited by receptor stimulation). Almost by definition, of course, electromechanical coupling is probably initiated by activation of VOCs. However, the mechanisms potential) and "pharmacomechanical coupling" (contraction elicited by receptor stimulation). Almost by definition, of course, electromechanical coupling is probably initiated by activation of VOCs. However, the mechanisms tion elicited by receptor stimulation). Almost by definition, of course, electromechanical coupling is probably<br>initiated by activation of VOCs. However, the mecha-<br>nisms underlying pharmacomechanical coupling are un-<br>doub tion, of course, electromechanical coupling is probably yetnitiated by activation of VOCs. However, the mechanisms underlying pharmacomechanical coupling are undoubtedly more complex. Either ROCs, SMOCs, GOCs, nation any c initiated by activation of VOCs. However, the mechanisms underlying pharmacomechanical coupling are undoubtedly more complex. Either ROCs, SMOCs, GOCs, na or any combination could be involved, since all of these compossibl nisms underlying pharmacomechanical coupling are undoubtedly more complex. Either ROCs, SMOCs, GOCs, or any combination could be involved, since all of these are activated by receptor occupation. Of course, the possible se doubtedly more complex. Either ROCs, SMOCs, GOCs, nall<br>or any combination could be involved, since all of these con<br>are activated by receptor occupation. Of course, the evol<br>possible secondary involvement of VOCs opening i or any combination could be involved, since all of these are activated by receptor occupation. Of course, the possible secondary involvement of VOCs opening in response to changes in membrane potential caused by changes in are activated by receptor occupation. Of course, the event possible secondary involvement of VOCs opening in response to changes in membrane potential caused by blochanges in the permeability of the other channels, cannot possible secondary involvement of VOCs opening in response to changes in membrane potential caused by blochanges in the permeability of the other channels, cannot and be discounted. Clearly, the potential for confusion is sponse to ch<br>changes in the<br>be discounte<br>great, and m<br>the situation.<br>There has anges in the permeability of the other channels, cannot discounted. Clearly, the potential for confusion is eat, and much more work will be necessary to clarify e situation.<br>There has been only one report of single channe be discounted. Clearly, the potential for confusion is great, and much more work will be necessary to clarify the situation.<br>There has been only one report of single channel recordings of a probable receptor-operated  $Ca^{2$ 

great, and much more work will be necessary to clarify set<br>the situation. ag<br>There has been only one report of single channel se<br>recordings of a probable receptor-operated  $Ca^{2+}$  channel. in<br>Benham and Tsien (19) recentl the situation.<br>
There has been only one report of single channel secordings of a probable receptor-operated  $Ca^{2+}$  channel. in<br>
Benham and Tsien (19) recently described a novel type ti<br>
of channel opened by ATP in arteri There has been only one report of single channel<br>recordings of a probable receptor-operated  $Ca^{2+}$  channel.<br>Benham and Tsien (19) recently described a novel type<br>of channel opened by ATP in arterial smooth muscle<br>cells. recordings of a probable receptor-operated  $Ca^{2+}$  channel.<br>Benham and Tsien (19) recently described a novel type<br>of channel opened by ATP in arterial smooth muscle<br>cells. These channels are 3-fold more permeable to  $Ca^{2+$ Benham and Tsien (19) recently described a novel type tion of channel opened by ATP in arterial smooth muscle in cells. These channels are 3-fold more permeable to  $Ca^{2+}$  the than to Na<sup>+</sup> and are resistant to inhibition of channel opened by ATP in arterial smooth muscle incells. These channels are 3-fold more permeable to  $Ca^{2+}$  the than to  $Na^+$  and are resistant to inhibition by cadmium, changer these channels were sore observed in ex cells. These channels are 3-fold more permeable to  $Ca^{2+}$  than to Na<sup>+</sup> and are resistant to inhibition by cadmium, magnesium, and nifedipine. Since these channels were observed in excised patches, it was proposed that t than to Na<sup>+</sup> and are resistant to inhibit<br>magnesium, and nifedipine. Since the<br>observed in excised patches, it was pr<br>are activated directly by ligand without<br>of second messenger substances (19).<br>Also, very few Ca<sup>2+</sup> ch agnesium, and nifedipine. Since these channels were so<br>served in excised patches, it was proposed that they ble<br>e activated directly by ligand without the involvement wl<br>second messenger substances (19). pc<br>Also, very few

observed in excised patches, it was proposed that the are activated directly by ligand without the involvemen<br>of second messenger substances (19).<br>Also, very few Ca<sup>2+</sup> channels activated by either secon<br>messengers or G p are activated directly by ligand without the involvement whore second messenger substances  $(19)$ . pos<br>Also, very few Ca<sup>2+</sup> channels activated by either second by messengers or G proteins have been unequivocally iden-<br>ti of second messenger substances (19).<br>Also, very few Ca<sup>2+</sup> channels activated by either secomessengers or G proteins have been unequivocally id<br>tified and characterized. Kuno et al. (194) and v<br>Tscharner et al. (361) have Also, very few Ca<sup>2+</sup> channels activated by either secomes<br>sengers or G proteins have been unequivocally identified and characterized. Kuno et al. (194) and v<br>Tscharner et al. (361) have reported evidence for volta<br>insens messengers or G proteins have been unequivocally identified and characterized. Kuno et al.  $(194)$  and von Tscharner et al.  $(361)$  have reported evidence for voltage-insensitive Ca<sup>2+</sup> channels in T-lymphocytes and neutr tified and characterized. Kuno et al. (194) and von m<br>Tscharner et al. (361) have reported evidence for voltage-<br>insensitive  $Ca^{2+}$  channels in T-lymphocytes and neutro-<br>bhils which are activated by agonists. Kuno and Ga Tscharner et al. (361) have reported evidence for voltage-<br>insensitive Ca<sup>2+</sup> channels in T-lymphocytes and neutro-<br>phils which are activated by agonists. Kuno and Gardner<br>(193) reported that the channels in lymphocytes w insensitive Ca<sup>2+</sup> channels in T-lymphocytes and neutro-<br>phils which are activated by agonists. Kuno and Gardner<br>(193) reported that the channels in lymphocytes were<br>activated by Ins(1,4,5)P<sub>3</sub>, supporting the possibility

more sensitive than N or L), and omega-conotoxin (N This effect is blocked by pertussis toxin and restored by<br>and L more sensitive than T) (108, 223). Undoubtedly, microinjection of certain G proteins (136). Similarly<br>mor receptor interactions even in muscles which were already (149, 206, 283). Yatani et al. (369) have presented evi-<br>depolarized with high potassium solutions (34, 100, 321). dence that G proteins directly affect  $Ca^{2+}$  cha EPTOR SUBTYPES<br>between GOCs and SMOCs since receptor-mediated in<br>creases in second messenger accumulation usually als EPTOR SUBTYPES<br>between GOCs and SMOCs since receptor-mediated in-<br>creases in second messenger accumulation usually also<br>involve G proteins. For example, opioid peptides reduce EPTOR SUBTYPES 95<br>between GOCs and SMOCs since receptor-mediated in-<br>creases in second messenger accumulation usually also<br>involve G proteins. For example, opioid peptides reduce<br> $Ca^{2+}$  currents in clonal neuroblastoma between GOCs and SMOCs since receptor-mediated in-<br>creases in second messenger accumulation usually also<br>involve G proteins. For example, opioid peptides reduce<br> $Ca^{2+}$  currents in clonal neuroblastoma  $\times$  glioma cells.<br> creases in second messenger accumulation usually also<br>involve G proteins. For example, opioid peptides reduce<br> $Ca^{2+}$  currents in clonal neuroblastoma  $\times$  glioma cells.<br>This effect is blocked by pertussis toxin and resto involve G proteins. For example, opioid peptides reduced  $Ca^{2+}$  currents in clonal neuroblastoma  $\times$  glioma cell This effect is blocked by pertussis toxin and restored microinjection of certain G proteins (136). Simila microinjection of certain G proteins (136). Similarly I ms effect is blocked by pertussis toxin and restored by<br>microinjection of certain G proteins (136). Similarly<br>somatostatin,  $\gamma$ -aminobutyric acid (GABA), and norep-<br>inephrine have been reported to reduce Ca<sup>2+</sup> current somatostatin,  $\gamma$ -aminobutyric acid (GABA), and norep-<br>inephrine have been reported to reduce Ca<sup>2+</sup> currents in<br>certain cells through mechanisms which are mimicked<br>by GTP analogs and blocked by guanosine  $5'$ -[ $\beta$ -thio inephrine have been reported to reduce  $Ca^{2+}$  currents in certain cells through mechanisms which are mimicked by GTP analogs and blocked by guanosine  $5'$ -[ $\beta$ -thio] diphosphate (GDP $\beta S$ ) (92, 149, 206). However,  $Ca^{2+$ certain cells through mechanisms which are mimicked<br>by GTP analogs and blocked by guanosine  $5'$ -[ $\beta$ -thio]<br>diphosphate (GDP $\beta S$ ) (92, 149, 206). However, Ca<sup>2+</sup><br>currents are also reduced by activators of protein kinase by GTP analogs and blocked by guanosine  $5'$ -[ $\beta$ -thio]<br>diphosphate (GDP $\beta$ S) (92, 149, 206). However, Ca<sup>2+</sup><br>currents are also reduced by activators of protein kinase<br>C, such as synthetic diacylglycerols and phorbol es diphosphate (GDP $\beta$ S) (92, 149, 206). However, Ca<sup>2+</sup><br>currents are also reduced by activators of protein kinase<br>C, such as synthetic diacylglycerols and phorbol esters<br>(149, 206, 283). Yatani et al. (369) have presented currents are also reduced by activators of protein kinase C, such as synthetic diacylglycerols and phorbol esters  $(149, 206, 283)$ . Yatani et al.  $(369)$  have presented evidence that G proteins directly affect  $Ca^{2+}$  ch C, such as synthetic diacylglycerols and phorbol esters (149, 206, 283). Yatani et al. (369) have presented evidence that G proteins directly affect  $Ca^{2+}$  channel survival in excised patches of guinea pig or bovine card (149, 206, 283). Yatani et al. (369) have presented evi-<br>dence that G proteins directly affect  $Ca^{2+}$  channel sur-<br>vival in excised patches of guinea pig or bovine cardiac<br>ventricular membranes, suggesting that, at least vival in excised patches of guinea pig or bovine cardiac ventricular membranes, suggesting that, at least in some cases, there are direct effects of G proteins on  $Ca^{2+}$  channels without involvement of second messenger s vival in excised patches of guinea pig or bovine cardiac ventricular membranes, suggesting that, at least in some cases, there are direct effects of G proteins on  $Ca^{2+}$  channels without involvement of second messenger s ventricular membranes, suggesting that, at least in some cases, there are direct effects of G proteins on  $Ca^{2+}$  channels without involvement of second messenger substances (369). Hopefully, as recording techniques get i cases, there are direct effects of G proteins on  $Ca^{2+}$ <br>channels without involvement of second messenger sub-<br>stances (369). Hopefully, as recording techniques get<br>increasingly more sophisticated, more such channels will channels without involvement of second messenger substances (369). Hopefully, as recording techniques get increasingly more sophisticated, more such channels will be identified and their properties delineated. At the mome stances (369). Hopefully, as recording techniques get<br>increasingly more sophisticated, more such channels will<br>be identified and their properties delineated. At the<br>moment, it is clear that there are multiple types of  $Ca^{$ increasingly more sophisticated, more such channels will<br>be identified and their properties delineated. At the<br>moment, it is clear that there are multiple types of  $Ca^{2+}$ <br>channels in cells, VOCs, ROCs, SMOCs, and GOCs, b be identified and th<br>moment, it is clear th<br>channels in cells, VO<br>the number and ident<br>yet firmly established<br>The question of wl oment, it is clear that there are multiple types of  $Ca^{2+}$ <br>
annels in cells, VOCs, ROCs, SMOCs, and GOCs, but<br>
e number and identities of the different types are not<br>
t firmly established.<br>
The question of which  $Ca^{2+}$ 

channels in cells, VOCs, ROCs, SMOCs, and GOCs, but<br>the number and identities of the different types are no<br>yet firmly established.<br>The question of which  $Ca^{2+}$  channels are blocked b<br>organic  $Ca^{2+}$  entry blockers is st the number and identities of the different types are not<br>yet firmly established.<br>The question of which  $Ca^{2+}$  channels are blocked by<br>organic  $Ca^{2+}$  entry blockers is still unclear. It was origi-<br>nally found that verapa yet firmly established.<br>The question of which  $Ca^{2+}$  channels are block<br>organic  $Ca^{2+}$  entry blockers is still unclear. It was<br>nally found that verapamil blocked potassium-e<br>contractions much more effectively than norep The question of which  $Ca^{2+}$  channels are blocked by<br>organic  $Ca^{2+}$  entry blockers is still unclear. It was origi-<br>nally found that verapamil blocked potassium-evoked<br>contractions much more effectively than norepinephri organic Ca<sup>2+</sup> entry blockers is still unclear. It was originally found that verapamil blocked potassium-evoked contractions much more effectively than norepinephrine-evoked contractions in smooth muscle (118, 125, 272). nally found that verapamil blocked potassium-evoked<br>contractions much more effectively than norepinephrine-<br>evoked contractions in smooth muscle (118, 125, 272). It<br>was suggested by Bolton (34) that organic  $Ca^{2+}$  entry<br> contractions much more effectively than norepinephrine<br>evoked contractions in smooth muscle (118, 125, 272).<br>was suggested by Bolton (34) that organic  $Ca^{2+}$  enti<br>blockers blocked VOCs more readily than ROCs. Furthe<br>anal evoked contractions in smooth muscle (118, 125, 272). It<br>was suggested by Bolton (34) that organic  $Ca^{2+}$  entry<br>blockers blocked VOCs more readily than ROCs. Further<br>analysis of many muscles revealed that, although depowas suggested by Bolton (34) that organic  $Ca^{2+}$  entry blockers blocked VOCs more readily than ROCs. Further analysis of many muscles revealed that, although depolarization-induced contractions were almost always very se blockers blocked VOCs more readily than ROCs. Further<br>analysis of many muscles revealed that, although depo-<br>larization-induced contractions were almost always very<br>sensitive to inhibition by organic  $Ca^{2+}$  entry blocker analysis of many muscles revealed that, although<br>larization-induced contractions were almost alway<br>sensitive to inhibition by organic  $Ca^{2+}$  entry blo<br>agonist-induced responses showed great variatio<br>sensitivity (54, 162) larization-induced contractions were almost always vertical sensitive to inhibition by organic  $Ca^{2+}$  entry blocke agonist-induced responses showed great variations sensitivity (54, 162). In some tissues, norepinephrical sensitive to inhibition by organic  $Ca^{2+}$  entry blo<br>agonist-induced responses showed great variatio<br>sensitivity (54, 162). In some tissues, norepinepl<br>induced contractions were much less sensitive to it<br>tion by  $Ca^{2+}$  e agonist-induced responses showed great variations in<br>sensitivity  $(54, 162)$ . In some tissues, norepinephrine-<br>induced contractions were much less sensitive to inhibi-<br>tion by  $Ca^{2+}$  entry blockers than were depolarizati sensitivity  $(54, 162)$ . In some tissues, norepinephrine-<br>induced contractions were much less sensitive to inhibi-<br>tion by  $Ca^{2+}$  entry blockers than were depolarization-<br>induced contractions (233, 308), while in other t induced contractions were much less sensitive to inhibition by  $Ca^{2+}$  entry blockers than were depolarization-<br>induced contractions (233, 308), while in other tissues<br>the situation was reversed (26, 54, 364). From the si tion by  $Ca^{2+}$  entry blockers than were depolarization-<br>induced contractions (233, 308), while in other tissues<br>the situation was reversed (26, 54, 364). From the single<br>channel recording data discussed above, it is clea induced contractions (233, 308), while in other tissues<br>the situation was reversed (26, 54, 364). From the single<br>channel recording data discussed above, it is clear that<br>some, but not all, voltage-operated  $Ca^{2+}$  channe the situation was reversed (26, 54, 364). From the single channel recording data discussed above, it is clear that some, but not all, voltage-operated  $Ca^{2+}$  channels are blocked by organic  $Ca^{2+}$  entry blockers. It is some, but not all, voltage-operated  $Ca^{2+}$  channels are blocked by organic  $Ca^{2+}$  entry blockers. It is not yet clear whether any ROCs are blocked by these drugs. It is possible that the receptor-mediated responses bloc blocked by organic  $Ca^{2+}$  entry blockers. It is not yet clear whether any ROCs are blocked by these drugs. It is possible that the receptor-mediated responses blocked by organic  $Ca^{2+}$  entry blockers are secondarily med blocked by organic  $Ca^{2+}$  entry blockers. It is not yet clear<br>whether any ROCs are blocked by these drugs. It is<br>possible that the receptor-mediated responses blocked<br>by organic  $Ca^{2+}$  entry blockers are secondarily med whether any ROCs are blocked by these drugs. It is<br>possible that the receptor-mediated responses blocked<br>by organic  $Ca^{2+}$  entry blockers are secondarily mediated<br>by VOCs, although the dissociation from changes in<br>membra possible that the receptor-mediated responses blocked<br>by organic  $Ca^{2+}$  entry blockers are secondarily mediated<br>by VOCs, although the dissociation from changes in<br>membrane potential (97, 135) makes this less likely. The<br> by organic Ca<sup>2+</sup> entry blockers are secondarily mediated<br>by VOCs, although the dissociation from changes in<br>membrane potential (97, 135) makes this less likely. The<br>situation is complicated further by the fact that the<br>b by VOCs, although the dissociation from changes in membrane potential (97, 135) makes this less likely. The situation is complicated further by the fact that the blockade of VOCs by dihydropyridine-type  $Ca^{2+}$  entry bloc membrane potential (97, 135) makes this less likely. The situation is complicated further by the fact that the blockade of VOCs by dihydropyridine-type  $Ca^{2+}$  entry blockers is strongly state dependent, occurring most po situation is complicated further by the fact that the blockade of VOCs by dihydropyridine-type  $Ca^{2+}$  entry blockers is strongly state dependent, occurring most potently and effectively during prolonged depolarizations w blockade of VOCs by dihydropyridine-type  $Ca^{2+}$  entry<br>blockers is strongly state dependent, occurring most po-<br>tently and effectively during prolonged depolarizations<br>which open and/or inactivate the channels (108, 273,<br>

96<br>various channels may be fraught with potential difficulties. *C. Reciprocal Effects* rious channels may be fraught with potential difficul-<br>s.<br>Reciprocal Effects<br>Of course the various sources of intracellular and ex-<br>acellular Ca<sup>2+</sup> do not exist in isolation from each other.

ties.<br>C. Reciprocal Effects<br>Of course the various sources of intracellular and ex-<br>tracellular Ca<sup>2+</sup> do not exist in isolation from each other.<br>The intracellular storage pools from which Ca<sup>2+</sup> is re-C. Reciprocal Effects<br>Of course the various sources of intracellular and ex-<br>tracellular Ca<sup>2+</sup> do not exist in isolation from each other.<br>The intracellular storage pools from which  $Ca^{2+}$  is re-<br>leased are rapidly refil C. Reciprocal Effects<br>
Of course the various sources of intracellular and ex-<br>
tracellular Ca<sup>2+</sup> do not exist in isolation from each other.<br>
The intracellular storage pools from which Ca<sup>2+</sup> is re-<br>
leased are rapidly re Of course the various sources of intracellular and ex-<br>tracellular Ca<sup>2+</sup> do not exist in isolation from each other.<br>The intracellular storage pools from which Ca<sup>2+</sup> is re-<br>leased are rapidly refilled, either by Ca<sup>2+</sup> l tracellular Ca<sup>2+</sup> do not exist in isolation from each other.<br>
The intracellular storage pools from which Ca<sup>2+</sup> is re-<br>
leased are rapidly refilled, either by Ca<sup>2+</sup> leakage across<br>
the membrane, exchange for other ions, The intracellular storage pools from which  $Ca^{2+}$  is re-<br>leased are rapidly refilled, either by  $Ca^{2+}$  leakage across<br>the membrane, exchange for other ions, or influx through<br>membrane channels. In many cells, it appears The intracellular storage pools from which Ca<sup>2+</sup> is re-<br>leased are rapidly refilled, either by  $Ca^{2+}$  leakage across<br>the membrane, exchange for other ions, or influx through<br>membrane channels. In many cells, it appears the membrane, exchange for other ions, or influx throug<br>membrane channels. In many cells, it appears that the<br>is an initial transient increase in intracellular  $Ca^{2+}$  i<br>response to receptor activation which is caused by membrane channels. In many cells, it appears that there is an initial transient increase in intracellular Ca<sup>2+</sup> in idease from intracellular pools. Following this transient internally derived increase in cytosolic Ca<sup>2+</sup> is an initial transient increase in intracellular  $Ca^{2+}$  ir response to receptor activation which is caused by release from intracellular pools. Following this transient internally derived increase in cytosolic  $Ca^{2+}$ , response to receptor activation which is caused by release<br>from intracellular pools. Following this transient inter-<br>nally derived increase in cytosolic  $Ca^{2+}$ , however, there<br>is a sustained influx of  $Ca^{2+}$  across the from intracellular pools. Following this transient inter-<br>nally derived increase in cytosolic  $Ca^{2+}$ , however, there<br>is a sustained influx of  $Ca^{2+}$  across the plasma membrane.<br>This sustained influx probably serves to c nally derived increase in cytosolic  $Ca^{2+}$ , however, there is a sustained influx of  $Ca^{2+}$  across the plasma membrane.<br>This sustained influx probably serves to continuously activate the cell after intracellular stores a is a sustained influx of  $Ca^{2+}$  across the plasma membrane.<br>This sustained influx probably serves to continuously<br>activate the cell after intracellular stores are depleted<br>and also to replenish the intracellular storage This sustained influx probably serves to continuously<br>activate the cell after intracellular stores are depleted<br>and also to replenish the intracellular storage pools (278).<br>It is likely that the initial release of stored activate the cell after intracellular stores are depleted<br>and also to replenish the intracellular storage pools (278).<br>It is likely that the initial release of stored intracellular<br>Ca<sup>2+</sup> may, in many cases, promote the s and also to replenish the intracellular storage pools (278).<br>It is likely that the initial release of stored intracellular<br>Ca<sup>2+</sup> may, in many cases, promote the secondary influx<br>of extracellular Ca<sup>2+</sup>. Kuno and Gardner It is likely that the initial release of stored intracellula:<br>Ca<sup>2+</sup> may, in many cases, promote the secondary influs<br>of extracellular Ca<sup>2+</sup>. Kuno and Gardner (193) showed<br>that Ins(1,4,5)P<sub>3</sub> might gate Ca<sup>2+</sup> channels (  $Ca^{2+}$  may, in many cases, promote the secondary influx  $\frac{1}{100}$  of extracellular  $Ca^{2+}$ . Kuno and Gardner (193) showed lula that  $\text{Ins}(1,4,5)P_3$  might gate  $Ca^{2+}$  channels (see above).  $352$  Putney (279) has recen of extracellular Ca<sup>2+</sup>. Kuno and Gardner (193) showed<br>that  $\text{Ins}(1,4,5)P_3$  might gate Ca<sup>2+</sup> channels (see above).<br>Putney (279) has recently suggested that a certain frac-<br>tion of the endoplasmic or sarcoplasmic reticul that  $\text{Ins}(1,4,5)P_3$  might gate  $\text{Ca}^{2+}$  channels (see above).<br>
Putney (279) has recently suggested that a certain fraction of the endoplasmic or sarcoplasmic reticulum in<br>
cells which lies closely adjacent to the pla Putney (279) has recently suggested that a certain fraction of the endoplasmic or sarcoplasmic reticulum in<br>cells which lies closely adjacent to the plasma membrane<br>may have some direct connection which would allow  $Ca^{2+}$ tion of the endoplasmic or sarcoplasmic reticulum in<br>cells which lies closely adjacent to the plasma membrane<br>may have some direct connection which would allow Ca<sup>2-</sup><br>entry directly from the extracellular fluid (possibly may have some direct connection which would allow  $Ca^{2+}$  intry directly from the extracellular fluid (possibly similar to a gap junction regulated by  $Ca^{2+}$  or second messengers). Ins(1,4,5) $P_3$ -induced release of  $Ca^{2$ entry directly from the extracellular fluid (possibly sim-<br>ilar to a gap junction regulated by  $Ca^{2+}$  or second mes-<br>sengers). Ins(1,4,5) $P_3$ -induced release of  $Ca^{2+}$  from this lustructure would then stimulate refilli ilar to a gap junction regulated by  $Ca^{2+}$  or second messengers). Ins(1,4,5)P<sub>3</sub>-induced release of  $Ca^{2+}$  from this structure would then stimulate refilling by direct  $Ca^{2+}$  influx. Evidence for  $Ca^{2+}$ -activated  $Ca^{2$ sengers). Ins(1,4,5)P<sub>3</sub>-induced release of Ca<sup>2+</sup> from this lul<br>structure would then stimulate refilling by direct Ca<sup>2+</sup><br>influx. Evidence for Ca<sup>2+</sup>-activated Ca<sup>2+</sup> channels has<br>been reported (361). Alternatively, init structure would then stimulate refilling by direct  $Ca^{2+}$  influx. Evidence for  $Ca^{2+}$ -activated  $Ca^{2+}$  channels has  $\alpha$  been reported (361). Alternatively, initial influx of  $Ca^{2+}$  the caused by channel opening may p influx. Evidence for Ca<sup>2+</sup>-activated Ca<sup>2+</sup> channels has  $\alpha$  been reported (361). Alternatively, initial influx of Ca<sup>2+</sup> the caused by channel opening may promote release of stored the Ca<sup>2+</sup> (203, 278). Such "Ca<sup>2+</sup>-i been reported (361). Alternatively, initial influx of  $Ca^{2+}$ <br>caused by channel opening may promote release of stored<br> $Ca^{2+}$  (203, 278). Such " $Ca^{2+}$ -induced  $Ca^{2+}$  release" has<br>been proposed to play a major role in ac caused by channel opening may promote release of stored the Ca<sup>2+</sup> (203, 278). Such "Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release" has election proposed to play a major role in activation of also speed inactivation of proposes in cytoso Ca<sup>2+</sup> (203, 278). Such "Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release" has<br>been proposed to play a major role in activation of<br>smooth muscle contraction (177). Finally, it is likely that<br>increases in cytosolic Ca<sup>2+</sup> also speed inactiva been proposed to play a major role in activation of amsmooth muscle contraction (177). Finally, it is likely that of increases in cytosolic  $Ca^{2+}$  also speed inactivation of respection types of  $Ca^{2+}$  channels (179). Th smooth muscle contraction<br>increases in cytosolic  $Ca^2$ <br>certain types of  $Ca^{2+}$  chan<br>tween these phenomena are<br>beginning to be understood<br>VIII Role of Intre-ene certain types of  $Ca^{2+}$  channels (179). The linkages be-<br>tween these phenomena are obviously complex and only<br>beginning to be understood.<br>VIII. Role of Intra- and Extracellular  $Ca^{2+}$  in  $\alpha$ -<br>Adrenergic Receptor-Mediat

## **VIII.** Role of Intra- and Extracellular Ca<sup>2+</sup> in  $\alpha$ -Smooth **Muscle** Variabilities in the importance of extracellular Ca<sup>2+</sup> in  $\alpha$ -<br>Adrenergic Receptor-Mediated Contractions of 5.1%<br>Smooth Muscle<br>Variabilities in the importance of extracellular Ca<sup>2+</sup> in cellu<br>adrenergic receptor-mediate

VIII. Kole of Intra- and Extracellular Ca<sup>-1</sup> In  $\alpha$ -<br>Adrenergic Receptor-Mediated Contractions of 5.1<br>Smooth Muscle contractions of 5.1<br>Variabilities in the importance of extracellular Ca<sup>2+</sup> in  $\alpha$ -adrenergic receptor **Extremely intriguing and have received much attentions**<br>in smooth Muscle<br>and adventure of extracellular Ca<sup>2+</sup> in<br>extremely intriguing and have received much attention<br>in smooth muscle. It is clear that  $\alpha_1$ - and  $\alpha_2$ SMOOTH MUSCIE<br>
Variabilities in the importance of extracellular Ca<sup>2+</sup> in<br>  $\alpha$ -adrenergic receptor-mediated contractile responses are<br>
extremely intriguing and have received much attention<br>
in smooth muscle. It is clear Variabilities in the importance of extracellular Ca<sup>2+</sup> in  $\alpha$ -adrenergic receptor-mediated contractile responses are extremely intriguing and have received much attention is in smooth muscle. It is clear that  $\alpha_1$ - an  $\alpha$ -adrenergic receptor-mediated contractile responses are<br>extremely intriguing and have received much attention<br>in smooth muscle. It is clear that  $\alpha_1$ - and  $\alpha_2$ -adrenergic<br>receptors coexist on many postjunctional s extremely intriguing and have received much attention<br>in smooth muscle. It is clear that  $\alpha_1$ - and  $\alpha_2$ -adrenergic<br>receptors coexist on many postjunctional smooth muscle<br>cells, and that activation of either subtype ac in smooth muscle. It is clear that  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors coexist on many postjunctional smooth muscle cells, and that activation of either subtype activates contraction (90, 96, 198, 199, 227, 322, 339, receptors coexist on many postjunctional smooth muscle point cells, and that activation of either subtype activates tricontraction (90, 96, 198, 199, 227, 322, 339, 344, 345). to The contractile responses caused by activa cells, and that activation of either subtype activates to<br>contraction (90, 96, 198, 199, 227, 322, 339, 344, 345). The contractile responses caused by activation of either the<br>subtype are thought to be due to an increase contraction (90, 96, 198, 199, 227, 322, 339, 344, 345). The contractile responses caused by activation of either the subtype are thought to be due to an increase in free acytosolic Ca<sup>2+</sup> in the muscle cells (341). Since The contractile responses caused by activation of either<br>subtype are thought to be due to an increase in frequention of all cytosolic  $Ca^{2+}$  in the muscle cells (341). Since  $Ca^{2+}$  ior<br>play an obligatory role in transfe subtype are thought to be due to an increase in free act<br>cytosolic  $Ca^{2+}$  in the muscle cells  $(341)$ . Since  $Ca^{2+}$  ions tio<br>play an obligatory role in transferring the signal of Intersection to contraction of myofilame

MAN<br>used as a bioassay for changes in the concentration of<br>intracellular free  $Ca^{2+}$ . These increases in cytosolic  $Ca^{2+}$ MAN<br>used as a bioassay for changes in the concentration of<br>intracellular free Ca<sup>2+</sup>. These increases in cytosolic Ca<sup>2+</sup><br>cause, through calmodulin, activation of myosin light MAN<br>used as a bioassay for changes in the concentration of<br>intracellular free  $Ca^{2+}$ . These increases in cytosolic  $Ca^{2+}$ <br>cause, through calmodulin, activation of myosin light<br>chain kinase. This enzyme phosphorylates th used as a bioassay for changes in the concentration of intracellular free  $Ca^{2+}$ . These increases in cytosolic  $Ca^{2+}$  cause, through calmodulin, activation of myosin light chain kinase. This enzyme phosphorylates the my intracellular free  $Ca^{2+}$ . These increases in cytosolic  $Ca^{2+}$  cause, through calmodulin, activation of myosin light chain kinase. This enzyme phosphorylates the myosin light chain and thereby increases the interaction cause, through calmodulin, activation of myosin light<br>chain kinase. This enzyme phosphorylates the myosin<br>light chain and thereby increases the interaction between<br>actin and myosin. This results in contraction of the<br>musc chain kinase. This enzyme phosphorylates the myosin light chain and thereby increases the interaction between

light chain and thereby increases the interaction betweed actin and myosin. This results in contraction of muscle cell (34, 352, 354).<br>In order to determine the importance of Ca<sup>2+</sup> influx a contractile response, one can actin and myosin. This results in contraction of muscle cell  $(34, 352, 354)$ .<br>In order to determine the importance of  $Ca^{2+}$  influx contractile response, one can simply remove extra lular  $Ca^{2+}$  or block influx with or muscle cell (34, 352, 354).<br>
In order to determine the importance of Ca<sup>2+</sup> influx to<br>
a contractile response, one can simply remove extracel-<br>
lular Ca<sup>2+</sup> or block influx with organic, (e.g., dihydropyr-<br>
idine) or inor In order to determine the importance of  $Ca^{2+}$  influx to<br>a contractile response, one can simply remove extracel-<br>lular  $Ca^{2+}$  or block influx with organic, (e.g., dihydropyr-<br>idine) or inorganic (e.g., lanthanum, cobalt a contractile response, one can simply remove extracel-<br>lular Ca<sup>2+</sup> or block influx with organic, (e.g., dihydropyr-<br>idine) or inorganic (e.g., lanthanum, cobalt, cadmium,<br>mickel) Ca<sup>2+</sup> entry blockers. The contribution idine) or inorganic (e.g., lanthanum, cobalt, cadmium, nickel)  $Ca^{2+}$  entry blockers. The contribution of stored intracellular  $Ca^{2+}$  can sometimes be determined by depleting releasable intracellular pools by repeated e nickel)  $Ca^{2+}$  entry blockers. The contribution of stored nickel)  $Ca^{2+}$  entry blockers. The contribution of stored<br>intracellular  $Ca^{2+}$  can sometimes be determined by de-<br>pleting releasable intracellular pools by repeated expo-<br>sure to agonists or to caffeine and determining intracellular Ca<sup>2+</sup> can sometimes be determined by depleting releasable intracellular pools by repeated exposure to agonists or to caffeine and determining the residual contractile response. Coupling these two approaches pleting releasable intracellular pools by repeated exposure to agonists or to caffeine and determining the residual contractile response. Coupling these two approaches allows one to determine (subject to equilibration betw sure to agonists or to caffeine and determining the real contractile response. Coupling these two approacellows one to determine (subject to equilibration between pools and limitations of interpretation) the relative cont allows one to determine (subject to equilibration between<br>pools and limitations of interpretation) the relative con-<br>tribution of intracellular  $Ca^{2+}$  mobilization and extracel-<br>lular  $Ca^{2+}$  influx to an observed contra 352).

may have some direct connection which would allow Ca<sup>2+</sup> importance of extracellular Ca<sup>2+</sup>. This is in contrast to entry directly from the extracellular fluid (possibly sim-<br>ilar to a gap junction regulated by Ca<sup>2+</sup> or As discussed above, it has been known for many years that  $\alpha$ -adrenergic receptor-mediated contractions of different smooth muscles show a marked variation in the flular Ca<sup>2+</sup> influx to an observed contractile response (33, 352).<br>
As discussed above, it has been known for many years<br>
that  $\alpha$ -adrenergic receptor-mediated contractions of dif-<br>
ferent smooth muscles show a marked v 352).<br>
As discussed above, it has been known for many years<br>
that  $\alpha$ -adrenergic receptor-mediated contractions of dif-<br>
ferent smooth muscles show a marked variation in the<br>
importance of extracellular Ca<sup>2+</sup>. This is i As discussed above, it has been known for many yes<br>that  $\alpha$ -adrenergic receptor-mediated contractions of d<br>ferent smooth muscles show a marked variation in t<br>importance of extracellular Ca<sup>2+</sup>. This is in contrast<br>depola that  $\alpha$ -adrenergic receptor-mediated contractions of ferent smooth muscles show a marked variation in importance of extracellular Ca<sup>2+</sup>. This is in contrast depolarization-evoked contractions, which are ess tially comp ferent smooth muscles show a marked variation in the<br>importance of extracellular  $Ca^{2+}$ . This is in contrast to<br>depolarization-evoked contractions, which are essen-<br>tially completely dependent on the presence of extracel importance of extracellular Ca<sup>2+</sup>. This is in contrast to<br>depolarization-evoked contractions, which are essen-<br>tially completely dependent on the presence of extracel-<br>lular Ca<sup>2+</sup> in every smooth muscle examined (33, 15 depolarization-evoked contractions, which are essentially completely dependent on the presence of extracel-<br>lular Ca<sup>2+</sup> in every smooth muscle examined (33, 152,<br>153, 320, 353). The importance of extracellular Ca<sup>2+</sup> for tially completely dependent on the presence of extracel-<br>lular Ca<sup>2+</sup> in every smooth muscle examined (33, 152,<br>153, 320, 353). The importance of extracellular Ca<sup>2+</sup> for<br> $\alpha$ -adrenergic receptor-mediated contractions dep 153, 320, 353). The importance of extracellular  $Ca^{2+}$  for  $\alpha$ -adrenergic receptor-mediated contractions depends on the particular muscle and animal species being used and the phase of contraction studied (36, 115, 353)  $\alpha$ -adrenergic receptor-mediated contractions depends on  $\alpha$ -adrenergic receptor-mediated contractions depends on<br>the particular muscle and animal species being used and<br>the phase of contraction studied (36, 115, 353). Devine<br>et al. (87) showed that there was a general correla the particular muscle and animal species being used and<br>the phase of contraction studied (36, 115, 353). Devine<br>et al. (87) showed that there was a general correlation<br>among different smooth muscles between the importance the phase of contraction studied  $(36, 115, 353)$ . Devinet al.  $(87)$  showed that there was a general correlatio among different smooth muscles between the importance of extracellular  $Ca^{2+}$  in receptor-mediated contract et al.  $(87)$  showed that there was a general correlation<br>among different smooth muscles between the importance<br>of extracellular  $Ca^{2+}$  in receptor-mediated contractile<br>responses and the relative volume of sarcoplasmic r among different smooth muscles between the importance<br>of extracellular  $Ca^{2+}$  in receptor-mediated contractile<br>responses and the relative volume of sarcoplasmic retic-<br>ulum in the muscle. For example, rabbit mesenteric v of extracellular  $Ca^{2+}$  in receptor-mediated contractile<br>responses and the relative volume of sarcoplasmic retic-<br>ulum in the muscle. For example, rabbit mesenteric veir<br>had only 2.2% sarcoplasmic reticulum and depended<br> responses and the relative volume of sarcoplasmic retic-<br>ulum in the muscle. For example, rabbit mesenteric vein<br>had only 2.2% sarcoplasmic reticulum and depended<br>completely on extracellular  $Ca^{2+}$  for agonist-induced co ulum in the muscle. For example, rabbit mesenteric vein<br>had only  $2.2\%$  sarcoplasmic reticulum and depended<br>completely on extracellular  $Ca^{2+}$  for agonist-induced con-<br>tractions, while strips of main pulmonary artery ha had only 2.2% sarcoplasmic reticulum and depend<br>completely on extracellular  $Ca^{2+}$  for agonist-induced co<br>tractions, while strips of main pulmonary artery ha<br>5.1% sarcoplasmic reticulum and retained a significa<br>contracti completely on extracellular  $Ca^{2+}$  for agonist-induced cotractions, while strips of main pulmonary artery h.<br>5.1% sarcoplasmic reticulum and retained a signification<br>contractile response to agonists in the absence of ext tractions, while strips of main pulmonary artery had 5.1% sarcoplasmic reticulum and retained a significant contractile response to agonists in the absence of extracellular  $Ca^{2+}$  (87). The extensive ramifications of sar 5.1% sarcoplasmic reticulum and retained a significant contractile response to agonists in the absence of extra-<br>cellular  $Ca^{2+}$  (87). The extensive ramifications of sarco-<br>plasmic reticulum in skeletal muscle, where con contractile response to agonists in the absence of extra-<br>cellular  $Ca^{2+}$  (87). The extensive ramifications of sarco-<br>plasmic reticulum in skeletal muscle, where contraction<br>is completely independent of extracellular  $Ca^{$ cellular Ca<sup>2+</sup> (87). The extensive ramifications of sarco-<br>plasmic reticulum in skeletal muscle, where contraction<br>is completely independent of extracellular Ca<sup>2+</sup>, support<br>such an interpretation. Possibly the size of t plasmic reticulum in skeletal muscle, where contraction<br>is completely independent of extracellular  $Ca^{2+}$ , support<br>such an interpretation. Possibly the size of the storage<br>pool for releasable calcium influences the relat is completely independent of extracellular  $Ca^{2+}$ , support such an interpretation. Possibly the size of the storage pool for releasable calcium influences the relative contribution which extracellular and intracellular pool for releasable calcium influences the relative contribution which extracellular and intracellular Ca<sup>2+</sup> make<br>to agonist-mediated responses in smooth muscle, al-<br>though this does not necessarily explain how receptor pool for releasable calcium influences the relative contribution which extracellular and intracellular  $Ca^{2+}$  makto agonist-mediated responses in smooth muscle, although this does not necessarily explain how recepto acti tribution which extracellular and intracellular  $Ca^{2+}$  make<br>to agonist-mediated responses in smooth muscle, al-<br>though this does not necessarily explain how receptor<br>activation is linked to both sources. One possibility to agonist-mediated responses in smooth muscle, although this does not necessarily explain how receptor activation is linked to both sources. One possibility mentioned above and proposed by Putney (279) is that  $\text{Ins}(1,4,$ though this does not necessarily explain how recepto<br>activation is linked to both sources. One possibility men<br>tioned above and proposed by Putney (279) is the<br>Ins(1,4,5)P<sub>3</sub> controls both the release of intracellularl<br>st activation is<br>tioned abov<br> $\text{Ins}(1,4,5)P_3$ <br>stored  $\text{Ca}^{2+}$  a<br> $\text{Ca}^{2+}$  store.

PHARMACOLOGICAL REVIEWS

*A. Phasic versus Tonic*  $\alpha_1$ -ADRENERGIC RECE<br>
Phasic versus Tonic<br>
Bohr (32) suggested that contraction of rat aorta<br>
used by epinephrine could be divided into two compo-A. Phasic versus Tonic<br>
Bohr (32) suggested that contraction of rat ao:<br>
caused by epinephrine could be divided into two compo-<br>
nents. The initial fast phasic response (phase I) could A. Phasic versus Tonic<br>
Bohr (32) suggested that contraction of rat aorta<br>
caused by epinephrine could be divided into two compo-<br>
nents. The initial fast phasic response (phase I) could be<br>
distinguished from a later slow A. Phasic bersus Tonic<br>Bohr (32) suggested that contraction of rat aorta<br>caused by epinephrine could be divided into two compo-<br>nents. The initial fast phasic response (phase I) could be<br>distinguished from a later slow ton Bohr  $(32)$  suggested that contraction of rat aorta<br>caused by epinephrine could be divided into two compo-<br>nents. The initial fast phasic response (phase I) could be<br>distinguished from a later slow tonic response (phase I nents. The initial fast phasic response (phase I) could be distinguished from a later slow tonic response (phase II). Similar two-phase responses can be observed in many other smooth muscles, and in some cases further comp ments. The initial fast phasic response (phase I) could be<br>distinguished from a later slow tonic response (phase II).<br>Similar two-phase responses can be observed in many<br>other smooth muscles, and in some cases further comdistinguished from a later slow tonic response (phase II).<br>
Similar two-phase responses can be observed in many<br>
other smooth muscles, and in some cases further com-<br>
ponents of contractions have been suggested (34). The<br> Similar two-phase responses can be observed in many<br>other smooth muscles, and in some cases further com-<br>ponents of contractions have been suggested (34). The<br>relative sizes of these phasic and tonic components of<br>contract other smooth muscles, and in some cases further com-<br>ponents of contractions have been suggested (34). The<br>relative sizes of these phasic and tonic components of<br>contraction vary with the muscle studied and the con-<br>tracti ponents of contractions have been suggested  $(34)$ . The relative sizes of these phasic and tonic components contraction vary with the muscle studied and the c tractile stimulus. In many muscles, the different phase of con relative sizes of these phasic and tonic components of<br>contraction vary with the muscle studied and the con-<br>tractile stimulus. In many muscles, the different phases<br>of contraction have a different dependence on extracelcontraction vary with the muscle studied and the con-<br>tractile stimulus. In many muscles, the different phases<br>of contraction have a different dependence on extracel-<br>lular  $Ca^{2+}$  (27). Differential effects on different tractile stimulus. In many muscles, the different phases<br>of contraction have a different dependence on extracel-<br>lular Ca<sup>2+</sup> (27). Differential effects on different phases<br>of contraction can complicate interpretations of of contraction have a different dependence on extractular  $Ca^{2+}$  (27). Differential effects on different phase of contraction can complicate interpretations of studion the importance of extracellular  $Ca^{2+}$  in smooth mu lular  $Ca^{2+}$  (27). Differential effects on different phases<br>of contraction can complicate interpretations of studies<br>on the importance of extracellular  $Ca^{2+}$  in smooth muscle<br>contractile responses. However, there is no of contraction can complicate interpretations of studies<br>on the importance of extracellular  $Ca^{2+}$  in smooth muscle<br>contractile responses. However, there is no clear corre-<br>lation between phasic and tonic contractions an on the importance of extracellular  $Ca^{2+}$  in smooth muscle<br>contractile responses. However, there is no clear corre-<br>lation between phasic and tonic contractions and the<br>sumportance of  $Ca^{2+}$  influx. In rabbit aorta and contractile responses. However, there is no clear correlation between phasic and tonic contractions and the importance of  $Ca^{2+}$  influx. In rabbit aorta and ear artery, rapid phasic contractions caused by norepinephrine lation between phasic and tonic contractions and the<br>importance of  $Ca^{2+}$  influx. In rabbit aorta and ear artery,<br>rapid phasic contractions caused by norepinephrine are<br>not dependent on the presence of extracellular  $Ca^{2$ rapid phasic contractions caused by norepinephrine are<br>not dependent on the presence of extracellular Ca<sup>2+</sup> (86, 176), while in rat mesenteric arteries or resistance ves-<br>sels, norepinephrine-induced rapid phasic contrac 176), while in rat mesenteric arteries or resistance ves-176), while in rat mesenteric arteries or resistance vessels, norepinephrine-induced rapid phasic contractions in are abolished in  $Ca^{2+}$ -free medium (116, 264). In rat enanococcygeus muscle, slow tonic contractions to n sels, norepinephrine-induced rapid phasic contractions in are abolished in  $Ca^{2+}$ -free medium (116, 264). In rat encococcygeus muscle, slow tonic contractions to norepi-<br>nephrine are less sensitive to inhibition by  $Ca^{2+$ are abolished in  $Ca^{2+}$ -free medium (116, 264). In rat anococcygeus muscle, slow tonic contractions to norepi-<br>nephrine are less sensitive to inhibition by  $Ca^{2+}$  entry blockers than are phasic contractions (227, 266), anococcygeus muscle, slow tonic contractions to norepi-<br>nephrine are less sensitive to inhibition by  $Ca^{2+}$  entry<br>blockers than are phasic contractions (227, 266), while<br>the reverse holds true in rabbit aorta (85, 86). C nephrine are less sensitive to inhibition by  $Ca^{2+}$  entry<br>blockers than are phasic contractions (227, 266), while<br>the reverse holds true in rabbit aorta (85, 86). Clearly,<br>differences in types of contraction cannot simpl been well summarized by Timmermans and Thoolen (341). for smooth muscle contraction. This subject has recently<br>been well summarized by Timmermans and Thoolen<br>(341).<br>*B.*  $\alpha_2$ - versus  $\alpha_1$ -<br>Another possible explanation for the differential de-<br>pendence on extracellular  $Ca$ 

(341).<br>
B.  $\alpha_2$ - versus  $\alpha_1$ -<br>
Another possible explanation for the differential de-<br>
pendence on extracellular Ca<sup>2+</sup> is that there might be<br>
different  $\alpha$ -adrenergic receptor subtypes involved in con-B.  $\alpha_2$ - versus  $\alpha_1$ -<br>Another possible explanation for the differential dependence on extracellular  $Ca^{2+}$  is that there might be<br>different  $\alpha$ -adrenergic receptor subtypes involved in con-<br>traction of different smo to  $\alpha_2$ - *oersus*  $\alpha_1$ -<br>Another possible explanation for the differential dependence on extracellular Ca<sup>2+</sup> is that there might be different *α*-adrenergic receptor subtypes involved in contraction of different smoo Another possible explanation for the differential dependence on extracellular Ca<sup>2+</sup> is that there might be call different  $\alpha$ -adrenergic receptor subtypes involved in contraction of different smooth muscles. van Meel et pendence on extracellular  $Ca^{2+}$  is that there might be different  $\alpha$ -adrenergic receptor subtypes involved in contraction of different smooth muscles. van Meel et al. (355) first reported that a variety of organic  $Ca^{2$ traction of different smooth muscles. van Meel et al.<br>
(355) first reported that a variety of organic Ca<sup>2+</sup> entry<br>
blockers inhibited pressor responses elicited by the  $\alpha_2$ -<br>
adrenergic receptor agonist 6-allyl-2-amino blockers inhibited pressor responses elicited by the  $\alpha_2$ -<br>adrenergic receptor agonist 6-allyl-2-amino-5,6,7,8-tet-<br>rahydro-4H-thiazolo[4,5d]azepine (BHT 920) in pithed<br>rats without affecting pressor responses to the  $\$ rahydro-4H-thiazolo[4,5d]azepine (BHT 920) in pithed adrenergic receptor agonist 6-allyl-2-amino-5,6,7,8-tet-<br>rahydro-4H-thiazolo[4,5d]azepine (BHT 920) in pithed<br>rats without affecting pressor responses to the  $\alpha_1$ -adre-<br>mergic receptor agonists phenylephrine or methoxam rahydro-4H-thiazolo[4,5d]azepine (BHT 920) in pithed<br>rats without affecting pressor responses to the  $\alpha_1$ -adre-<br>nergic receptor agonists phenylephrine or methoxamine.<br>These authors also showed that manganese, nickel, an nergic receptor agonists phenylephrine or methoxamine. (I<br>These authors also showed that manganese, nickel, and<br>cobalt also selectively inhibited the response to  $\alpha_2$ -adre-<br>nergic receptor agonists (356). Similar result These authors also showed that manganese, nickel, and anoco cobalt also selectively inhibited the response to  $\alpha_2$ -adre-<br>nergic receptor agonists (356). Similar results were ob-<br>tained by the same group (338, 357, 358), cobalt also selectively inhibited the responergic receptor agonists (356). Similar retained by the same group (338, 357, 35 others (56, 212) in other tissues. Similarly entry promoter methyl-1,4-dihydro-2,6-tro-4-(2-triflu tro-4-(2-trifluoromethylphenyl)pyridinetained by the same group (338, 357, 358), as well as<br>others (56, 212) in other tissues. Similarly, the calcium<br>entry promoter methyl-1,4-dihydro-2,6-dimethyl-3-ni-<br>tro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate<br>(Ba others (56, 212) in other tissues. Similarly, the calcium<br>entry promoter methyl-1,4-dihydro-2,6-dimethyl-3-ni-<br>tro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate<br>(Bay K 8644) was shown to potentiate the pressor re-<br>spo

mediated by  $\alpha_1$ -adrenergic receptors did not. This hypothesis was consistent with the evolving mechanism of action of  $\alpha_1$ -adrenergic receptor activation, since forma-EPTOR SUBTYPES<br>mediated by  $\alpha_1$ -adrenergic receptors did not. This h<br>pothesis was consistent with the evolving mechanism<br>action of  $\alpha_1$ -adrenergic receptor activation, since form<br>tion of Ins(1,4,5)P<sub>3</sub> and release of mediated by  $\alpha_1$ -adrenergic receptors did not. This hypothesis was consistent with the evolving mechanism of action of  $\alpha_1$ -adrenergic receptor activation, since formation of Ins(1,4,5)P<sub>3</sub> and release of intracellula mediated by  $\alpha_1$ -adrenergic receptors did not. This hypothesis was consistent with the evolving mechanism of action of  $\alpha_1$ -adrenergic receptor activation, since formation of Ins(1,4,5)P<sub>3</sub> and release of intracellula fluid. tion of  $\alpha_1$ -adrenergic receptor activation, since formation of  $\text{Ins}(1,4,5)P_3$  and release of intracellular  $\text{Ca}^{2+}$  ould not require influx of  $\text{Ca}^{2+}$  from the extracellular id.<br>However, further examination of should not require influx of  $Ca^{2+}$  from the extracellular<br>fluid.<br>However, further examination of the dependence of<br>smooth muscle contraction on extracellular  $Ca^{2+}$  revealed

not dependent on the presence of extracellular Ca<sup>2+</sup> (86, 343). It has since become clear that  $\alpha_1$ -adrenergic recep-<br>176), while in rat mesenteric arteries or resistance ves-<br>sels, norepinephrine-induced rapid phasic blockers than are phasic contractions (227, 266), while tions of smooth muscle are potently blocked by organic<br>the reverse holds true in rabbit aorta (85, 86). Clearly,  $Ca^{2+}$  entry blockers still holds true at the time should not require influx of  $Ca^{2+}$  from the extracellular<br>fluid.<br>However, further examination of the dependence of<br>smooth muscle contraction on extracellular  $Ca^{2+}$  revealed<br>several instances where  $\alpha_1$ -adrenergic re However, further examination of the dependence of smooth muscle contraction on extracellular  $Ca^{2+}$  revealed several instances where  $\alpha_1$ -adrenergic receptor-mediated contractions were clearly blocked by organic  $Ca^{2+}$ several instances where  $\alpha_1$ -adrenergic receptor-mediat<br>contractions were clearly blocked by organic Ca<sup>2+</sup> ent<br>blockers. Timmermans et al. (340) showed that vasoco<br>striction in pithed rats caused by the selective  $\alpha_1$ contractions were clearly blocked by organic  $Ca^{2+}$  entry<br>blockers. Timmermans et al. (340) showed that vasocon-<br>striction in pithed rats caused by the selective  $\alpha_1$ -adre-<br>nergic receptor agonist 2-(2-methyl-indazol-4 contractions were clearly blocked by organic  $Ca^{2+}$  entry<br>blockers. Timmermans et al. (340) showed that vasocon-<br>striction in pithed rats caused by the selective  $\alpha_1$ -adre-<br>nergic receptor agonist 2-(2-methyl-indazol-4 blockers. Timmermans et al. (340) showed that vasoconstriction in pithed rats caused by the selective  $\alpha_1$ -adrenergic receptor agonist 2-(2-methyl-indazol-4-im-<br>ino)imidazolidine (Sgd 101/75) was completely blocked<br>by o striction in pithed rats caused by the selective  $\alpha_1$ -adre-<br>nergic receptor agonist 2-(2-methyl-indazol-4-im-<br>ino)imidazolidine (Sgd 101/75) was completely blocked<br>by organic Ca<sup>2+</sup> entry blockers. Further studies in pi nergic receptor agonist 2-(2-methyl-indazol-4-im-<br>ino)imidazolidine (Sgd 101/75) was completely blocked<br>by organic Ca<sup>2+</sup> entry blockers. Further studies in pithed<br>rats demonstrated that vasoconstrictor responses to<br>some ino)imidazolidine (Sgd 101/75) was completely blocked<br>by organic Ca<sup>2+</sup> entry blockers. Further studies in pithed<br>rats demonstrated that vasoconstrictor responses to<br>some  $\alpha_1$ -adrenergic receptor agonists are much more<br> by organic Ca<sup>2+</sup> entry blockers. Further studies in pithed<br>rats demonstrated that vasoconstrictor responses to<br>some  $\alpha_1$ -adrenergic receptor agonists are much more<br>effectively blocked by Ca<sup>2+</sup> entry blockers than are rats demonstrated that vasoconstrictor responses to some  $\alpha_1$ -adrenergic receptor agonists are much more effectively blocked by Ca<sup>2+</sup> entry blockers than are responses to other  $\alpha_1$ -adrenergic receptor agonists (16, sponses to other  $\alpha_1$ -adrenergic receptor agonists (16, 342, sponses to other  $\alpha_1$ -adrenergic receptor agonists (16, 342, 343). It has since become clear that  $\alpha_1$ -adrenergic receptor-mediated contractile responses in many tissues both in vitro as well as in vivo are blocked by 343). It has since become clear that  $\alpha_1$ -adrenergic rector-mediated contractile responses in many tissues b<br>in vitro as well as in vivo are blocked by organic C<br>entry blockers, while in other tissues they are not affec tor-mediated contractile responses in many tissues b<br>in vitro as well as in vivo are blocked by organic C<br>entry blockers, while in other tissues they are not affec<br>(37, 67, 146, 208, 222, 230, 271, 290, 303). The gener<br>za in vitro as well as in vivo are blocked by organic  $Ca^{2+}$ <br>entry blockers, while in other tissues they are not affected<br>(37, 67, 146, 208, 222, 230, 271, 290, 303). The generali-<br>zation that all  $\alpha_2$ -adrenergic receptor entry blockers, while in other tissues they are not affected<br>
(37, 67, 146, 208, 222, 230, 271, 290, 303). The generali-<br>
zation that all  $\alpha_2$ -adrenergic receptor-mediated contrac-<br>
tions of smooth muscle are potently b (37, 67, 146, 208, 222, 230, 271, 290, 303). The gener<br>zation that all  $\alpha_2$ -adrenergic receptor-mediated contr<br>tions of smooth muscle are potently blocked by orge<br>Ca<sup>2+</sup> entry blockers still holds true at the time this Example is a potently blocked by organic<br>  $Ca^{2+}$  entry blockers still holds true at the time this review<br>
is being written (341). However,  $\alpha_1$ -adrenergic receptor-<br>
mediated contractions appear to be much more heterois being written (341). However,  $\alpha_1$ -adrenergic receptoris being written (341). However,  $\alpha_1$ -adrenergic receptor-<br>mediated contractions appear to be much more hetero-<br>geneous. Some such contractions are potently blocked by<br>organic Ca<sup>2+</sup> entry blockers, while others are not

tro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate agonists in the same muscle can be differentially affected<br>(Bay K 8644) was shown to potentiate the pressor re-<br>sponses produced during  $\alpha_2$ - but not  $\alpha_1$ -adrenerg geneous. Some such contractions are potently blocked by<br>organic  $Ca^{2+}$  entry blockers, while others are not (341).<br>The differential effects of organic  $Ca^{2+}$  entry blockers<br>on  $\alpha_1$ -adrenergic receptor-mediated contrac organic Ca<sup>2+</sup> entry blockers, while others are not (341).<br>The differential effects of organic Ca<sup>2+</sup> entry blockers<br>on  $\alpha_1$ -adrenergic receptor-mediated contractile responses<br>in smooth muscle can be demonstrated in two on  $\alpha_1$ -adrenergic receptor-mediated contractile responses<br>in smooth muscle can be demonstrated in two different<br>ways. First, contractile responses to the same agonist<br>can be differentially affected in different muscles on  $\alpha_1$ -adrenergic receptor-mediated contractile responses<br>in smooth muscle can be demonstrated in two different<br>ways. First, contractile responses to the same agonist<br>can be differentially affected in different muscles ways. First, contractile responses to the same agonist<br>can be differentially affected in different muscles. For<br>example, the contractile response to the selective  $\alpha_1$ -<br>adrenergic receptor agonist phenylephrine is marke can be differentially affected in different muscles. lexample, the contractile response to the selective adrenergic receptor agonist phenylephrine is marke reduced by  $0.01 \mu$ M nifedipine in dog circumflex coron artery, b example, the contractile response to the selective  $\alpha_1$ -<br>adrenergic receptor agonist phenylephrine is markedly<br>reduced by 0.01  $\mu$ M nifedipine in dog circumflex coronary<br>artery, but unaffected by 1  $\mu$ M nifedipine in adrenergic receptor agonist phenylephrine is markedly<br>reduced by 0.01  $\mu$ M nifedipine in dog circumflex coronary<br>artery, but unaffected by 1  $\mu$ M nifedipine in dog saphen-<br>ous vein (255). Similarly, the contractile resp reduced by 0.01  $\mu$ M nifedipine in dog circumflex coronar<br>artery, but unaffected by 1  $\mu$ M nifedipine in dog sapher<br>ous vein (255). Similarly, the contractile response to th<br>selective  $\alpha_1$ -adrenergic receptor agonist artery, but unaffected by 1  $\mu$ M nifedipine in dog saphen-<br>ous vein (255). Similarly, the contractile response to the<br>selective  $\alpha_1$ -adrenergic receptor agonist Sgd 101/75 is<br>markedly reduced by 10  $\mu$ M methoxy-verapa ous vein (255). Similarly, the contractile response to the selective  $\alpha_1$ -adrenergic receptor agonist Sgd 101/75 is markedly reduced by 10  $\mu$ M methoxy-verapamil-HCl (D600) in rat aorta, but not in guinea pig aorta or markedly reduced by 10  $\mu$ M methoxy-verapamil-HCl (D600) in rat aorta, but not in guinea pig aorta or rat anococcygeus muscle (16, 359). Finally, 1  $\mu$ M felodipine abolishes the contractile response to norepinephrine in markedly reduced by 10  $\mu$ M methoxy-verapamil-HCl (D600) in rat aorta, but not in guinea pig aorta or rat anococcygeus muscle (16, 359). Finally, 1  $\mu$ M felodipine abolishes the contractile response to norepinephrine in (D600) in rat aorta, but not in guinea pig aorta or rat anococcygeus muscle (16, 359). Finally, 1  $\mu$ M felodipine abolishes the contractile response to norepinephrine in rat portal vein, reduces it in rat aorta, but does anococcygeus muscle (16, 359). Finally, 1  $\mu$ M felodipine<br>abolishes the contractile response to norepinephrine in<br>rat portal vein, reduces it in rat aorta, but does not alter<br>it in rabbit aorta (fig. 4) (211), even thoug abolishes the contractile response to norepine<br>phrine in rat portal vein, reduces it in rat aorta, but does not alter<br>it in rabbit aorta (fig. 4) (211), even though  $\alpha_1$ -adrenergic<br>receptors seem to be mediating respons rat portal vein, reduces it in rat aorta, but does not alter<br>it in rabbit aorta (fig. 4) (211), even though  $\alpha_1$ -adrenergic<br>receptors seem to be mediating responses in all three<br>tissues. In addition, contractile respons it in rabbit aorta (fig. 4) (211), even though  $\alpha_1$ -adrenergic<br>receptors seem to be mediating responses in all three<br>tissues. In addition, contractile responses to different<br>agonists in the same muscle can be differenti receptors seem to be mediating responses in all three<br>tissues. In addition, contractile responses to different<br>agonists in the same muscle can be differentially affected<br>by organic Ca<sup>2+</sup> entry blockers. In rat aorta, for tissues. In addition, contractile responses<br>agonists in the same muscle can be different<br>by organic Ca<sup>2+</sup> entry blockers. In rat aorta<br>contractile responses to the selective<br>receptor agonists  $2-(2\text{-}chlor-5\text{-}trimuorm$ <br>imino)im agonists in the same muscle can be differentially affect by organic  $Ca^{2+}$  entry blockers. In rat aorta, for exameter contractile responses to the selective  $\alpha_1$ -adren receptor agonists 2-(2-chlor-5-trifluormethyl-phe hydro-8-methoxy(5-methylthio)-2-napthalenamine HC1





aorta. Note the markedly different sensitivities of each tissue to inhibition by felodipine. From Ljung and Kjellstedt (211) with permission.

FIG. 4. Effect of the organic Ca<sup>2+</sup> entry blocker felodipine on contractile responts. Note the markedly different sensitivities of each tissue to inhibition by fel<br>(1-SK&F 89748-A) are profoundly reduced by 10  $\mu$ M spon is alternative distribution of the marked very little (16, 222).<br>In alternative very little (16, 222).<br>C. Pole of Peesnice Peesnice *CAER 89748-A)* are profor (1-SK&F 89748-A) are profor D600, while the contractile reserve is altered very little (16, 222).<br>*C. Role of Receptor Reserve*<br>Several different hypothese

is altered very little (16, 222).<br>
C. Role of Receptor Reserve<br>
Several different hypotheses have been advanced to<br>
explain the differential sensitivities of  $\alpha_1$ -adrenergic re-<br>
ceptor-mediated contractile responses to C. Role of Receptor Reserve<br>
Several different hypotheses have been advanced to<br>
explain the differential sensitivities of  $\alpha_1$ -adrenergic re-<br>
ceptor-mediated contractile responses to blockade by<br>
organic Ca<sup>2+</sup> entry C. *Role of Receptor Reserve*<br>Several different hypotheses have been advanced<br>explain the differential sensitivities of  $\alpha_1$ -adrenergic reptor-mediated contractile responses to blockade lorganic Ca<sup>2+</sup> entry blockers. I Several different hypotheses have been advanced to differential receptor-mediated contractile responses to blockade by distorganic Ca<sup>2+</sup> entry blockers. It was suggested that differential receptor reserves could influenc explain the differential sensitivities of  $\alpha_1$ -adrenergic<br>ceptor-mediated contractile responses to blockade<br>organic Ca<sup>2+</sup> entry blockers. It was suggested that differential receptor reserves could influence the degree<br> ceptor-mediated contractile responses to blockade by<br>organic  $Ca^{2+}$  entry blockers. It was suggested that differ-<br>ential receptor reserves could influence the degree to<br>which  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptor-mediat organic Ca<sup>2+</sup> entry blockers. It was suggested that differ-<br>ential receptor reserves could influence the degree to<br>which  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptor-mediated contrac-<br>tions could be blocked by these drugs (129 ential receptor reserves could influence the degree to<br>which  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptor-mediated contrac-<br>tions could be blocked by these drugs (129, 293). Many<br>of the agonists whose contractile responses were which  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptor-mediated contracture in the belocked by these drugs (129, 293). Many of the agonists whose contractile responses were blocked diffeormation of  $Ca^{2+}$  entry blockers had low in tions could be blocked by these drugs  $(129, 293)$ . Many<br>of the agonists whose contractile responses were blocked<br>by  $Ca^{2+}$  entry blockers had low intrinsic efficacies, while<br>those whose contractile responses were not bl % of the agonists whose contractile responses were blocked differently blockers had low intrinsic efficacies, while those whose contractile responses were not blocked had existendatively high intrinsic efficacies. Respons by  $Ca^{2+}$  entry blockers had low intrinsic efficacies, while<br>those whose contractile responses were not blocked had<br>relatively high intrinsic efficacies. Responses to agonists<br>with low intrinsic efficacies will always be those whose contractile responses were not blocked had<br>relatively high intrinsic efficacies. Responses to agonists<br>with low intrinsic efficacies will always be easier to<br>functionally antagonize than responses to agonists relatively high intrinsic efficacies. Responses to agonists<br>with low intrinsic efficacies will always be easier to<br>functionally antagonize than responses to agonists with<br>high intrinsic efficacies, and such a difference co with low intrinsic efficacies will always be easier<br>functionally antagonize than responses to agonists w<br>high intrinsic efficacies, and such a difference co<br>explain the differential susceptibility of responses<br>different ag functionally antagonize than responses to agonists wish intrinsic efficacies, and such a difference counting explain the differential susceptibility of responses different agonists in the same tissue. A similar explain tio high intrinsic efficacies, and such a difference could explain the differential susceptibility of responses to different agonists in the same tissue. A similar explanation could be invoked to explain the differential susce explain the differential susceptibility of responses to different agonists in the same tissue. A similar explanation could be invoked to explain the differential susceptibility of responses to the same agonist in different different agonists in the same tissue. A similar explanation could be invoked to explain the differential susceptibility of responses to the same agonist in different tissues, since the tissues could have different recepto (293). tibility of responses to the same agonist in different<br>tissues, since the tissues could have different receptor<br>reserves and therefore different "buffering" capacities<br>(293).<br>Further work in this area has led to the genera

tissues, since the tissues could have different receptor<br>reserves and therefore different "buffering" capacities<br>(293).<br>Further work in this area has led to the general con-<br>clusion that variations in receptor reserves exp reserves and therefore different "buffering" capacities (293).<br>
Further work in this area has led to the general conclusion that variations in receptor reserves explains<br>
some, but not all, of the differences in the susce (293). Further work in this area has led to the general conclusion that variations in receptor reserves explains some, but not all, of the differences in the susceptibility of  $\alpha_1$ -adrenergic receptor-mediated contracti Further work in this area has led to the general conclusion that variations in receptor reserves explains some, but not all, of the differences in the susceptibility of  $\alpha_1$ -adrenergic receptor-mediated contractions to clusion that variations in receptor reserves explains<br>some, but not all, of the differences in the susceptibility<br>of  $\alpha_1$ -adrenergic receptor-mediated contractions to inhi-<br>bition by organic Ca<sup>2+</sup> entry blockers (166, some, but not all, of the<br>of  $\alpha_1$ -adrenergic recepte<br>bition by organic  $Ca^{2+}$ <br>337, 343). Differences<br>reserves are eliminated<br> $D$ . Different Counling S bition by organic Ca<sup>2+</sup> entry blockers (166, 205, 260, 270, 337, 343). Differences remain even when the receptor reserves are eliminated.<br>*D. Different Coupling States or Receptor Subtypes* 7, 343). Differences remain even when the receptor<br>serves are eliminated.<br>Different Coupling States or Receptor Subtypes<br>Another explanation which has been suggested is that<br>ere may be distinct coupling states of the  $\alpha_$ 

there may be diminated.<br>
D. Different Coupling States or Receptor Subtypes<br>
Another explanation which has been suggested is that<br>
there may be distinct coupling states of the  $\alpha_1$ -adrenergic<br>
receptor, and the receptor D. Different Coupling States or Receptor Subtypes<br>Another explanation which has been suggested is that<br>there may be distinct coupling states of the  $\alpha_1$ -adrenergic<br>receptor, and the receptor would activate different sig D. Different Coupling States or Receptor Subtypes in<br>
Another explanation which has been suggested is that<br>
there may be distinct coupling states of the  $\alpha_1$ -adrenergic<br>
receptor, and the receptor would activate differe Another explanation which has been suggested is that<br>there may be distinct coupling states of the  $\alpha_1$ -adrenergic<br>receptor, and the receptor would activate different signal<br>transduction mechanisms depending on the local there may be distinct coupling states of the  $\alpha_1$ -adrenergic<br>receptor, and the receptor would activate different signal<br>transduction mechanisms depending on the local tissue<br>environment (230, 265). O'Brien et al. (265) receptor, and the receptor would activate different signal<br>transduction mechanisms depending on the local tissue<br>environment (230, 265). O'Brien et al. (265) examined<br>the effects of manipulating arterial blood gases and in

D600, while the contractile response to norepinephrine They concluded that, although these factors altered re-<br>is altered very little (16, 222).<br>C. Role of Receptor Reserve reserve The possibility that a single receptor s Le responses to norepinephrine in rat portal vein, rat aorta, and rabbit<br>1 by felodipine. From Ljung and Kjellstedt (211) with permission.<br>1 sponses to  $\alpha$ -adrenergic receptor agonists in pithed rats.<br>They concluded that They concluded that, although these factors altered re-<br>sponses to  $\alpha$ -adrenergic receptor agonists in pithed rats.<br>They concluded that, although these factors altered re-<br>sponsiveness to many agonists, they had no predi sponses to  $\alpha$ -adrenergic receptor agonists in pithed rats.<br>They concluded that, although these factors altered re-<br>sponsiveness to many agonists, they had no predictable<br>relationship to the apparent receptor subtype invo sponses to  $\alpha$ -adrenergic receptor agonists in pithed rats.<br>They concluded that, although these factors altered re-<br>sponsiveness to many agonists, they had no predictable<br>relationship to the apparent receptor subtype inv sponses to  $\alpha$ -adrenergic receptor agonists in pithed rats.<br>They concluded that, although these factors altered responsiveness to many agonists, they had no predictable<br>relationship to the apparent receptor subtype invol They concluded that, although these factors altered re-<br>sponsiveness to many agonists, they had no predictable<br>relationship to the apparent receptor subtype involved.<br>The possibility that a single receptor subtype initiate  $\frac{1}{2}$  sponsiveness to many agonists, they had no predictable relationship to the apparent receptor subtype involved.<br>The possibility that a single receptor subtype initiates different signal transduction mechanisms de relationship to the apparent receptor subtype involved.<br>The possibility that a single receptor subtype initiates<br>different signal transduction mechanisms depending on<br>the local tissue environment will obviously be difficul The possibility that a single receptor subtype initiates<br>different signal transduction mechanisms depending on<br>the local tissue environment will obviously be difficult to<br>distinguish from the existence of two similar but s the local tissue environment will obviously be difficult to distinguish from the existence of two similar but slightly different receptors whose relative contributions to the response are dependent on the tissue environmen below).

The simplest explanation which would account for the different receptors whose relative contributions to the response are dependent on the tissue environment (see below).<br>The simplest explanation which would account for the differential importance of  $Ca^{2+}$  influx in  $\alpha_1$ response are dependent on the tissue environment (see<br>below).<br>The simplest explanation which would account for the<br>differential importance of  $Ca^{2+}$  influx in  $\alpha_1$ -adrenergic<br>receptor-mediated contractile responses wou below).<br>
The simplest explanation which would account for the<br>
differential importance of  $Ca^{2+}$  influx in  $\alpha_1$ -adrenergic<br>
receptor-mediated contractile responses would be the<br>
existence of two distinct receptor subty The simplest explanation which would account for the differential importance of  $Ca^{2+}$  influx in  $\alpha_1$ -adrenergic receptor-mediated contractile responses would be the existence of two distinct receptor subtypes linked t receptor-mediated contractile responses would be the existence of two distinct receptor subtypes linked to different signal transduction mechanisms. Some evidence for this was obtained shortly after the phenomenon was firs receptor-mediated contractile responses would be the existence of two distinct receptor subtypes linked to different signal transduction mechanisms. Some evidence for this was obtained shortly after the phenomenon was fir existence of two distinct receptor subtypes link<br>different signal transduction mechanisms. Some<br>dence for this was obtained shortly after the phenom<br>was first identified. McGrath (228) showed that the<br>of potencies of agoni of potencies of agonists in activating  $Ca^{2+}$  influx-dependent contractions of rat anococcygeus muscle was different from their order of potencies in activating responses dence for this was obtained shortly after the phenomenon<br>was first identified. McGrath (228) showed that the order<br>of potencies of agonists in activating  $Ca^{2+}$  influx-depend-<br>ent contractions of rat anococcygeus muscle was first identified. McGrath (228) showed that the order<br>of potencies of agonists in activating  $Ca^{2+}$  influx-depend-<br>ent contractions of rat anococcygeus muscle was differ-<br>ent from their order of potencies in activati of potencies of agonists in activating  $Ca^{2+}$  influx-depend-<br>ent contractions of rat anococcygeus muscle was differ-<br>ent from their order of potencies in activating responses<br>independently of  $Ca^{2+}$  influx. Based on dif ent contractions of rat anococcygeus muscle was different from their order of potencies in activating responses independently of  $Ca^{2+}$  influx. Based on differences in the importance of  $Ca^{2+}$  influx in contractile resp ent from their order of potencies in activating responses<br>independently of  $Ca^{2+}$  influx. Based on differences in the<br>importance of  $Ca^{2+}$  influx in contractile responses to<br>methoxamine and clonidine in rabbit aorta, Ho importance of  $Ca^{2+}$  influx in contractile responses to methoxamine and clonidine in rabbit aorta, Holck et al. (147) proposed that there might be different recognition sites for  $\alpha_1$ -adrenergic receptor agonists, "wit importance of  $Ca^{2+}$  influx in contractile response<br>methoxamine and clonidine in rabbit aorta, Holck e<br>(147) proposed that there might be different recognis<br>sites for  $\alpha_1$ -adrenergic receptor agonists, "with selec<br>stim methoxamine and clonidine in rabbit aorta, Holck et al.<br>(147) proposed that there might be different recognition<br>sites for  $\alpha_1$ -adrenergic receptor agonists, "with selective<br>stimulation of the imidazoline site leading t (147) proposed that there might be different recognition<br>sites for  $\alpha_1$ -adrenergic receptor agonists, "with selective<br>stimulation of the imidazoline site leading to transmem-<br>brane influx of extracellular Ca<sup>2+</sup>." The e sites for  $\alpha_1$ -adrenergic receptor agonists, "with selective<br>stimulation of the imidazoline site leading to transmem-<br>brane influx of extracellular Ca<sup>2+</sup>." The existence of two<br>different subtypes of  $\alpha_1$ -adrenergic r stimulation of the imidazoline site leading to transmem-<br>brane influx of extracellular Ca<sup>2+</sup>." The existence of two<br>different subtypes of  $\alpha_1$ -adrenergic receptors linked to<br>Ca<sup>2+</sup> influx-dependent and -independent con brane influx of extracellular  $Ca^{2+}$ ." The existence of two<br>different subtypes of  $\alpha_1$ -adrenergic receptors linked to<br> $Ca^{2+}$  influx-dependent and -independent contractile re-<br>sponses was not supported by other studies different subtypes of  $\alpha_1$ -adrenergic receptors linked Ca<sup>2+</sup> influx-dependent and -independent contractile is sponses was not supported by other studies. Korstant et al. (191) and Beckeringh et al. (16) showed that sev sponses was not supported by other studies. Korstanje<br>et al. (191) and Beckeringh et al. (16) showed that several<br>competitive antagonists had similar potencies in block-<br>ing both  $Ca^{2+}$  influx-dependent and -independent sponses was not supported by other studies. Korstanje<br>et al. (191) and Beckeringh et al. (16) showed that several<br>competitive antagonists had similar potencies in block-<br>ing both Ca<sup>2+</sup> influx-dependent and -independent r et al. (191) and Beckeringh et al. (16) showed that several<br>competitive antagonists had similar potencies in block-<br>ing both Ca<sup>2+</sup> influx-dependent and -independent re-<br>sponses to  $\alpha_1$ -adrenergic receptor agonists. On competitive antagonists had similar potencies in blocking both  $Ca^{2+}$  influx-dependent and -independent responses to  $\alpha_1$ -adrenergic receptor agonists. On the other hand, it is always difficult to disprove the existenc ing both  $Ca^{2+}$  influx-dependent and -independent responses to  $\alpha_1$ -adrenergic receptor agonists. On the other hand, it is always difficult to disprove the existence of pharmacologically distinct receptor subtypes, sin sponses to  $\alpha_1$ -adrenergic receptor agonists. On the other hand, it is always difficult to disprove the existence of pharmacologically distinct receptor subtypes, since other drugs not yet tested or newly discovered mig hand, it is always difficult to disprove the existence of pharmacologically distinct receptor subtypes, since other drugs not yet tested or newly discovered might better distinguish between closely related receptor subtyp pharmacologically distinct receptor subtypes, since other<br>drugs not yet tested or newly discovered might better<br>distinguish between closely related receptor subtypes. In<br>the past few years, much evidence has accumulated t

**a**spet

 $\alpha_1$ -ADRENERGIC RECE<br>mogeneous, and that at least two distinct receptor types<br>can be identified with appropriate antagonists. Han et  $\alpha_1$ -ADRENERGIC RECI<br>mogeneous, and that at least two distinct receptor types<br>can be identified with appropriate antagonists. Han et<br>al. (130, 131) have recently presented evidence that two  $\alpha_1$ -ADRENERGIC RECEPT<br>mogeneous, and that at least two distinct receptor types<br>can be identified with appropriate antagonists. Han et rece<br>al. (130, 131) have recently presented evidence that two flux<br>distinct  $\alpha_1$ -a mogeneous, and that at least two distinct receptor types<br>can be identified with appropriate antagonists. Han et<br>al. (130, 131) have recently presented evidence that two<br>distinct  $\alpha_1$ -adrenergic receptor subtypes activat mogeneous, and that at least two distinct receptor types<br>can be identified with appropriate antagonists. Han et<br>al. (130, 131) have recently presented evidence that two<br>distinct  $\alpha_1$ -adrenergic receptor subtypes activat distinct  $\alpha_1$ -adrenergic receptor subtypes activate rebefined a<sub>1</sub>-addeneight receptor sabtypes addition in the differentially sen-<br>ive to inhibition by organic Ca<sup>2+</sup> entry blockers. This<br>idence is discussed below.<br>IX. Direct Measurement of Ca<sup>2+</sup> Mobilization<br>and Fluxes asce which are<br>organic Ca<sup>2+</sup> e<br>rement of Ca<br>and Fluxes<br>thes have been

idence is discussed below.  $\begin{array}{cc}\n\textbf{IX. Direct Measurement of Ca}^{2+} \text{ Mobilization} & \text{ph} \\
\textbf{and Fluxes} & & \\
\text{Two major approaches have been utilized to obtain} & & \\
\text{or direct information on receptor-mediated altera} & & \\
\end{array}$ IX. Direct Measurement of Ca<sup>2+</sup> Mobilization<br>and Fluxes<br>Two major approaches have been utilized to obta<br>more direct information on receptor-mediated alter<br>tions in cellular Ca<sup>2+</sup> concentrations. Measuring the IX. Direct Measurement or Ca<sup>--</sup> Mobilization<br>and Fluxes<br>Two major approaches have been utilized to obtain<br>more direct information on receptor-mediated altera-<br>tions in cellular Ca<sup>2+</sup> concentrations. Measuring the ac-<br>cu **curves**<br>
Two major approaches have been utilized to obtain<br>
more direct information on receptor-mediated altera-<br>
tions in cellular Ca<sup>2+</sup> concentrations. Measuring the ac-<br>
cumulation, loss, or unidirectional flux of <sup>4</sup> Two major approaches have been utilized to obtain<br>more direct information on receptor-mediated altera-<br>tions in cellular  $Ca^{2+}$  concentrations. Measuring the ac-<br>cumulation, loss, or unidirectional flux of <sup>45</sup>Ca in an<br>i more direct information on receptor-mediated alterations in cellular  $Ca^{2+}$  concentrations. Measuring the ac-<br>cumulation, loss, or unidirectional flux of <sup>45</sup>Ca in an<br>intact tissue can give information on changes in  $Ca^{2$ tions in cellular  $Ca^{2+}$  concentrations. Measuring the accumulation, loss, or unidirectional flux of  $45Ca$  in an intact tissue can give information on changes in  $Ca^{2+}$  handling in response to acute perturbations such a cumulation, loss, or unidirectional flux of  ${}^{45}Ca$  in an intact tissue can give information on changes in  $Ca^{2+}$  tor to the handling in response to acute perturbations such as  $Ca^{2+}$  receptor activation. Conversely, f intact tissue can give information on changes in  $Ca^{2+}$  tool<br>handling in response to acute perturbations such as<br>receptor activation. Conversely, fluorescent dyes and ion-<br>selective electrodes have been employed in attem cells.

measure directly the intracellular concentration of free<br>ionized  $Ca^{2+}$  in intact tissues or in dispersed or cultured<br>cells.<br>Many studies of <sup>45</sup>Ca fluxes have been performed in<br>various smooth muscles. In general, both d ionized Ca<sup>2+</sup> in intact tissues or in dispersed or cultured age<br>cells.<br>Many studies of <sup>45</sup>Ca fluxes have been performed in<br>various smooth muscles. In general, both depolarization<br>and  $\alpha_1$ -adrenergic receptor activatio cells.<br>
Many studies of <sup>45</sup>Ca fluxes have been performed in<br>
various smooth muscles. In general, both depolarization<br>
and  $\alpha_1$ -adrenergic receptor activation have been found<br>
to stimulate influx of Ca<sup>2+</sup> from the extr Many studies of <sup>45</sup>Ca fluxes have been performed in various smooth muscles. In general, both depolarization and  $\alpha_1$ -adrenergic receptor activation have been found to stimulate influx of Ca<sup>2+</sup> from the extracellular f various smooth muscles. In general, both depolarization<br>and  $\alpha_1$ -adrenergic receptor activation have been found<br>to stimulate influx of Ca<sup>2+</sup> from the extracellular fluid,<br>but that only  $\alpha_1$ -adrenergic receptor activa and  $\alpha_1$ -adrenergic receptor activation have been found<br>to stimulate influx of Ca<sup>2+</sup> from the extracellular fluid,<br>but that only  $\alpha_1$ -adrenergic receptor activation also re-<br>leases intracellularly bound Ca<sup>2+</sup> (10, 5 to stimulate influx of  $Ca^{2+}$  from the extracellular fluid,<br>but that only  $\alpha_1$ -adrenergic receptor activation also re-<br>leases intracellularly bound  $Ca^{2+}$  (10, 53, 55, 117, 350,<br>352). It seems likely, however, that th but that only  $\alpha_1$ -adrenergic receptor activation also re-<br>leases intracellularly bound  $Ca^{2+}$  (10, 53, 55, 117, 350,<br>352). It seems likely, however, that the mechanisms by<br>which receptor activation and depolarization leases intracellularly bound  $Ca^{2+}$  (10, 53, 55, 117, 350,<br>352). It seems likely, however, that the mechanisms by<br>which receptor activation and depolarization promote<br> $Ca^{2+}$  influx are different. Meisheri et al. (233) m which receptor activation and depolarization promote  $Ca^{2+}$  influx are different. Meisheri et al. (233) measured net and unidirectional  $Ca^{2+}$  flux and compared them to contractile responses in rabbit aorta to determine which receptor activation and depolarization promote<br>Ca<sup>2+</sup> influx are different. Meisheri et al. (233) measured<br>net and unidirectional Ca<sup>2+</sup> flux and compared them to<br>contractile responses in rabbit aorta to determine<br>w Ca<sup>2+</sup> influx are different. Meisheri et al. (233) measured<br>net and unidirectional Ca<sup>2+</sup> flux and compared them to<br>contractile responses in rabbit aorta to determine<br>whether these two stimuli caused influx via the same o net and unidirectional Ca<sup>2+</sup> flux and compared them to<br>contractile responses in rabbit aorta to determine<br>whether these two stimuli caused influx via the same or<br>different mechanisms. The use of selective inhibitors and<br> contractile responses in rabbit aorta to detern<br>whether these two stimuli caused influx via the same<br>different mechanisms. The use of selective inhibitors<br>studies of the additivity of the responses to the<br>stimuli showed t studies of the additivity of the responses to the two adies of the additivity of the responses to the two muli showed that receptor activation and depolarize in probably activate separate pathways for  $Ca^{2+}$  influmis tissue (233). Caffeine is known to release  $Ca^{2+}$  from t stimuli showed that receptor activation and depolarization probably activate separate pathways for  $Ca^{2+}$  influx in this tissue (233).<br>Caffeine is known to release  $Ca^{2+}$  from the sarco-plasmic reticulum in cardiac and

tion probably activate separate pathways for  $Ca^{2+}$  influx<br>in this tissue (233).<br>Caffeine is known to release  $Ca^{2+}$  from the sarco-<br>plasmic reticulum in cardiac and skeletal muscle (101),<br>and it appears to have similar in this tissue (233).<br>
Caffeine is known to release  $Ca^{2+}$  from the sarco-<br>
plasmic reticulum in cardiac and skeletal muscle (101),<br>
and it appears to have similar effects in smooth muscle.<br>
Although the mechanism of act Caffeine is known to release  $Ca^{2+}$  from the samples plasmic reticulum in cardiac and skeletal muscle (1 and it appears to have similar effects in smooth must Although the mechanism of action is still unknown appears to plasmic reticulum in cardiac and skeletal muscle (101),<br>and it appears to have similar effects in smooth muscle.<br>Although the mechanism of action is still unknown, it<br>appears to be independent of actions on either phospho and it appears to have similar effects in smooth muscle.<br>Although the mechanism of action is still unknown, it<br>appears to be independent of actions on either phospho-<br>lipase C or cyclic nucleotide phosphodiesterase. In ma Although the mechanism of action is still unknown, it<br>appears to be independent of actions on either phospho-<br>lipase C or cyclic nucleotide phosphodiesterase. In many<br>tissues, caffeine and  $\alpha_1$ -adrenergic receptor activ appears to be independent of actions on either phospho-<br>lipase C or cyclic nucleotide phosphodiesterase. In many<br>tissues, caffeine and  $\alpha_1$ -adrenergic receptor activation<br>appear to release  $Ca^{2+}$  from the same intracel lipase C or cyclic nucleotide phosphodiesterase. In many<br>tissues, caffeine and  $\alpha_1$ -adrenergic receptor activation mu<br>appear to release  $Ca^{2+}$  from the same intracellular storage nis<br>pool, although some differences are tissues, caffeine and  $\alpha_1$ -adrenergic receptor activation m<br>appear to release Ca<sup>2+</sup> from the same intracellular storage ni<br>pool, although some differences are observed (83, 84, 126, di<br>159, 204). This limited pool of i appear to release Ca<sup>2+</sup> from the same intracellular storage nool, although some differences are observed (83, 84, 126, d<br>159, 204). This limited pool of intracellular Ca<sup>2+</sup> can be nepleted by caffeine or agonist exposur pool, although some differences are observed (83, 84, 126, 159, 204). This limited pool of intracellular  $Ca^{2+}$  can be depleted by caffeine or agonist exposure, but is rapidly refilled when extracellular  $Ca^{2+}$  is prese 159, 204). This limited pool of intracellular  $Ca^{2+}$  can be recept depleted by caffeine or agonist exposure, but is rapidly The refilled when extracellular  $Ca^{2+}$  is present (52, 176). This vatio has led to the suggesti depleted by caffeine or agonist exposure, but is rapidly<br>refilled when extracellular  $Ca^{2+}$  is present (52, 176). This<br>has led to the suggestion that there might be a physical in<br>coupling between the peripheral sarcoplas has led to the suggestion that there might be a physical coupling between the peripheral sarcoplasmic reticulum and the surface membrane (52) (see also ref. 279). If refilling is blocked (by lanthanum), the releasable pool has led to the suggestion that there might be a physic<br>coupling between the peripheral sarcoplasmic reticulu<br>and the surface membrane (52) (see also ref. 279).<br>refilling is blocked (by lanthanum), the releasable po<br>is rapi coupling between the peripheral sarcoplasmic reticulum<br>and the surface membrane  $(52)$  (see also ref. 279). If<br>refilling is blocked (by lanthanum), the releasable pool<br>is rapidly depleted by either caffeine or receptor st bilization of  $Ca^{2+}$  (352).

al. (130, 131) have recently presented evidence that two flux, and phosphatidylinositol metabolism in smooth distinct  $\alpha_1$ -adrenergic receptor subtypes activate re-<br>sponses in smooth muscle which are differentially senc intact tissue can give information on changes in Ca<sup>2+</sup> tor agonists to increase Ca<sup>2+</sup> uptake and release internal<br>handling in response to acute perturbations such as<br>receptor activation. Conversely, fluorescent dyes and Many studies of  $^{45}$ Ca fluxes have been performed in<br>various smooth muscles. In general, both depolarization<br>of agonists in causing release of intracellular  $Ca^{2+}$  and whether these two stimuli caused influx via the same or<br>different mechanisms. The use of selective inhibitors and<br>studies of the additivity of the responses to the two<br>stimuli showed that receptor activation and depolariz Several studies have attempted to relate  $\alpha_1$ -adrenergic<br>receptor-mediated release of intracellular Ca<sup>2+</sup>, Ca<sup>2+</sup> in-EPTOR SUBTYPES 99<br>Several studies have attempted to relate  $\alpha_1$ -adrenergic<br>receptor-mediated release of intracellular Ca<sup>2+</sup>, Ca<sup>2+</sup> in-<br>flux, and phosphatidylinositol metabolism in smooth EPTOR SUBTYPES 99<br>
Several studies have attempted to relate  $\alpha_1$ -adrenergic<br>
receptor-mediated release of intracellular Ca<sup>2+</sup>, Ca<sup>2+</sup> in-<br>
flux, and phosphatidylinositol metabolism in smooth<br>
muscle. Campbell et al. (5 Several studies have attempted to relate  $\alpha_1$ -adrenergic<br>receptor-mediated release of intracellular Ca<sup>2+</sup>, Ca<sup>2+</sup> in-<br>flux, and phosphatidylinositol metabolism in smooth<br>muscle. Campbell et al. (51) showed that the bip Several studies have attempted to relate  $\alpha_1$ -adrenergic<br>receptor-mediated release of intracellular Ca<sup>2+</sup>, Ca<sup>2+</sup> in-<br>flux, and phosphatidylinositol metabolism in smooth<br>muscle. Campbell et al. (51) showed that the bip receptor-mediated release of intracellular  $Ca^{2+}$ ,  $Ca^{2+}$  in-<br>flux, and phosphatidylinositol metabolism in smooth<br>muscle. Campbell et al. (51) showed that the biphasic<br>contraction of rabbit aorta caused by  $\alpha_1$ -adrene flux, and phosphatidylinositol metabolism in smooth<br>muscle. Campbell et al. (51) showed that the biphasic<br>contraction of rabbit aorta caused by  $\alpha_1$ -adrenergic re-<br>ceptor stimulation was associated with a rapid hydrolys muscle. Campbell et al. (51) showed that the biphasic contraction of rabbit aorta caused by  $\alpha_1$ -adrenergic receptor stimulation was associated with a rapid hydrolysis of  $\text{PIP}_2$  and a slower increase in <sup>32</sup>P incorpo contraction of rabbit aorta caused by  $\alpha_1$ -adrenergic receptor stimulation was associated with a rapid hydrolysis<br>of PIP<sub>2</sub> and a slower increase in <sup>32</sup>P incorporation into<br>phosphatidic acid. These authors proposed tha ceptor stimulation was associated with a rapid hydrolysis<br>of PIP<sub>2</sub> and a slower increase in <sup>32</sup>P incorporation into<br>phosphatidic acid. These authors proposed that the rapid<br>phasic response, mediated by release of intrac phosphatidic acid. These authors proposed that the rapid<br>phasic response, mediated by release of intracellular  $Ca^{2+}$ <br>(32), was caused by formation of  $Ins(1,4,5)P_3$ , while the<br>sustained influx of  $Ca^{2+}$  resulting in to phosphatidic acid. These authors proposed that the rapid<br>phasic response, mediated by release of intracellular  $Ca^{2+}$ <br>(32), was caused by formation of  $Ins(1,4,5)P_3$ , while the<br>sustained influx of  $Ca^{2+}$  resulting in ton phasic response, mediated by release of intracellular Ca<sup>2+</sup><br>(32), was caused by formation of  $\text{Ins}(1,4,5)P_3$ , while the<br>sustained influx of Ca<sup>2+</sup> resulting in tonic contractions<br>was due to increases in phosphatidic aci sustained influx of Ca<sup>2+</sup> resulting in tonic contractions<br>was due to increases in phosphatidic acid, although this<br>hypothesis has fallen into disfavor. Jim et al. (164)<br>compared the abilities of a series of  $\alpha_1$ -adrene hypothesis has fallen into disfavor. Jim et al. (164) was due to increases in phosphatidic acid, although this<br>hypothesis has fallen into disfavor. Jim et al. (164)<br>compared the abilities of a series of  $\alpha_1$ -adrenergic recep-<br>tor agonists to increase  $Ca^{2+}$  uptake and rel compared the abilities of a series of  $\alpha_1$ -adrenergic receptor agonists to increase  $Ca^{2+}$  uptake and release internal  $Ca^{2+}$  in canine saphenous vein. They found that  $\alpha_1$ -adrenergic receptor activation utilizes bo tor agonists to increase  $Ca^{2+}$  uptake and release internal  $Ca^{2+}$  in canine saphenous vein. They found that  $\alpha_1$ -<br>adrenergic receptor activation utilizes both intracellular<br>and extracellular  $Ca^{2+}$  for contractions Ca<sup>2+</sup> in canine saphenous vein. They found that  $\alpha$ <br>adrenergic receptor activation utilizes both intracellula<br>and extracellular Ca<sup>2+</sup> for contractions in this tissue, an<br>that the increase in Ca<sup>2+</sup> influx caused by dif adrenergic receptor activation utilizes both intracellula<br>and extracellular  $Ca^{2+}$  for contractions in this tissue, an<br>that the increase in  $Ca^{2+}$  influx caused by differer<br>agonists was directly proportional to the intr that the increase in  $Ca^{2+}$  influx caused by different that the increase in  $Ca^{2+}$  influx caused by different agonists was directly proportional to the intrinsic activities of the agonists in causing contractions (164). However, no correlation was observed between the effica agonists was directly proportional to the intrinsic activ-<br>ities of the agonists in causing contractions (164). How-<br>ever, no correlation was observed between the efficacies<br>of agonists in causing release of intracellular ities of the agonists in causing contractions (164). How-<br>ever, no correlation was observed between the efficacies<br>of agonists in causing release of intracellular  $Ca^{2+}$  and<br>contraction of saphenous vein (165). This rais ever, no correlation was observed between the efficacie<br>of agonists in causing release of intracellular  $Ca^{2+}$  and<br>contraction of saphenous vein (165). This raises the<br>possibility that release of intracellular  $Ca^{2+}$  is of agonists in causing release of intracellular  $Ca^{2+}$  and<br>contraction of saphenous vein (165). This raises the<br>possibility that release of intracellular  $Ca^{2+}$  is not the<br>sole mechanism initiating responses in this tis possibility that release of intracellular Ca<sup>2+</sup> is not the sole mechanism initiating responses in this tissue. Conversely, Chiu et al. (61) reported that activation of  $\alpha_1$ -adrenergic receptors in rat aorta caused both sole mechanism initiating responses in this tissue. Conversely, Chiu et al. (61) reported that activation of  $\alpha_1$ -<br>adrenergic receptors in rat aorta caused both release of<br>intracellular Ca<sup>2+</sup> and influx of extracellula versely, Chiu et al. (61) reported that activation of  $\alpha_1$ -<br>adrenergic receptors in rat aorta caused both release of<br>intracellular Ca<sup>2+</sup> and influx of extracellular Ca<sup>2+</sup>. Dif-<br>ferent agonists had different efficacies adrenergic receptors in rat aorta caused both release of intracellular  $Ca^{2+}$  and influx of extracellular  $Ca^{2+}$ . Different agonists had different efficacies in stimulating these two different responses. However, the ef intracellular Ca<sup>2+</sup> and influx of extracellular Ca<sup>2+</sup>. Different agonists had different efficacies in stimulating these two different responses. However, the efficacies of the agonists in causing contraction appeared to ferent agonists had different efficacies in stimulating<br>these two different responses. However, the efficacies of<br>the agonists in causing contraction appeared to depend<br>more heavily on their ability to release intracellul these two different responses. However, the efficacies of<br>the agonists in causing contraction appeared to depend<br>more heavily on their ability to release intracellular Ca<sup>2+</sup><br>(61). However, agonists which rely almost excl the agonists in causing contraction appeared to depend<br>more heavily on their ability to release intracellular Ca<sup>2+</sup><br>(61). However, agonists which rely almost exclusively on<br>Ca<sup>2+</sup> influx to cause contraction in rat aorta more heavily on their ability to release intracellular Ca<sup>2+</sup> (61). However, agonists which rely almost exclusively on Ca<sup>2+</sup> influx to cause contraction in rat aorta (Sgd 101/75) did not cause release of intracellular Ca (61). However, agonists which rely almost exclusively on  $Ca^{2+}$  influx to cause contraction in rat aorta (Sgd 101/75) did not cause release of intracellular  $Ca^{2+}$  or increase inositol phospholipid turnover (60). These Ca<sup>2+</sup> influx to cause contraction in rat aorta (Sgd 101/75) did not cause release of intracellular  $Ca^{2+}$  or increase inositol phospholipid turnover (60). These data suggest, therefore, that the influx of extracellular ositol phospholipid turnover (60). These data suggest,<br>erefore, that the influx of extracellular  $Ca^{2+}$  is not<br>bsequent to inositol phospholipid turnover in this tis-<br>e (60).<br>These studies again raise the possibility tha

therefore, that the influx of extracellular Ca<sup>2+</sup> is not<br>subsequent to inositol phospholipid turnover in this tis-<br>sue (60).<br>These studies again raise the possibility that release<br>of intracellular Ca<sup>2+</sup> and influx of ex subsequent to inositol phospholipid turnover in this tis-<br>sue (60).<br>These studies again raise the possibility that release<br>of intracellular Ca<sup>2+</sup> and influx of extracellular Ca<sup>2+</sup> in<br>response to  $\alpha_1$ -adrenergic recept sue (60).<br>These studies again raise the possibility that releated of intracellular Ca<sup>2+</sup> and influx of extracellular Ca<sup>2+</sup> response to  $\alpha_1$ -adrenergic receptor activation in smod muscle may be due to two different mol These studies again raise the possibility that release<br>of intracellular Ca<sup>2+</sup> and influx of extracellular Ca<sup>2+</sup> in<br>response to  $\alpha_1$ -adrenergic receptor activation in smooth<br>muscle may be due to two different molecular of intracellular Ca<sup>2+</sup> and influx of extracellular Ca<sup>2+</sup> in response to  $\alpha_1$ -adrenergic receptor activation in smooth muscle may be due to two different molecular mechanisms. The differences in agonist efficacies for response to  $\alpha_1$ -adrenergic receptor activatio<br>muscle may be due to two different molec<br>nisms. The differences in agonist efficacies f<br>different effects support the possibility that<br>receptor subtypes are involved (see b uscle may be due to two different molecular mechasms. The differences in agonist efficacies for these two fferent effects support the possibility that two distinct ceptor subtypes are involved (see below). The relationshi

nisms. The differences in agonist efficacies for these two<br>different effects support the possibility that two distinct<br>receptor subtypes are involved (see below).<br>The relationship between  $\alpha_1$ -adrenergic receptor acti-<br> receptor subtypes are involved (see below).<br>The relationship between  $\alpha_1$ -adrenergic receptor activation and increases in cytosolic Ca<sup>2+</sup> has been examined<br>in a number of isolated cell preparations using fluores-<br>cent receptor subtypes are involved (see below).<br>
The relationship between  $\alpha_1$ -adrenergic reception and increases in cytosolic Ca<sup>2+</sup> has been<br>
in a number of isolated cell preparations usin<br>
cent indicators such as 2-{[bis methyl)aminoquinoline-tetrakis(acetoxymethyl)ester in a number of isolated cell preparation<br>cent indicators such as 2-{{bis(carbox<br>5-methylphenoxy]methyl}-6'-methoxy<br>methyl)aminoquinoline-tetrakis(aceto-<br>(quin-2) or 1-[2-(5-carboxyoxazol-2-yl)<br>furan-5-oxy]-2-(2'-amino-5'-m '-amino-5'-methylpheno: 5-methylphenoxy]methyl}-6'-methoxy-8-bis(carboxy-<br>methyl)aminoquinoline-tetrakis(acetoxymethyl)ester<br>(quin-2) or 1-[2-(5-carboxyoxazol-2-yl)-6-aminobenzo-<br>furan-5-oxy]-2-(2'-amino-5'-methylphenoxy)ethane-<br>N,N,N',N'-tetraac

cytes, there appears to be a quantitative relationship adrenergic receptors coexist with  $\alpha_1$ -adrenergic receptors<br>between receptor-mediated formation of  $\text{Ins}(1,4,5)P_3$  and in smooth muscle and also cause contractile 100 MINNEMA<br>cytes, there appears to be a quantitative relationship adr<br>between receptor-mediated formation of Ins(1,4,5)P<sub>3</sub> and in in<br>mobilization of intracellular  $Ca^{2+}$  (174, 214). However, who 100<br>cytes, there appears to be a quantitative relationship<br>between receptor-mediated formation of  $\text{Ins}(1,4,5)P_3$  and<br>mobilization of intracellular  $\text{Ca}^{2+}$  (174, 214). However,<br> $\alpha_1$ -adrenergic receptor activation a cytes, there appears to be a quantitative relationship<br>between receptor-mediated formation of  $\text{Ins}(1,4,5)P_3$  and<br>mobilization of intracellular  $\text{Ca}^{2+}$  (174, 214). However,<br> $\alpha_1$ -adrenergic receptor activation also cytes, there appears to be a quantitative relationship<br>between receptor-mediated formation of  $\text{Ins}(1,4,5)P_3$  and<br>mobilization of intracellular  $\text{Ca}^{2+}$  (174, 214). However,<br> $\alpha_1$ -adrenergic receptor activation also between receptor-mediated formation of  $\text{Ins}(1,4,5)P_3$  and<br>mobilization of intracellular  $\text{Ca}^{2+}$  (174, 214). However,<br> $\alpha_1$ -adrenergic receptor activation also promotes  $\text{Ca}^{2+}$  in-<br>flux in liver (30, 288), and s mobilization of intracellular Ca<sup>2+</sup> (174, 214). However, w<br>  $\alpha_1$ -adrenergic receptor activation also promotes Ca<sup>2+</sup> in-<br>
flux in liver (30, 288), and some metabolic responses la<br>
seem to be dependent on this influx (2  $\alpha_1$ -adrenergic receptor activation also promotes Ca<sup>2+</sup> in-<br>flux in liver (30, 288), and some metabolic responses<br>seem to be dependent on this influx (288). Transient<br>responses to  $\alpha_1$ -adrenergic receptor activation, flux in liver (30, 288), and some metabolic responses to  $\alpha_1$ -adrenergic receptor activation, includion fluxes and changes in oxidation-reduction rates appeared to be obligatorily dependent on the mobilition of intracel seem to be dependent on this influx (288). Transie:<br>responses to  $\alpha_1$ -adrenergic receptor activation, includii<br>ion fluxes and changes in oxidation-reduction ratio<br>appeared to be obligatorily dependent on the mobiliz<br>tio responses to  $\alpha_1$ -adrenergic receptor activation, including with<br>ion fluxes and changes in oxidation-reduction ratios, nerg<br>appeared to be obligatorily dependent on the mobiliza-<br>tion of intracellular  $Ca^{2+}$  and were i ion fluxes and changes in oxidation-reduction rat<br>appeared to be obligatorily dependent on the mobili<br>tion of intracellular  $Ca^{2+}$  and were independent of ext<br>cellular  $Ca^{2+}$ . However, sustained responses appeared<br>requi tion of intracellular Ca<sup>2+</sup> and were independent of extra-<br>cellular Ca<sup>2+</sup>. However, sustained responses appeared to<br>require Ca<sup>2+</sup> influx (287). Recently, data from measure-<br>ment of cytosolic Ca<sup>2+</sup> in single hepatocyte tion of intracellular Ca<sup>2+</sup> and were independent of extra-<br>cellular Ca<sup>2+</sup>. However, sustained responses appeared to<br>require Ca<sup>2+</sup> influx (287). Recently, data from measure-<br>ment of cytosolic Ca<sup>2+</sup> in single hepatocyte cellular Ca<sup>2+</sup>. However, sustained responses appeared to require Ca<sup>2+</sup> influx (287). Recently, data from measurement of cytosolic Ca<sup>2+</sup> in single hepatocytes have suggested that  $\alpha_1$ -adrenergic receptor activation ma require Ca<sup>2+</sup> influx (287). Recently, data from measure-<br>ment of cytosolic Ca<sup>2+</sup> in single hepatocytes have sug-<br>gested that  $\alpha_1$ -adrenergic receptor activation may pro-<br>mote repetitive Ca<sup>2+</sup> transients, varying in f ment of cytosolic Ca<sup>2+</sup> in single hepatocytes have sug-<br>gested that  $\alpha_1$ -adrenergic receptor activation may pro-<br>mote repetitive Ca<sup>2+</sup> transients, varying in frequency, (80)<br>but not in shape or amplitude (367, 368). P gested that  $\alpha_1$ -adrenergic receptor activation may promote repetitive Ca<sup>2+</sup> transients, varying in frequency, (the relationship of such Ca<sup>2+</sup> transients may be important in responses to Ca<sup>2+</sup> mobilizing agents. The mote repetitive Ca<sup>2+</sup> transients, varying in frequency,  $(80)$ .<br>but not in shape or amplitude (367, 368). Possibly, the to c<br>frequency of such Ca<sup>2+</sup> transients may be important in cally<br>responses to Ca<sup>2+</sup> mobilizing ag but not in shape or amplitude (367, 368). Possibly, the<br>frequency of such Ca<sup>2+</sup> transients may be important in<br>responses to Ca<sup>2+</sup> mobilizing agents. The relationship of<br>such oscillations to inositel phospholipid metabol sponses to Ca<sup>2+</sup> transients may be important is<br>ponses to Ca<sup>2+</sup> mobilizing agents. The relationship consider oscillations to inositel phospholipid metabolism<br>mains to be clarified.<br>Similar comparison of  $\alpha_1$ -adrenergi

responses to  $Ca^{2+}$  mobilizing agents. The relationship of the such oscillations to inositol phospholipid metabolism whose remains to be clarified.<br>
Similar comparison of  $\alpha_1$ -adrenergic receptor occupancy and increase such oscillations to inositol phospholipid metabolism<br>remains to be clarified.<br>Similar comparison of  $\alpha_1$ -adrenergic receptor occu-<br>pancy and increases in intracellular Ca<sup>2+</sup> levels have been<br>made in smooth muscle cell remains to be clarified.<br>
Similar comparison of  $\alpha_1$ -adrenergic receptor occu-<br>
pancy and increases in intracellular Ca<sup>2+</sup> levels have been<br>
made in smooth muscle cells in culture. In some cases<br>
activation of  $\alpha_1$ -a Similar comparison of  $\alpha_1$ -adrenergic receptor oc<br>pancy and increases in intracellular  $Ca^{2+}$  levels have b<br>made in smooth muscle cells in culture. In some ca<br>activation of  $\alpha_1$ -adrenergic receptors mobilized  $Ca^{2+}$ pancy and increases in intracellular  $Ca^{2+}$  levels have been<br>made in smooth muscle cells in culture. In some cases<br>activation of  $\alpha_1$ -adrenergic receptors mobilized  $Ca^{2+}$  from<br>intracellular sites and also increased i made in smooth muscle cells in culture. In some cases<br>activation of  $\alpha_1$ -adrenergic receptors mobilized Ca<sup>2+</sup> from<br>intracellular sites and also increased influx of extracel-<br>lular Ca<sup>2+</sup> (289). In other cases the effec activation of  $\alpha_1$ -adrenergic receptors mobilized Ca<sup>2+</sup> from different affinities in binding to the receptors or having intracellular sites and also increased influx of extracel-<br>lular Ca<sup>2+</sup> (289). In other cases the intracellular sites and also increased influx of extracel-<br>lular Ca<sup>2+</sup> (289). In other cases the effect of receptor<br>activation appeared to be mainly due to release of intra-<br>cellular Ca<sup>2+</sup> (5-7, 314). Interestingly, Amb activation appeared to be mainly due to release of intra-<br>cellular  $Ca^{2+}$  (5-7, 314). Interestingly, Ambler et al. (6) equally well. Conversely, an agonist which has a higher<br>recently showed that, during the period of ma activation appeared to be mainly due to relevant<br>cellular Ca<sup>2+</sup> (5-7, 314). Interestingly, Amb<br>recently showed that, during the period of m<br>mobilization in a smooth muscle cell line, t<br>measurable increase in  $\text{Ins}(1,4,5)$ Ilular Ca<sup>2+</sup> (5-7, 314). Interestingly, Ambler et al.<br>cently showed that, during the period of maximal C<br>obilization in a smooth muscle cell line, there was<br>sasurable increase in Ins(1,4,5)P<sub>3</sub> levels.<br>It is apparent tha recently showed that, during the period of maximal  $Ca^{2+}$ <br>mobilization in a smooth muscle cell line, there was no<br>measurable increase in  $Ins(1,4,5)P_3$  levels.<br>It is apparent that the relationship between mobiliza-<br>tion o

mobilization in a smooth muscle cell line, there was no<br>measurable increase in  $\text{Ins}(1,4,5)P_3$  levels.<br>It is apparent that the relationship between mobiliza-<br>tion of intracellular  $\text{Ca}^{2+}$ , influx of extracellular  $\text$ measurable increase in  $\text{Ins}(1,4,5)P_3$  levels.<br>It is apparent that the relationship between mobiliza-<br>tion of intracellular  $\text{Ca}^{2+}$ , influx of extracellular  $\text{Ca}^{2+}$ ,<br>and increases in inositol phospholipid metabol It is apparent that the relationship between mobiliza-<br>tion of intracellular  $Ca^{2+}$ , influx of extracellular  $Ca^{2+}$ ,<br>and increases in inositol phospholipid metabolism is not<br>yet clear. Although Ins(1,4,5)P<sub>3</sub> clearly fu tion of intracellular Ca<sup>2+</sup>, influx of extracellular Ca<sup>2+</sup>, subt<br>and increases in inositol phospholipid metabolism is not<br>yet clear. Although Ins(1,4,5)P<sub>3</sub> clearly functions to mo-<br>of di<br>bilize intracellular Ca<sup>2+</sup> in and increases in inositol phospholipid metabolism is not<br>yet clear. Although Ins(1,4,5) $P_3$  clearly functions to mo-<br>bilize intracellular  $Ca^{2+}$  in some instances in many tis-<br>sues, it is not clear whether this is the o yet clear. Although Ins $(1,4,5)\tilde{P}_3$  clearly functions to mobilize intracellular  $Ca^{2+}$  in some instances in many tissues, it is not clear whether this is the only mechanism by which intracellular  $Ca^{2+}$  is mobilized. bilize intracellular Ca<sup>2+</sup> in son<br>sues, it is not clear whether the dy which intracellular Ca<sup>2+</sup> is<br>relationship of this event to t<br>Ca<sup>2+</sup> remains to be determined<br>Note:<br>Note that the difference of  $\alpha$  and  $\alpha$ by which intracellular  $Ca^{2+}$  is mobilized. Similarly, the relationship of this event to the influx of extracellular  $Ca^{2+}$  remains to be determined.<br>X. Subtypes of  $\alpha_1$ -Adrenergic Receptors<br>Increasing evidence sugges

relationship of this event to the influx of extracellular  $Ca^{2+}$  remains to be determined.<br>
X. Subtypes of  $\alpha_1$ -Adrenergic Receptors<br>
Increasing evidence suggests that  $\alpha_1$ -adrenergic recep-<br>
tors can be further subd Ca<sup>2+</sup> remains to be determined.<br>
X. Subtypes of  $\alpha_1$ -Adrenergic Receptors<br>
Increasing evidence suggests that  $\alpha_1$ -adrenergic recep-<br>
tors can be further subdivided into pharmacologically<br>
distinct subtypes. Although X. Subtypes of  $\alpha_1$ -Adrenergic Receptors<br>
Increasing evidence suggests that  $\alpha_1$ -adrenergic recep-<br>
tors can be further subdivided into pharmacologically<br>
distinct subtypes. Although there is still controversy as<br>
to Increasing evidence suggests that  $\alpha_1$ -adrenergic receptors can be further subdivided into pharmacologically distinct subtypes. Although there is still controversy as to the specificities of drugs, the mechanisms of sig tors can be further subdivided into pharmacologically distinct subtypes. Although there is still controversy as<br>to the specificities of drugs, the mechanisms of signal<br>transduction, and the localization of the various sub distinct subtypes. Although there is still controversy as<br>to the specificities of drugs, the mechanisms of signal<br>transduction, and the localization of the various subtypes<br>which have been proposed, many investigators now to the specificities of drugs, the mechanisms of signal transduction, and the localization of the various subtypes which have been proposed, many investigators now agree that  $\alpha_1$ -adrenergic receptors in different tissu transduction, and the localization of the various subtypes<br>which have been proposed, many investigators now agree<br>that  $\alpha_1$ -adrenergic receptors in different tissues do not<br>have identical properties (2, 95, 105, 138, 13 which have been proposed, many investigators now agree<br>that  $\alpha_1$ -adrenergic receptors in different tissues do not<br>have identical properties (2, 95, 105, 138, 139, 244, 253, type<br>254). There is still much confusion, howe that  $\alpha_1$ -adrenergic receptors in different tissues do r<br>have identical properties (2, 95, 105, 138, 139, 244, 2!<br>254). There is still much confusion, however, about t<br>exact nature of the differences between receptors<br>d have identical properties  $(2, 95, 105, 138, 139, 244, 253, 254)$ . There is still much confusion, however, about the exact nature of the differences between receptors in different tissues and the selectivity of various dru

## *a2-Adrenergic Receptors*

Frem tissues and the selectivity of various drugs. Contains the subclassification of  $\alpha_1$ -adrenergic receptors has contained much more difficult by the fact that  $\alpha_2$ - transferred much more difficult by the fact that A. Distinction from and Potential Similarity to  $\alpha_2$ -Adrenergic Receptors<br>The subclassification of  $\alpha_1$ -adrenergic receptors has<br>been made much more difficult by the fact that  $\alpha_2$ -

MAN<br>adrenergic receptors coexist with  $\alpha_1$ -adrenergic receptors<br>in smooth muscle and also cause contractile responses MAN<br>adrenergic receptors coexist with  $\alpha_1$ -adrenergic receptors<br>in smooth muscle and also cause contractile responses<br>when activated.  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors, although MAN<br>adrenergic receptors coexist with  $\alpha_1$ -adrenergic receptors<br>in smooth muscle and also cause contractile responses<br>when activated.  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors, although<br>pharmacologically different, of cou adrenergic receptors coexist with  $\alpha_1$ -adrenergic receptor<br>in smooth muscle and also cause contractile response<br>when activated.  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors, although<br>pharmacologically different, of course sh adrenergic receptors coexist with  $\alpha_1$ -adrenergic recepto<br>in smooth muscle and also cause contractile respons<br>when activated  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors, althoup<br>pharmacologically different, of course share in smooth muscle and also cause contractile responses<br>when activated.  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors, although<br>pharmacologically different, of course share many simi-<br>larities. They are both activated by the natu when activated.  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors, although<br>pharmacologically different, of course share many sinducties. They are both activated by the naturally occ<br>ring catecholamines epinephrine and norepinephr<br> pharmacologically different, of course share many sim<br>larities. They are both activated by the naturally occuring cate<br>cholamines epinephrine and norepinephrine with approximately equal potencies, and many  $\alpha$ -adre<br>nergi larities. They are both activated by the naturally occurring catecholamines epinephrine and norepinephrine with approximately equal potencies, and many  $\alpha$ -adrenergic receptor blocking drugs, including phentolamine, have with approximately equal potencies, and many  $\alpha$ -adre-<br>nergic receptor blocking drugs, including phentolamine,<br>have similar potencies in blocking both subtypes. Al-<br>though many agonists and antagonists exist which are<br>re with approximately equal potencies, and many  $\alpha$ -adrespic receptor blocking drugs, including phentolamin<br>have similar potencies in blocking both subtypes. A<br>though many agonists and antagonists exist which a<br>relatively s nergic receptor blocking drugs, including phentolamin<br>have similar potencies in blocking both subtypes.  $\ell$ <br>though many agonists and antagonists exist which a<br>relatively selective for either  $\alpha_1$  or  $\alpha_2$ -adrenergic r have similar potencies in blocking both subtypes. Although many agonists and antagonists exist which are relatively selective for either  $\alpha_1$  or  $\alpha_2$ -adrenergic receptors, such selectivity is never absolute. Selective though many agonists and antagonists exist which are<br>relatively selective for either  $\alpha_1$  or  $\alpha_2$ -adrenergic recep-<br>tors, such selectivity is never absolute. Selective antag-<br>onists routinely have 50- to 1000-fold dif relatively selective for either  $\alpha_1$  or  $\alpha_2$ -adrenergic receptors, such selectivity is never absolute. Selective antagonists routinely have 50- to 1000-fold differences in their affinities for binding to  $\alpha_1$ - and tors, such selectivity is never absolute. Selective a<br>onists routinely have 50- to 1000-fold differences in<br>affinities for binding to  $\alpha_1$ - and  $\alpha_2$ -adrenergic rece<br>(80). Although such differences in affinity are suff onists routinely have 50- to 1000-fold differences in their<br>affinities for binding to  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors<br>(80). Although such differences in affinity are sufficient<br>to clearly differentiate these recep affinities for binding to  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors (80). Although such differences in affinity are sufficient to clearly differentiate these receptors pharmacologically, they are usually insufficient to com (80). Although such differences in affinity are sufficient<br>to clearly differentiate these receptors pharmacologi-<br>cally, they are usually insufficient to completely block<br>the response to one subtype but not another, partic to clearly differentiate these recepto<br>cally, they are usually insufficient to<br>the response to one subtype but not and<br>when high concentrations of agonists<br>might surmount competitive blockade.<br>Selective agonists present ev lly, they are usually insufficient to completely blocle response to one subtype but not another, particularly<br>hen high concentrations of agonists are used which<br>ight surmount competitive blockade.<br>Selective agonists presen

the response to one subtype but not another, particularly<br>when high concentrations of agonists are used which<br>might surmount competitive blockade.<br>Selective agonists present even more problems. Ago-<br>nists may be selective when high concentrations of agonists are used which<br>might surmount competitive blockade.<br>Selective agonists present even more problems. Ago-<br>nists may be selective in two different ways, either having<br>different affinities might surmount competitive blockade.<br>Selective agonists present even more problems. A<br>nists may be selective in two different ways, either have<br>different affinities in binding to the receptors or have<br>different efficacies Selective agonists present even more problems. Agonists may be selective in two different ways, either havine different affinities in binding to the receptors or havine different efficacies in activating them. These two pa nists may be selective in two different ways, either having<br>different affinities in binding to the receptors or having<br>different efficacies in activating them. These two param-<br>eters vary independently, and an agonist whic different affinities in binding to the receptors or having<br>different efficacies in activating them. These two param-<br>eters vary independently, and an agonist which selec-<br>tively activates only a single subtype may bind to different emcacles in activating them. I nese two parameters vary independently, and an agonist which selectively activates only a single subtype may bind to both equally well. Conversely, an agonist which has a higher aff equally well. Conversely, an agonist which has a higher affinity in binding to one subtype than the other may, once it is bound, activate both subtypes equally well. Again, specificity is usually only relative and not abso equally well. Conversely, an agonist which has a higher<br>affinity in binding to one subtype than the other may,<br>once it is bound, activate both subtypes equally well.<br>Again, specificity is usually only relative and not abso affinity in binding to one subtype than the other may, once it is bound, activate both subtypes equally well.<br>Again, specificity is usually only relative and not absolute. An agonist which selectively activates only a sing once it is bound, activate both subtypes equally well.<br>Again, specificity is usually only relative and not abso-<br>lute. An agonist which selectively activates only a single<br>subtype may have a small efficacy at the other sub lute. An agonist which selectively activates only a single subtype may have a small efficacy at the other subtype.<br>Such problems are greatly compounded by the existence of differential receptor reserves in different tissu subtype may have a small efficacy at the other subtype.<br>Such problems are greatly compounded by the existence<br>of differential receptor reserves in different tissues and<br>for different receptor types. For example, clonidine Such problems are greatly compounded by the existence<br>of differential receptor reserves in different tissues and<br>for different receptor types. For example, clonidine has<br>a much greater efficacy for activating  $\alpha_2$ -adren of differential receptor reserves in different tissues and<br>for different receptor types. For example, clonidine has<br>a much greater efficacy for activating  $\alpha_2$ -adrenergic receptors<br>(table<br>1), but in a tissue with a larg (80). Athrough such dimerences in alminity are summative is approached to clearly differentiate these receptors pharmacologically, they are usually insufficient to completely block the response to one subtype but not anot a much greater efficacy for activating  $\alpha_2$ -adrenergic receptors (table 1), but in a tissue with a large  $\alpha_1$ -adrenergic receptor reserve the contractile response to clonidine may be mediated by activation of  $\alpha_1$ -a ceptors than for activating  $\alpha_1$ -adrenergic receptors (tab 1), but in a tissue with a large  $\alpha_1$ -adrenergic recept<br>reserve the contractile response to clonidine may levelective and integral in the most selective  $\alpha_2$ 1), but in a tissue with a large  $\alpha_1$ -adrenergic recensive the contractile response to clonidine mandiated by activation of  $\alpha_1$ -adrenergic receptors (Similarly, two of the most selective  $\alpha_2$ -adrenergic receptors ( reserve the contractile response to clonidine may be<br>mediated by activation of  $\alpha_1$ -adrenergic receptors (147).<br>Similarly, two of the most selective  $\alpha_2$ -adrenergic recep-<br>tor agonists, BHT 920 and 5-bromo-6-(2-imidaz Similarly, two of the most selective  $\alpha_2$ -adrenergic receptor agonists, BHT 920 and 5-bromo-6-(2-imidazolin-2-<br>ylamino)quinoxaline (UK 14, 304), have sufficient effi-<br>cacies at  $\alpha_1$ -adrenergic receptors to activate  $\$ Similarly, two of the most selective  $\alpha_2$ -adrenergic receptor agonists, BHT 920 and 5-bromo-6-(2-imidazolin-2-<br>ylamino)quinoxaline (UK 14, 304), have sufficient effi-<br>cacies at  $\alpha_1$ -adrenergic receptors to activate  $\$ tor agonists, BHT 920 and 5-bromo-6-(2-imidazolin-2-<br>ylamino)quinoxaline (UK 14, 304), have sufficient effi-<br>cacies at  $\alpha_1$ -adrenergic receptors to activate  $\alpha_1$ -adrener-<br>gic receptor-mediated contractions in tissues ylamino)quinoxaline (UK 14, 304), have sufficient effi-<br>cacies at  $\alpha_1$ -adrenergic receptors to activate  $\alpha_1$ -adrener-<br>gic receptor-mediated contractions in tissues with a large<br>receptor reserve, such as rat and guinea cacies at  $\alpha_1$ -adrenergic receptors to activate  $\alpha_1$ -adrenergic receptor-mediated contractions in tissues with a large receptor reserve, such as rat and guinea pig aortae (17). Clearly, if there are two types of  $\alpha_1$ gic receptor-mediated contractions in tissues with a large<br>receptor reserve, such as rat and guinea pig aortae (17).<br>Clearly, if there are two types of  $\alpha_1$ -, and one or more<br>types of  $\alpha_2$ -adrenergic receptors activat receptor reserve, such as rat and guinea pig aortae (17).<br>Clearly, if there are two types of  $\alpha_1$ -, and one or more<br>types of  $\alpha_2$ -adrenergic receptors activating contraction<br>of a smooth muscle, and all of the drugs av Clearly, if there are two types of  $\alpha_1$ -, and one or more<br>types of  $\alpha_2$ -adrenergic receptors activating contraction<br>of a smooth muscle, and all of the drugs available can<br>interact with all of the receptor subtypes at pes of  $\alpha_2$ -adrenergic receptors activating contraction<br>a smooth muscle, and all of the drugs available can<br>teract with all of the receptor subtypes at appropriate<br>ncentrations, the potential for confusion is very great

of a smooth muscle, and all of the drugs available cointeract with all of the receptor subtypes at appropria<br>concentrations, the potential for confusion is very gree<br>Experimentally, this means that all assumptions mu<br>be co interact with all of the receptor subtypes at appropriate<br>concentrations, the potential for confusion is very great.<br>Experimentally, this means that all assumptions must<br>be constantly checked and rechecked when using diffe concentrations, the potential for confusion is very gre<br>Experimentally, this means that all assumptions m<br>be constantly checked and rechecked when using different drugs, or when using the same drug under different<br>conditio Experimentally, this means that all assumptions must<br>be constantly checked and rechecked when using differ-<br>ent drugs, or when using the same drug under different<br>conditions or in different tissues. Values for log concen-<br>



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 $\alpha_1$ -ADRENERGIC RECEPTOR SUBTYPES<br>ulation (pA<sub>2</sub>) must always be determined for antagonists,<br>and the slopes and shapes of the Schild plots must be  $\alpha_1$ -ADRENERGIC RECEP<br>ulation (pA<sub>2</sub>) must always be determined for antagonists,<br>and the slopes and shapes of the Schild plots must be<br>carefully scrutinized (8, 182). The types of receptors  $\alpha_1$ -ADRENERGIC REC<br>ulation (pA<sub>2</sub>) must always be determined for antagonists,<br>and the slopes and shapes of the Schild plots must be<br>carefully scrutinized (8, 182). The types of receptors<br>activated by agonists must be c ulation  $(pA_2)$  must always be determined for antagonists,<br>and the slopes and shapes of the Schild plots must be<br>carefully scrutinized  $(8, 182)$ . The types of receptors<br>activated by agonists must be carefully verified un ulation  $(pA_2)$  must always be determined for antagonists,<br>and the slopes and shapes of the Schild plots must be<br>carefully scrutinized  $(8, 182)$ . The types of receptors<br>activated by agonists must be carefully verified un and the slopes and shapes of the Schild plots must be carefully scrutinized (8, 182). The types of receptors activated by agonists must be carefully verified under each experimental condition and with each new drug and dru carefully scrutinized (8, 182). The types of receptors activated by agonists must be carefully verified under each experimental condition and with each new drug and drug concentration tested. The extent of the receptor res activated by agonists must be carefully verified under<br>each experimental condition and with each new drug and<br>drug concentration tested. The extent of the receptor<br>reserve must also be taken into account (112, 182). For<br>e each experimental condition and with each new drug and<br>drug concentration tested. The extent of the receptor<br>reserve must also be taken into account (112, 182). For<br>example, a particular agonist which may be causing<br>contr drug concentration tested. The extent of the receptor reserve must also be taken into account (112, 182). For example, a particular agonist which may be causing contraction in control tissues through an  $\alpha_1$ -adrenergic reserve must also be taken into account (112, 182). For<br>example, a particular agonist which may be causing<br>contraction in control tissues through an  $\alpha_1$ -adrenergic<br>receptor may, after partial receptor inactivation or a contraction in control tissues through an  $\alpha_1$ -adrenergic<br>receptor may, after partial receptor inactivation or ad-<br>dition of an  $\alpha_1$ -selective competitive antagonist, begin to<br>cause contraction through  $\alpha_2$ -adrenerg contraction in control tissues through an  $\alpha_1$ -adrenergic<br>receptor may, after partial receptor inactivation or ad-<br>dition of an  $\alpha_1$ -selective competitive antagonist, begin to<br>cause contraction through  $\alpha_2$ -adrenerg receptor may, after partial receptor inactivation or addition of an  $\alpha_1$ -selective competitive antagonist, begin to cause contraction through  $\alpha_2$ -adrenergic receptors. Unfortunately, because of practical limitations dition of an  $\alpha_1$ -selective competitive antacause contraction through  $\alpha_2$ -adrenergic<br>fortunately, because of practical limitation many different drugs and tissues, absorthese parameters is not always possible.<br>Becaus use contraction through  $\alpha_2$ -adrenergic receptors. Un-<br>tunately, because of practical limitations in the use of<br>any different drugs and tissues, absolute control of<br>ese parameters is not always possible.<br>Because of this

fortunately, because of practical limitations in the use of<br>many different drugs and tissues, absolute control of<br>these parameters is not always possible.<br>Because of this complexity, it is perhaps not surprising<br>that many many different drugs and tissues, absolute control of<br>these parameters is not always possible.<br>Because of this complexity, it is perhaps not surprising<br>that many confusing and conflicting data have been<br>generated.  $\alpha_2$ these parameters is not always possible.<br>Because of this complexity, it is perhaps not surprising<br>that many confusing and conflicting data have been<br>generated.  $\alpha_2$ -Adrenergic receptor-mediated pressor re-<br>sponses can b Because of this complexity, it is perhaps not surprising<br>that many confusing and conflicting data have been<br>generated.  $\alpha_2$ -Adrenergic receptor-mediated pressor re-<br>sponses can be readily observed after  $\alpha_1$ -adrenergi that many confusing and conflicting data have been<br>generated.  $\alpha_2$ -Adrenergic receptor-mediated pressor re-<br>sponses can be readily observed after  $\alpha_1$ -adrenergic re-<br>ceptor blockade in pithed rats (200, 227, 344). How generated.  $\alpha_2$ -Adrenergic receptor-mediated pressor re-<br>sponses can be readily observed after  $\alpha_1$ -adrenergic re-<br>ceptor blockade in pithed rats (200, 227, 344). However,<br>it has been much more difficult to demonstrat sponses can be readily observed after  $\alpha_1$ -adrenergic receptor blockade in pithed rats (200, 227, 344). However, it has been much more difficult to demonstrate similar responses in vitro. Only in a few isolated tissues, ceptor blockade in pithed rats (200, 227, 344). However,<br>it has been much more difficult to demonstrate similar<br>responses in vitro. Only in a few isolated tissues, such as<br>dog saphenous vein (81), rabbit saphenous vein (3 it has been much more difficult to demonstrate similar<br>responses in vitro. Only in a few isolated tissues, such as<br>dog saphenous vein (81), rabbit saphenous vein (309),<br>and dog cerebral arteries (300), can clear  $\alpha_2$ -ad vitro.

have  $\alpha$ -adrenergic receptors mediating contractile rereceptor-mediated contractile responses be observed in blocking<br>vitro.<br>
On the other hand, some isolated tissues appear to prazosi<br>
have  $\alpha$ -adrenergic receptors mediating contractile re-<br>
sponses with pharmacological ch vitro.<br>
On the other hand, some isolated tissues appear to<br>
have  $\alpha$ -adrenergic receptors mediating contractile re-<br>
sponses with pharmacological characteristics which seem<br>
to be intermediate between the  $\alpha_1$ - and  $\alpha$ On the other hand, some isolated tissues appear to<br>have  $\alpha$ -adrenergic receptors mediating contractile re-<br>sponses with pharmacological characteristics which seem<br>to be intermediate between the  $\alpha_1$ - and  $\alpha_2$ -adrener have  $\alpha$ -adrenergic receptors mediating contractile responses with pharmacological characteristics which seem<br>to be intermediate between the  $\alpha_1$ - and  $\alpha_2$ -adrenergic<br>receptor subtypes. Ruffolo et al. (299) first sho sponses with pharmacological characteristics which seem<br>to be intermediate between the  $\alpha_1$ - and  $\alpha_2$ -adrenergic<br>receptor subtypes. Ruffolo et al. (299) first showed that<br>rat aorta was exceptionally sensitive to contr receptor subtypes. Ruffolo et al. (299) first showed that rat aorta was exceptionally sensitive to contraction caused by clonidine, and that this response was potently inhibited by yohimbine (297). Based on these results, receptor subtypes. Ruffolo et al. (299) first showed that rat aorta was exceptionally sensitive to contraction caused by clonidine, and that this response was potently inhibited by yohimbine (297). Based on these results, rat aorta was exceptionally sensitive to contraction<br>caused by clonidine, and that this response was potently<br>inhibited by yohimbine (297). Based on these results<br>these authors proposed that rat aorta had  $\alpha_2$ -adrenergi caused by clonidine, and that this response was potently<br>inhibited by yohimbine (297). Based on these results,<br>these authors proposed that rat aorta had  $\alpha_2$ -adrenergic<br>receptors on the postsynaptic smooth muscle cells. inhibited by yohimbine (297). Based on these results, in<br>these authors proposed that rat aorta had  $\alpha_2$ -adrenergic sp<br>receptors on the postsynaptic smooth muscle cells. Fur-<br>ther work substantiated the differences betwe receptors on the postsynaptic smooth muscle cells. Further work substantiated the differences between the  $\alpha$ -<br>adrenergic receptors mediating contraction of rat aorta<br>and those of other species (298). However, the classi receptors on the postsynaptic smooth muscle cells. Fur-<br>ther work substantiated the differences between the  $\alpha$ -<br>adrenergic receptors mediating contraction of rat aorta<br>and those of other species (298). However, the clas ther work substantiated the differences between the adrenergic receptors mediating contraction of rat ao and those of other species (298). However, the class cation of this receptor as being of the  $\alpha_2$ -subtype v clearl adrenergic receptors mediating contraction of rat aorta<br>and those of other species (298). However, the classifi-<br>cation of this receptor as being of the  $\alpha_2$ -subtype was<br>clearly suspect, since both  $\alpha_1$ -selective agon and those of other species (298). However, the classification of this receptor as being of the  $\alpha_2$ -subtype was clearly suspect, since both  $\alpha_1$ -selective agonists (phenyl-<br>ephrine and methoxamine) and antagonists (pr cation of this receptor as being of the  $\alpha_2$ -subtype was clearly suspect, since both  $\alpha_1$ -selective agonists (phenyl-<br>ephrine and methoxamine) and antagonists (prazosin)<br>are quite potent in this tissue (91, 94, 294). ephrine and methoxamine) and antagonists (prazosin) in dog splenic vein (141) although it is very effective in<br>are quite potent in this tissue (91, 94, 294). Ruffolo et al. tissues with clear  $\alpha_2$ -adrenergic receptor-me ephrine and methoxamine) and antagonists (prazosin) in<br>are quite potent in this tissue (91, 94, 294). Ruffolo et al.<br>(298) concluded that the  $\alpha$ -adrenergic receptors of rat<br>aorta "possesses properties of both alpha-1 an are quite potent in this tissue (91, 94, 294). Ruffolo et al. tiss<br>(298) concluded that the  $\alpha$ -adrenergic receptors of rat tra<br>aorta "possesses properties of both alpha-1 and alpha-2 uni<br>adrenergic receptors" (fig. 5). (298) concluded that the  $\alpha$ -adrenergic receptors of rat aorta "possesses properties of both alpha-1 and alpha-2 adrenergic receptors" (fig. 5). Further analysis of these receptors, however, has shown that they must clea aorta "possesses properties of both alpha-1 and alpha-2 unadrenergic receptors" (fig. 5). Further analysis of these sureceptors, however, has shown that they must clearly be Holassified as  $\alpha_1$ . The contractile effects adrenergic receptors" (fig. 5). Further analysis of these<br>receptors, however, has shown that they must clearly be<br>classified as  $\alpha_1$ . The contractile effects of all agonists<br>studied, including highly  $\alpha_1$ -selective ag receptors, however, has shown that they must clearly be Hovelassified as  $\alpha_1$ . The contractile effects of all agonists wolls studied, including highly  $\alpha_1$ -selective agonists such as subphenylephrine and methoxamine a classified as  $\alpha_1$ . The contractile effects of all agonists studied, including highly  $\alpha_1$ -selective agonists such as phenylephrine and methoxamine and highly  $\alpha_2$ -selective agonists such as BHT 920, are much more s studied, including highly  $\alpha_1$ -selective agonists such as phenylephrine and methoxamine and highly  $\alpha_2$ -selective agonists such as BHT 920, are much more sensitive to blockade by prazosin than by yohimbine (16, 78, 21 phenylephrine and methoxamine and highly  $\alpha_2$ -selective sele-<br>agonists such as BHT 920, are much more sensitive to prop<br>blockade by prazosin than by yohimbine (16, 78, 216). envi-<br>Although selective  $\alpha_2$ -adrenergic re agonists such as BHT 920, are much more sensitive blockade by prazosin than by yohimbine (16, 78, Although selective  $\alpha_2$ -adrenergic receptor antagosuch as yohimbine and rauwolscine are more potent aorta than in blockin blockade by prazosin than by yohimbine (16, 78, 216). elective  $\alpha_2$ -adrenergic receptor antagonists such as yohimbine and rauwolscine are more potent in rat aorta than in blocking  $\alpha_1$ -adrenergic receptor-mediated con



**norepinephrine-stimulated contractions in aortae from** 7 different spa-**FIG.** 5. Differences in the  $pA_2$  values for yohimbine in blocking<br>norepinephrine-stimulated contractions in aortae from 7 different spe-<br>cies. The more than 30-fold differences in potencies observed in the<br>different ti FIG. 5. Differences in the  $pA_2$  values for yohimbine in blonorepinephrine-stimulated contractions in aortae from 7 differencies. The more than 30-fold differences in potencies observed in different tissues suggest that norepine<br>phrime-stimulated contractions in aortae from 7 different species. The more than 30-fold differences in potencies observed in the<br>different tissues suggest that the receptors have different pharmacolog-<br>ical prop

dog saphenous vein (81), rabbit saphenous vein (309),<br>and dog cerebral arteries (300), can clear  $\alpha_2$ -adrenergic<br>receptor-mediated contractile responses be observed in blocking contractile responses of rat aorta, indica cles. The more than 30-101 differences in potencies observed in the different tissues suggest that the receptors have different pharmacological properties. From Ruffolo et al. (298) with permission *Bars*, SE. selective a contractive antagonist prazosin is also more potent in rate<br>selective antagonist prazosin is also more potent in rate<br>aorta than in blocking  $\alpha_1$ -adrenergic receptor-mediated<br>contractile responses in other tissues (88, selective antagonist prazosin is also more potent in rat<br>aorta than in blocking  $\alpha_1$ -adrenergic receptor-mediated<br>contractile responses in other tissues (88, 128) (see be-<br>low). With both  $\alpha_1$ - and  $\alpha_2$ -selective ag selective antagonist prazosin is also more potent in rat<br>aorta than in blocking  $\alpha_1$ -adrenergic receptor-mediated<br>contractile responses in other tissues (88, 128) (see be-<br>low). With both  $\alpha_1$ - and  $\alpha_2$ -selective ag aorta than in blocking  $\alpha_1$ -adrenergic receptor-mediated<br>contractile responses in other tissues (88, 128) (see be-<br>low). With both  $\alpha_1$ - and  $\alpha_2$ -selective agonists, prazosin is<br>more than 300-fold more potent than y contractile responses in other tissues (88, 128) (see be-<br>low). With both  $\alpha_1$ - and  $\alpha_2$ -selective agonists, prazosin is<br>more than 300-fold more potent than yohimbine in<br>blocking contractile responses of rat aorta, in more than 300-fold more potent than yohimbine in blocking contractile responses of rat aorta, indicating that this receptor is clearly of the  $\alpha_1$ -subtype. Why both prazosin and yohimbine, and other drugs such as clonimore than 300-fold more potent than yohimbine in blocking contractile responses of rat aorta, indicating that this receptor is clearly of the  $\alpha_1$ -subtype. Why both prazosin and yohimbine, and other drugs such as clonid better contractile responses of rat aorta, indicating<br>at this receptor is clearly of the  $\alpha_1$ -subtype. Why both<br>azosin and yohimbine, and other drugs such as cloni-<br>ne, are unusually potent in this tissue is not yet cle

that this receptor is clearly of the  $\alpha_1$ -subtype. Why both prazosin and yohimbine, and other drugs such as clonidine, are unusually potent in this tissue is not yet clear.<br>There are also tissues where the difference be prazosin and yohimbine, and other drugs such as clo<br>dine, are unusually potent in this tissue is not yet clee<br>There are also tissues where the difference betwe<br>the affinities of prazosin and yohimbine is not so la<br>(139). P dine, are unusually potent in this tissue is not yet clear.<br>There are also tissues where the difference between<br>the affinities of prazosin and yohimbine is not so large<br>(139). Prazosin is only 20-fold more potent than rauw There are also tissues where the difference between<br>the affinities of prazosin and yohimbine is not so large<br>(139). Prazosin is only 20-fold more potent than rauwol-<br>scine in blocking norepinephrine-induced contractions<br>of the affinities of prazosin and yohimbine is not so large (139). Prazosin is only 20-fold more potent than rauwolscine in blocking norepinephrine-induced contractions of cat mesenteric arteries (316), only 10-fold more pote FIG. 5. Differences in the possibility and solven in blocking<br>norepinephrine-stimulated contractions in aortae from 7 different speecas.<br>The more than 30-fold differences in potencies observed in the<br>different tissues sug scine in blocking norepinephrine-induced contractions<br>of cat mesenteric arteries (316), only 10-fold more potent<br>in dog splenic artery, and only 3-fold more potent in dog<br>splenic vein (141). This raises the possibility th of cat mesenteric arteries (316), only 10-fold more pot<br>in dog splenic artery, and only 3-fold more potent in  $\alpha$ <br>splenic vein (141). This raises the possibility that bo<br> $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors might cont in dog splenic artery, and only 3-fold more potent in dog<br>splenic vein (141). This raises the possibility that both<br> $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors might contribute to con-<br>tractile responses in these muscles. How splenic vein (141). This raises the possibility that both  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors might contribute to contractile responses in these muscles. However, if  $\alpha_2$ -adrenergic receptors were contributing to th tractile responses in these muscles. However, if  $\alpha_2$ -adre-<br>nergic receptors were contributing to the contractile re-<br>sponse to norepinephrine in dog splenic vein, then  $\alpha_2$ -<br>selective agonists such as BHT 920 should mergic receptors were contributing to the contractile response to norepinephrine in dog splenic vein, then  $\alpha_2$ -<br>selective agonists such as BHT 920 should also produce<br>a response. But, BHT 920 does not activate contract sponse to norepinephrine in dog splenic vein, then  $\alpha$  selective agonists such as BHT 920 should also produce a response. But, BHT 920 does not activate contraction in dog splenic vein (141) although it is very effective selective agonists such as BHT 920 should also produce<br>a response. But, BHT 920 does not activate contraction<br>in dog splenic vein (141) although it is very effective in<br>tissues with clear  $\alpha_2$ -adrenergic receptor-mediat a response. But, BHT 920 does not activate contraction<br>in dog splenic vein (141) although it is very effective in<br>tissues with clear  $\alpha_2$ -adrenergic receptor-mediated con-<br>tractile responses, such as dog saphenous vein in dog splenic vein (141) although it is very effective in<br>tissues with clear  $\alpha_2$ -adrenergic receptor-mediated con-<br>tractile responses, such as dog saphenous vein (107). The<br>uniformly high affinity of these receptors f tissues with clear  $\alpha_2$ -adrenergic receptor-mediated contractile responses, such as dog saphenous vein (107). The uniformly high affinity of these receptors for prazosin suggests that each of these receptors is of the tractile responses, such as dog saphenous vein (107). The uniformly high affinity of these receptors for prazosin suggests that each of these receptors is of the  $\alpha_1$ -subtype. However, the variable affinity for yohimbin uniformly high affinity of these receptors for prazosin<br>suggests that each of these receptors is of the  $\alpha_1$ -subtype.<br>However, the variable affinity for yohimbine and rau-<br>wolscine raises the possibility that there are However, the variable affinity for yohimbine and rau-<br>wolscine raises the possibility that there are distinct<br>subtypes of this receptor with differing affinities for  $\alpha_2$ -<br>selective antagonists. Conversely, the pharmaco However, the variable affinity for yohimbine and rau-<br>wolscine raises the possibility that there are distinct<br>subtypes of this receptor with differing affinities for  $\alpha_2$ -<br>selective antagonists. Conversely, the pharmaco wolscine raises the possibility that there are distinct subtypes of this receptor with differing affinities for  $\alpha_2$ -<br>selective antagonists. Conversely, the pharmacological<br>properties of the receptor may be influenced b

### *B. Differentiation using Selective Agonists*

operties of the receptor may be influenced by its tissue<br>vironment, or some other unknown factor (see below).<br>Differentiation using Selective Agonists<br>In the studies described above,  $\alpha_1$ -adrenergic receptors<br>ree differ environment, or some other unknown factor (see below).<br>
B. Differentiation using Selective Agonists<br>
In the studies described above,  $\alpha_1$ -adrenergic receptors<br>
were differentiated by their affinity for drugs which are

102 MINNEM<br>usually  $\alpha_2$ -selective. Many studies have also suggested pothat other drugs can also differentiate between  $\alpha_1$ -adre-102<br>
usually  $\alpha_2$ -selective. Many studies have also suggest<br>
that other drugs can also differentiate between  $\alpha_1$ -ad<br>
nergic receptors in different tissues. Based on sm MINNE<br>usually  $\alpha_2$ -selective. Many studies have also suggested<br>that other drugs can also differentiate between  $\alpha_1$ -adre-<br>nergic receptors in different tissues. Based on small<br>differences in pA<sub>2</sub> values for phentolam usually  $\alpha_2$ -selective. Many studies have also suggested<br>that other drugs can also differentiate between  $\alpha_1$ -adre-<br>nergic receptors in different tissues. Based on small<br>differences in pA<sub>2</sub> values for phentolamine in usually  $\alpha_2$ -selective. Many studies have also suggested that other drugs can also differentiate between  $\alpha_1$ -adre nergic receptors in different tissues. Based on smal differences in  $pA_2$  values for phentolamine in that other drugs can also differentiate between  $\alpha_1$ -ad<br>nergic receptors in different tissues. Based on sm<br>differences in  $pA_2$  values for phentolamine in differ<br>tissues, Sheys and Green (313) undertook a careful co<br>pa nergic receptors in different tissues. Based on small and differences in  $pA_2$  values for phentolamine in different altissues, Sheys and Green (313) undertook a careful comparison of the pharmacological properties of the differences in  $pA_2$  values for phentolamine in different abotissues, Sheys and Green (313) undertook a careful comparison of the pharmacological properties of the  $\alpha$ -adrection of rabbit aorta 101 and spleen. They foun tissues, Sheys and Green (313) undertook a careful comparison of the pharmacological properties of the  $\alpha$ -adrenergic receptors mediating contraction of rabbit aorta<br>and spleen. They found relatively large differences (u parison of the pharmacological properties of the  $\alpha$ -adre-<br>nergic receptors mediating contraction of rabbit aorta<br>and spleen. They found relatively large differences (up<br>to 10-fold) in the  $K_a$  values for agonists in act nergic receptors mediating contraction of rabbit aorta<br>and spleen. They found relatively large differences (up<br>to 10-fold) in the  $K_a$  values for agonists in activating<br>contraction in the two tissues, with agonists being and spleen. They found relatively large differences (up<br>to 10-fold) in the  $K_a$  values for agonists in activating tre<br>contraction in the two tissues, with agonists being more<br>repotent in aorta. These data raised the possi to 10-fold) in the  $K_a$  values for agonists in activating to<br>contraction in the two tissues, with agonists being more<br>potent in aorta. These data raised the possibility that<br>the  $\alpha$ -adrenergic receptors in rabbit aorta a contraction in the two tissues, with agonists being more potent in aorta. These data raised the possibility that the  $\alpha$ -adrenergic receptors in rabbit aorta and spleen might differ from each other (313). Many other stud potent in aorta. These data raised the possibility that two<br>the  $\alpha$ -adrenergic receptors in rabbit aorta and spleen acti<br>might differ from each other (313). Many other studies acti<br>have subsequently substantiated the fac the  $\alpha$ -adrenergic receptors in rabbit aorta and spleemight differ from each other (313). Many other studie<br>have subsequently substantiated the fact that the  $\alpha$ <br>adrenergic receptors in rabbit aorta generally show<br>much might differ from each other (313). Many other studies act<br>have subsequently substantiated the fact that the  $\alpha$ - 10<br>adrenergic receptors in rabbit aorta generally show a bo<br>much higher affinity for norepinephrine (a low have subsequently substantiated the fact that the  $\alpha$ -<br>adrenergic receptors in rabbit aorta generally show a<br>much higher affinity for norepinephrine (a lower func-<br>tional  $K_a$  value) and other phenethylamine agonists tha much higher affinity for norepine thrine (a lower functional  $K_a$  value) and other phenethylamine agonists than is found in other tissues  $(24, 181, 241, 242, 244, 281, 334)$  (see below). is found in other tissues (24, 181, 241, 242, 244, 281, 334)

is found in other tissues  $(24, 181, 241, 242, 244, 281, 334)$ <br>(see below).<br>
1. Imidazolines versus phenethylamines. In examining<br>
desensitization of rat vas deferens, Ruffolo et al.  $(295)$ <br>
showed that long-term exposur (see below).  $\qquad \qquad \qquad$  ined<br>1. Imidazolines versus phenethylamines. In examining an is<br>desensitization of rat vas deferens, Ruffolo et al. (295) (not<br>showed that long-term exposure to imidazoline-type ag-<br>onists would d 1. Imidazolines versus phenethylamines. In examining desensitization of rat vas deferens, Ruffolo et al. (295) showed that long-term exposure to imidazoline-type agonists would decrease the contractile responsiveness to th desensitization of rat vas deferens, Ruffolo et al. (295)<br>showed that long-term exposure to imidazoline-type ag-<br>onists would decrease the contractile responsiveness to<br>this class of agonists, but not to the phenethylamine showed that long-term exposure to imidazoline-type ag-<br>onists would decrease the contractile responsiveness to<br>this class of agonists, but not to the phenethylamine<br>class of agonists. This differential desensitization to onists would decrease the contractile responsiveness to<br>this class of agonists, but not to the phenethylamine<br>class of agonists. This differential desensitization to ag-<br>onists of different structural classes might be exp this class of agonists, but not to the phenethylamine seclass of agonists. This differential desensitization to agonists of different structural classes might be explained G by the existence of two different types of  $\alpha_$ onists of different structural classes might be explained<br>by the existence of two different types of  $\alpha_1$ -adrenergic<br>receptors, or by different attachment sites on the same by the existence of two different types of  $\alpha_1$ -adrenergic tagence receptors, or by different attachment sites on the same the receptor. These studies stimulated much interest in comparing these two classes of drugs, bu receptors, or by different attachment sites on the same<br>receptor. These studies stimulated much interest in com-<br>paring these two classes of drugs, but are complicated by<br>the fact that most imidazoline-type agonists have a paring these two classes of drugs, but are complicated by<br>the fact that most imidazoline-type agonists have a much<br>lower efficacy than phenethylamine-type agonists (80),<br>vand only maximal doses of drugs were tested. In thi the fact that most imidazoline-type agonists have a much 10<br>lower efficacy than phenethylamine-type agonists (80), va<br>and only maximal doses of drugs were tested. In this the<br>case, a marked reduction in receptor reserve mi lower efficacy than phenethylamine-type agonists (and only maximal doses of drugs were tested. In the case, a marked reduction in receptor reserve might red the response to low efficacy agonists (imidazolines) m more than and only maximal doses of drugs were tested. In the case, a marked reduction in receptor reserve might reduction the response to low efficacy agonists (imidazolines) mumore than to high efficacy agonists (phenethylamine Al the response to low efficacy agonists (imidazolines) much<br>more than to high efficacy agonists (phenethylamines).<br>Although Ruffolo et al. (295) argued against this expla-<br>nation of their data, it was not clearly ruled out.<br> e response to low efficacy agonists (imidazolines) much to<br>ore than to high efficacy agonists (phenethylamines).<br>though Ruffolo et al. (295) argued against this expla-<br>tion of their data, it was not clearly ruled out.<br>Base more than to high efficacy agonists (phenethylamines).<br>Although Ruffolo et al. (295) argued against this explanation of their data, it was not clearly ruled out.<br>Based on a review of the literature and work from his<br>own l

Although Ruffolo et al. (295) argued against this explanation of their data, it was not clearly ruled out.<br>Based on a review of the literature and work from his own laboratory, McGrath (227) raised the possibility that  $\$ mation of their data, it was not clearly ruled out. <br>Based on a review of the literature and work from his di<br>own laboratory, McGrath (227) raised the possibility that re<br> $\alpha_1$ -adrenergic receptors should be divided into Based on a review of the literature and work from his<br>own laboratory, McGrath (227) raised the possibility that<br> $\alpha_1$ -adrenergic receptors should be divided into two sub-<br>classes,  $\alpha_{1a}$ - and  $\alpha_{1b}$ -. His arguments w own laboratory, McGrath (227) raised the possibility that rec $\alpha_1$ -adrenergic receptors should be divided into two sub-<br>classes,  $\alpha_{1a}$ - and  $\alpha_{1b}$ -. His arguments were based mainly inv<br>on (a) the complexity of agoni  $\alpha_1$ -adrenergic receptors should be divided into two sub<br>classes,  $\alpha_{1a}$ - and  $\alpha_{1b}$ -. His arguments were based mainly<br>on (*a*) the complexity of agonist dose-response curves<br>which sometimes consist of two component classes,  $\alpha_{1a}$ - and  $\alpha_{1b}$ -. His arguments were based mainly<br>on (*a*) the complexity of agonist dose-response curves,<br>which sometimes consist of two components (25); (*b*) the<br>differential effects of imidazolines and on  $(a)$  the complexity of agonist dose-response curves,<br>which sometimes consist of two components  $(25)$ ;  $(b)$  the adifferential effects of imidazolines and phenethylamines ta<br> $(295, 299)$ ;  $(c)$  the differences in types o which sometimes consist of two components  $(25)$ ;  $(b)$  the differential effects of imidazolines and phenethylamines  $(295, 299)$ ;  $(c)$  the differences in types of contractile responses  $(226)$ ; and  $(d)$  differences in the differential effects of imidazolines and phenethylamines (295, 299); (c) the differences in types of contractile responses (226); and  $(d)$  differences in the potencies of antagonists in blocking agonist- and nerve-mediate 95, 299); (c) the differences in types of contractile ansponses (226); and (d) differences in the potencies of effettagonists in blocking agonist- and nerve-mediated con-<br>actile responses (224, 226). values agonist has be

responses (226); and (*d*) differences in the potencies of examtagonists in blocking agonist- and nerve-mediated contractile responses (224, 226).<br>
Another imidazoline agonist has been used to obtain ravidence for the exi antagonists in blocking agonist- and nerve-mediated con-<br>tractile responses (224, 226). We can be also described by the antiomediate revidence for the existence of discrete subtypes of  $\alpha_1$ -<br>adrenergic receptors. Sgd 10 Another imidazoline agonist has been used to obtain ra<br>evidence for the existence of discrete subtypes of  $\alpha_1$ -<br>adrenergic receptors. Sgd 101/75 was shown to have<br>er markedly different intrinsic activities relative to n evidence for the existence of discrete subtypes of  $\alpha_1$ -<br>adrenergic receptors. Sgd 101/75 was shown to have<br>markedly different intrinsic activities relative to norepi-<br>nephrine in activating contraction of different smo adrenergic receptors. Sgd 101/75 was shown to have<br>markedly different intrinsic activities relative to norepi-<br>nephrine in activating contraction of different smooth<br>muscle preparations (157). Coates et al. (62) showed tha

much higher affinity for norepinephrine (a lower func-<br>  $\frac{1}{2}$  However, further analysis of the receptors mediating<br>
tional  $K_a$  value) and other phenethylamine agonists than<br>
is found in other tissues (24, 181, 241, 2 onists of different structural classes might be explained Grath (229) obtained similar results with selective an-<br>by the existence of two different types of  $\alpha_1$ -adrenergic tagonists. James and Leighton (161) directly e paring these two classes of drugs, but are complicated by receptors as norepinephrine. When the response to Sgd<br>the fact that most imidazoline-type agonists have a much 101/75 was abolished following partial receptor inact MAN<br>phenoxybenzamine preferentially reduced the effects of<br>Sgd 101/75 relative to those of norepinephrine in rat MAN<br>phenoxybenzamine preferentially reduced the effects of<br>Sgd 101/75 relative to those of norepinephrine in rat<br>anococcygeus muscle. When the effect of Sgd 101/75 was MAN<br>phenoxybenzamine preferentially reduced the effects of<br>Sgd 101/75 relative to those of norepinephrine in rat<br>anococcygeus muscle. When the effect of Sgd 101/75 was<br>abolished by pretreatment with high concentrations of phenoxybenzamine preferentially reduced the effects of Sgd 101/75 relative to those of norepinephrine in rat anococcygeus muscle. When the effect of Sgd 101/75 was abolished by pretreatment with high concentrations of phen phenoxybenzamine preferentially reduced the effects of Sgd 101/75 relative to those of norepinephrine in rat anococcygeus muscle. When the effect of Sgd 101/75 was abolished by pretreatment with high concentrations of phen Sgd 101/75 relative to those of norepinephrine in rat<br>anococcygeus muscle. When the effect of Sgd 101/75 was<br>abolished by pretreatment with high concentrations of<br>phenoxybenzamine, norepinephrine could still activate a<br>con anococcygeus muscle. When the effect of Sgd 101/75 was<br>abolished by pretreatment with high concentrations of<br>phenoxybenzamine, norepinephrine could still activate a<br>contractile response in the continued presence of Sgd<br>101 abolished by pretreatment with high concentrations<br>phenoxybenzamine, norepinephrine could still activate<br>contractile response in the continued presence of S<br>101/75 (which should then be acting as a competiti<br>antagonist). S phenoxybenzamine, norephrephrine could still activate a<br>contractile response in the continued presence of Sgd<br>101/75 (which should then be acting as a competitive<br>antagonist). Similar results were obtained when benex-<br>tra 101/75 (which should then be acting as a competitive antagonist). Similar results were obtained when benex-<br>tramine was used as the alkylating agent (63). These<br>results suggested that rat anococcygeus muscle contained<br>two antagonist). Similar results were obtained when benex-<br>tramine was used as the alkylating agent (63). These<br>results suggested that rat anococcygeus muscle contained<br>two  $\alpha_1$ -adrenergic receptor subtypes, both of which w tramine was used as the alkylating agent (63). These<br>results suggested that rat anococcygeus muscle contained<br>two  $\alpha_1$ -adrenergic receptor subtypes, both of which were<br>activated by norepinephrine but only one of which w results suggested that rat anococcygeus muscle contained<br>two  $\alpha_1$ -adrenergic receptor subtypes, both of which were<br>activated by norepinephrine but only one of which was<br>activated by Sgd 101/75. The receptor sensitive to two  $\alpha_1$ -adrenergic receptor subtypes, both of which were<br>activated by norepinephrine but only one of which was<br>activated by Sgd 101/75. The receptor sensitive to Sgd<br>101/75 ( $\alpha_{1s}$ ) appeared to be preferentially inac activated by norepinephrine but only one of which was<br>activated by Sgd 101/75. The receptor sensitive to Sgd<br>101/75 ( $\alpha_{1s}$ ) appeared to be preferentially inactivated by<br>both phenoxybenzamine and benextramine (62, 63).<br> activated by Sgd 101/75. The receptor sensitive to Sgd 101/75  $(\alpha_{1s})$  appeared to be preferentially inactivated by both phenoxybenzamine and benextramine (62, 63). However, further analysis of the receptors mediating con 101/75  $(\alpha_{1s})$  appeared to be preferentially inactivated both phenoxybenzamine and benextramine (62, 6:<br>However, further analysis of the receptors mediation<br>traction of rat anococcygeus muscle has not suported this hypot both phenoxybenzamine and benextramine (62, 63).<br>However, further analysis of the receptors mediating<br>contraction of rat anococcygeus muscle has not sup-<br>ported this hypothesis. Kenakin (181) carefully exam-<br>ined the effec However, further analysis of the receptors mediating<br>contraction of rat anococcygeus muscle has not sup-<br>ported this hypothesis. Kenakin (181) carefully exam-<br>ined the effect of receptor alkylation on the responses to<br>an i contraction of rat anococcygeus muscle has not sup-<br>ported this hypothesis. Kenakin (181) carefully exam-<br>ined the effect of receptor alkylation on the responses to<br>an imidazoline (oxymetazoline) and a phenethylamine<br>(nore ported this hypothesis. Kenakin (181) carefully examined the effect of receptor alkylation on the responses to an imidazoline (oxymetazoline) and a phenethylamine (norepinephrine) in rat anococcygeus and vas deferens.<br>He f ined the effect of receptor alkylation on the responses to<br>an imidazoline (oxymetazoline) and a phenethylamine<br>(norepinephrine) in rat anococcygeus and vas deferens.<br>He found that the differential responsiveness to these<br>t an imidazoline (oxymetazoline) and a phenethylamine<br>(norepinephrine) in rat anococcygeus and vas deferens.<br>He found that the differential responsiveness to these<br>two drugs could be explained by different receptor re-<br>serve (norepinephrine) in rat anococcygeus and vas deferens.<br>He found that the differential responsiveness to these<br>two drugs could be explained by different receptor re-<br>serves, and that a variety of selective antagonists showe He found that the differential responsiveness to these<br>two drugs could be explained by different receptor re-<br>serves, and that a variety of selective antagonists showed<br>no differences in affinity for the receptors (181). M two drugs could be explained by different receptor reserves, and that a variety of selective antagonists showed<br>no differences in affinity for the receptors (181). Mc-<br>Grath (229) obtained similar results with selective an serves, and that a variety of selective antagonists showed<br>no differences in affinity for the receptors (181). Mc-<br>Grath (229) obtained similar results with selective an-<br>tagonists. James and Leighton (161) directly examin no differences in affinity for the receptors (181). Mc-<br>Grath (229) obtained similar results with selective an-<br>tagonists. James and Leighton (161) directly examined<br>the effect of Sgd 101/75 on rat anococcygeus muscle and<br> Grath (229) obtained similar results with selective antagonists. James and Leighton (161) directly examined<br>the effect of Sgd 101/75 on rat anococcygeus muscle and<br>showed clearly that this drug was activating the same<br>rece tagonists. James and Leighton (161) directly examin<br>the effect of Sgd 101/75 on rat anococcygeus muscle a<br>showed clearly that this drug was activating the san<br>receptors as norepinephrine. When the response to S<br>101/75 was the effect of Sgd 101/75 on rat anococcygeus muscle and<br>showed clearly that this drug was activating the same<br>receptors as norepinephrine. When the response to Sgd<br>101/75 was abolished following partial receptor inacti-<br>va receptors as norepinephrine. When the response to Sgd 101/75 was abolished following partial receptor inactivation, this compound could competitively antagonize the response to norepinephrine with a potency similar to its vation, this compound could competitively antagonize<br>the response to norepinephrine with a potency similar to<br>its potency in activating the receptors. James and Leigh-<br>ton (161) suggested that previous results had been con vation, this compound could competitively antagonize<br>the response to norepinephrine with a potency similar to<br>its potency in activating the receptors. James and Leigh-<br>ton (161) suggested that previous results had been con the response to norepinephrine with a potency similar its potency in activating the receptors. James and Leighton (161) suggested that previous results had been cor fused by technical problems, such as insufficient time or its potency in activating the receptors. James and Leigton (161) suggested that previous results had been cofused by technical problems, such as insufficient time drug equilibration with tissue. Although this was original ton (161) suggested that previous results had been confused by technical problems, such as insufficient time of drug equilibration with tissue. Although this was originally thought to be one of the first pharmacological d fused by technical problems, such as insufficient time of<br>drug equilibration with tissue. Although this was origi-<br>nally thought to be one of the first pharmacological<br>distinctions between true  $\alpha_1$ - (not  $\alpha_2$ -like) a drug equilibration with tissue. Although this was originally thought to be one of the first pharmacological distinctions between true  $\alpha_1$ - (not  $\alpha_2$ -like) adrenergic receptors in different tissues, it is now clear th nally thought to be one of the first phare<br>distinctions between true  $\alpha_1$ - (not  $\alpha_2$ -like)<br>receptors in different tissues, it is now cle<br>differences were related to the various technic<br>involved in using agonists discu distinctions between true  $\alpha_1$ - (not  $\alpha_2$ -like) adrenergic<br>receptors in different tissues, it is now clear that the<br>differences were related to the various technical problems<br>involved in using agonists discussed above

differences were related to the various technical problems<br>involved in using agonists discussed above.<br>The studies suggesting heterogeneity between the  $\alpha$ -<br>adrenergic receptors causing contractile responses in aor-<br>tae involved in using agonists discussed above.<br>The studies suggesting heterogeneity between the  $\alpha$ -<br>adrenergic receptors causing contractile responses in aor-<br>tae from different species discussed above led Ruffolo<br>and Wadd The studies suggesting heterogeneity between the  $\alpha$ -<br>adrenergic receptors causing contractile responses in aor-<br>tae from different species discussed above led Ruffolo<br>and Waddell (296) to determine the affinities and re adrenergic receptors causing contractile responses in aortae from different species discussed above led Ruffolo<br>and Waddell (296) to determine the affinities and relative<br>efficacies of a series of imidazoline agonists in r tae from different species discussed above led Ruffolo and Waddell (296) to determine the affinities and relative efficacies of a series of imidazoline agonists in rat and rabbit aortae. They found that the affinities of t and Waddell (296) to determine the affinities and relative<br>efficacies of a series of imidazoline agonists in rat and<br>rabbit aortae. They found that the affinities of the drugs<br>varied substantially between the two tissues. efficacies of a series of imidazoline agonists in rat and rabbit aortae. They found that the affinities of the dru<br>varied substantially between the two tissues. In fact, t<br>rank order of affinities was exactly opposite for rabbit aortae. They found that the affinities of the drugs<br>varied substantially between the two tissues. In fact, the<br>rank order of affinities was exactly opposite for the<br>receptors in rat and rabbit aortae. Similarly, lar varied substantially between the two tissues. In fact, the rank order of affinities was exactly opposite for the receptors in rat and rabbit aortae. Similarly, large differences in the efficacies of these compounds relativ rank order of affinities was exactly opposite for the receptors in rat and rabbit aortae. Similarly, large differences in the efficacies of these compounds relative to norepinephrine were observed in the two tissues (296). receptors in rat and rabbit aortae. Similarly, large differences in the efficacies of these compounds relative to norepinephrine were observed in the two tissues (296).<br>Clonidine was about 100-fold more potent in binding t ences in the efficacies of these compounds relative to norepinephrine were observed in the two tissues (296).<br>Clonidine was about 100-fold more potent in binding to the receptors in rat than rabbit aorta, although it had s

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 $\alpha_1$ -ADRENERGIC RECEI<br>oxymetazoline was only slightly more potent in binding<br>to the receptors in rabbit than rat aorta, but had an  $\alpha_1$ -ADRENERGIC RECEPT<br>oxymetazoline was only slightly more potent in binding<br>to the receptors in rabbit than rat aorta, but had an<br>almost 20-fold greater efficacy in rabbit aorta (296).  $\alpha_1$ -ADRENERGIC RECT and almost 20-fold greater efficacy in rabbit aorta, but had an almost 20-fold greater efficacy in rabbit aorta (296).<br>Similar conclusions were reached by Digges and Sumoxymetazoline was only slightly more potent in bindin<br>to the receptors in rabbit than rat aorta, but had a<br>almost 20-fold greater efficacy in rabbit aorta (296)<br>Similar conclusions were reached by Digges and Sum<br>mers (88), oxymetazoline was only slightly more potent in binding<br>to the receptors in rabbit than rat aorta, but had an<br>almost 20-fold greater efficacy in rabbit aorta (296).<br>Similar conclusions were reached by Digges and Sum-<br>mers ( to the receptors in rabbit than rat aorta, but had an almost 20-fold greater efficacy in rabbit aorta (296).<br>Similar conclusions were reached by Digges and Summers (88), who compared contractile responses in rat aorta and affinity and steader efficing in fability and (200).<br>Similar conclusions were reached by Digges and Summers (88), who compared contractile responses in rat<br>aorta and rat portal vein. These authors found that the<br>affinity o Similar conclusions were reached by Digges and Summers (88), who compared contractile responses in rat<br>aorta and rat portal vein. These authors found that the<br>affinity of clonidine was approximately 20-fold higher in<br>contr mers (88), who compared contractile responses in rat<br>aorta and rat portal vein. These authors found that the<br>affinity of clonidine was approximately 20-fold higher in<br>contracting aorta than portal vein, while the affinity aorta and rat portal vein. These authors found that the affinity of clonidine was approximately 20-fold higher in contracting aorta than portal vein, while the affinity for oxymetazoline was about 20-fold lower in contract affinity of clonidine was approximately 20-fold higher is<br>contracting aorta than portal vein, while the affinity for<br>symetazoline was about 20-fold lower in contractine<br>aorta than portal vein (88). However, the  $K_a$  value contracting aorta than portal vein, while the affinity in oxymetazoline was about 20-fold lower in contractive aorta than portal vein (88). However, the  $K_a$  values is both clonidine and oxymetazoline in rat aorta detaini oxymetazoline was about 20-fold lower in contracting<br>aorta than portal vein (88). However, the  $K_a$  values for<br>both clonidine and oxymetazoline in rat aorta deter-<br>mined by Digges and Summers (1.3 and 15  $\mu$ M, respec-<br>ti both clonidine and oxymetazoline in rat aorta deter-<br>mined by Digges and Summers (1.3 and 15  $\mu$ M, respec-<br>tively) were about 20-fold higher than those found by<br>Ruffolo and Waddell (296) in the same tissue (0.04 and<br>0.7 both clonidine and oxymetazoline in rat aorta deter-<br>mined by Digges and Summers (1.3 and 15  $\mu$ M, respec-<br>tively) were about 20-fold higher than those found by<br>Ruffolo and Waddell (296) in the same tissue (0.04 and<br>0.7 mined by Digges and Summers (1.3 and 15  $\mu$ M, respectively) were about 20-fold higher than those found by Ruffolo and Waddell (296) in the same tissue (0.04 and 0.7  $\mu$ M, respectively). The reason for this discrepancy i tively) were about 20-fold higher than those found by<br>Ruffolo and Waddell (296) in the same tissue (0.04 and<br>0.7  $\mu$ M, respectively). The reason for this discrepancy is<br>not clear, but could be related to animal or techni Ruffolo and Waddell (296) in the same tissue (0.04 and 0.7  $\mu$ M, respectively). The reason for this discrepancy is not clear, but could be related to animal or technical differences between laboratories. However, these s 0.7  $\mu$ M, respectively). The reason for this discrepancy inot clear, but could be related to animal or technice differences between laboratories. However, these studies upport the hypothesis that the  $\alpha_1$ -adrenergic re erties. Ferences between laboratories. However, these studies<br>pport the hypothesis that the  $\alpha_1$ -adrenergic receptors<br>different tissues have different pharmacological prop-<br>ries.<br>Similar results have been obtained in comparison

support the hypothesis that the  $\alpha_1$ -adrenergic receptors<br>in different tissues have different pharmacological prop-<br>erties.<br>Similar results have been obtained in comparison of<br>the properties of the  $\alpha_1$ -adrenergic rec in different tissues have different pharmacological properties.<br>
Similar results have been obtained in comparison of rest<br>
the properties of the  $\alpha_1$ -adrenergic receptors mediating to to<br>
contraction of the ear artery a erties. The Similar results have been obtained in comparison of rest<br>the properties of the  $\alpha_1$ -adrenergic receptors mediating to origin<br>contraction of the ear artery and thoracic aorta of the<br>rabbit (276, 277). Followi Similar results have been obtained in comparison of<br>the properties of the  $\alpha_1$ -adrenergic receptors mediating<br>contraction of the ear artery and thoracic aorta of the<br>rabbit (276, 277). Following previous reports that th contraction of the ear artery and thoracic aorta of the rabbit (276, 277). Following previous reports that the affinities for agonists were substantially higher in rabbit aorta than in other tissues (see above), Purdy and contraction of the ear artery and thoracic aorta of the<br>rabbit (276, 277). Following previous reports that the<br>affinities for agonists were substantially higher in rabbit<br>water in the affinity of norepinephrine in<br>pecky s rabbit (276, 277). Following previous reports that the affinities for agonists were substantially higher in rabbit aorta than in other tissues (see above), Purdy and Stupecky showed that the affinity of norepinephrine in and the sixtence of two different receptor sub-<br>affinities for agonists were substantially higher in rabbit<br>aorta than in other tissues (see above), Purdy and Stu-<br>pecky showed that the affinity of norepinephrine in<br>activ aorta than in other tissues (see above), Purdy and Stu-<br>pecky showed that the affinity of norepinephrine in<br>activating contractile responses ( $K_a$  values) varied by<br>more than 30-fold between rabbit ear artery ( $4 \mu$ M) and pecky showed that the affinity of norepinephrine in<br>activating contractile responses  $(K_a$  values) varied by<br>more than 30-fold between rabbit ear artery  $(4 \mu M)$  and<br>aorta  $(0.1 \mu M)$ .  $K_a$  values for epinephrine varied by activating contractile responses  $(K_a$  values)<br>more than 30-fold between rabbit ear artery (<br>aorta (0.1  $\mu$ M).  $K_a$  values for epinephrine varia<br>fold, while  $K_a$  values for clonidine and methoxa<br>not different between the *2. Propertional S0-fold between rabbit ear artery*  $(4 \mu M)$  and *Bev*<br>*2. Receptor microenvironment.* When efficacies and values for approximate were the tissues (276, 277).<br>2. *Receptor microenvironment*. When efficacie

**According the U.S. Assumed in the V.200-** fold, while  $K_a$  values for clonidine and methoxamine were<br>
not different between the tissues (276, 277).<br>
2. *Receptor microenvironment*. When efficacies and  $K_a$  values for ago fold, while  $K_a$  values for clonidine and methoxamine were<br>not different between the tissues (276, 277).<br>2. Receptor microenvironment. When efficacies and<br> $K_a$  values for agonists are carefully determined following<br>partia not different between the tissues (276, 277).<br>
2. Receptor microenvironment. When efficacies and<br>  $K_a$  values for agonists are carefully determined following<br>
partial receptor inactivation, significant differences be-<br>
tw 2. Receptor microenvironment. When efficacies and  $K_a$  values for agonists are carefully determined following partial receptor inactivation, significant differences between these parameters in different tissues are genera partial receptor inactivation, significant differences be-<br>tween these parameters in different tissues are generally<br>thought to reflect the existence of pharmacologically<br>distinct receptor subtypes. Recently, however, Bev partial receptor inactivation, significant differences be-<br>tween these parameters in different tissues are generally<br>thought to reflect the existence of pharmacologically<br>distinct receptor subtypes. Recently, however, Beva tween these parameters in different tissues are generally<br>thought to reflect the existence of pharmacologically<br>distinct receptor subtypes. Recently, however, Bevan and<br>colleagues have proposed that agonist affinity for a thought to reflect the existence of pharmacologically<br>distinct receptor subtypes. Recently, however, Bevan and<br>colleagues have proposed that agonist affinity for a re<br>ceptor is not an intrinsic property of the receptor mol ceptor is not an intrinsic property of the receptor molecule, but may vary depending on the tissue environment<br>in which the receptor is found. Bevan et al. (28) deter-<br>mined 50% effective concentration ( $EC_{50}$ ) and  $K_a$  colleagues have proposed that agonist affinity for a receptor is not an intrinsic property of the receptor mole-<br>cule, but may vary depending on the tissue environment<br>in which the receptor is found. Bevan et al. (28) det ceptor is not an intrinsic property of the receptor mole-<br>cule, but may vary depending on the tissue environment<br>in which the receptor is found. Bevan et al. (28) deter-<br>mined 50% effective concentration (EC<sub>50</sub>) and  $K_a$ cule, but may vary depending on the tissue environment<br>in which the receptor is found. Bevan et al. (28) deter-<br>inding drugs. Only covalent modifications of receptor<br>mined 50% effective concentration (EC<sub>50</sub>) and  $K_a$  val mined 50% effective concentration (EC<sub>50</sub>) and  $K_a$  values<br>for norepinephrine in 12 rabbit arteries and found that<br>there was more than a 200-fold difference between the<br> $K_a$  values determined in different arteries. Intere for norepinephrine in 12 rabbit arteries and found there was more than a 200-fold difference between  $K_a$  values determined in different arteries. Interesting the  $K_a$  values correlated strongly with the  $EC_{50}$  values de  $K_a$  values determined in different arteries. Interestingly, onists. The binding constant for an antagonist has been<br>the  $K_a$  values correlated strongly with the  $EC_{50}$  values generally shown to be the same for a particu  $K_a$  values determined in different arteries. Interestingly, onis<br>the  $K_a$  values correlated strongly with the  $EC_{50}$  values generated before partial receptor inactivation, suggest-<br>ing that the potency of norepinephrine the  $K_a$  values correlated strongly with the  $EC_{50}$  values<br>determined before partial receptor inactivation, suggest-<br>ing that the potency of norepinephrine is determined<br>mainly by differences in affinity for the receptor determined before partial receptor inactivation, suggest-<br>ing that the potency of norepinephrine is determined In<br>mainly by differences in affinity for the receptors in<br>condifferent tissues, rather than by differences in ing that the potency of norepinephrine is determined In<br>mainly by differences in affinity for the receptors in co<br>different tissues, rather than by differences in receptor su<br>reserve (fig. 6) (28). Less variation was foun mainly by differences in affinity for the receptors in different tissues, rather than by differences in receptor reserve (fig. 6) (28). Less variation was found in the  $K_a$  values for phenylephrine ( $\leq$ 20-fold). Some va different tissues, rather than by differences in receptor<br>reserve (fig. 6) (28). Less variation was found in the  $K_a$ <br>values for phenylephrine (<20-fold). Some variation was<br>found in the potency of the antagonist prazosin reserve (fig. 6) (28). Less variation was found in the  $K_a$  techniques to the study of receptors, it has been shown values for phenylephrine (<20-fold). Some variation was that the affinity of a receptor for an antagonist



3<br>
5<br>
5<br>
6<br>
pD<sub>2</sub><br>
FIG. 6. Correlation between  $-\log EC_{\infty} (pD_2)$  and  $-\log K_a (pK_A)$  for<br>
norepinephrine-induced contractions in 12 different rabbit arteries.<br>
The strong correlation suggests that agonist affinity may be prima FIG. 6. Correlation between  $-\log EC_{\omega} (pD_2)$  and  $-\log K_{\omega} (pK_A)$  for norepinephrine-induced contractions in 12 different rabbit arteries.<br>The strong correlation suggests that agonist affinity may be primarily responsible fo norepinephrine-induced contractions in 12 different rabbit arteries.<br>The strong correlation suggests that agonist affinity may be primarily<br>responsible for differences in the sensitivity of different blood vessels<br>to contr In the storm of the existence of two different blood vessels<br>to contraction by norepinephrine. From Bevan et al. (28) with permis-<br>ion.<br>supporting the existence of two different receptor sub-<br>types with different affinitie to contraction by norepinephrine. From Bevan et al. (28) with permission.

because of the impressive correlation between the obsupporting the existence of two different receptor sub-<br>types with different affinities for agonists, but existing<br>in different proportions in different arteries. However,<br>because of the impressive correlation between the supporting the existence of two different receptor sub-<br>types with different affinities for agonists, but existing<br>in different proportions in different arteries. However,<br>because of the impressive correlation between the types with different affinities for agonists, but existing<br>in different proportions in different arteries. However,<br>because of the impressive correlation between the ob-<br>served  $EC_{50}$  and the calculated  $K_a$ s in these ar in different proportions in different arteries. However, because of the impressive correlation between the observed  $EC_{50}$  and the calculated  $K_a$ s in these arteries, Bevan et al. (28) proposed that the affinity of a rec because of the impressive correlation between the observed  $EC_{50}$  and the calculated  $K_a$ s in these arteries, Bevan et al. (28) proposed that the affinity of a receptor for an agonist might be a locally regulated charact served  $EC_{50}$  and the calculated  $K_a$ s in these a<br>Bevan et al. (28) proposed that the affinity of a ifor an agonist might be a locally regulated chara<br>and is not necessarily constant across different<br>where receptors are Evan et al. (28) proposed that the affinity of a receptor an agonist might be a locally regulated characterist<br>d is not necessarily constant across different tissue<br>nere receptors are in different microenvironments.<br>These

for an agonist might be a locally regulated characteristic<br>
and is not necessarily constant across different tissues,<br>
where receptors are in different microenvironments.<br>
These data are very intriguing, although their in and is not necessarily constant across different tissues,<br>where receptors are in different microenvironments.<br>These data are very intriguing, although their inter-<br>pretation is far from clear. It has long been assumed by<br>p where receptors are in different microenvironments.<br>These data are very intriguing, although their inter-<br>pretation is far from clear. It has long been assumed by<br>pharmacologists that the affinity of a drug for its recepto These data are very intriguing, although their inter-<br>pretation is far from clear. It has long been assumed by<br>pharmacologists that the affinity of a drug for its receptor<br>is a physical constant dependent only on the struc pretation is far from clear. It has long been assumed by<br>pharmacologists that the affinity of a drug for its receptor<br>is a physical constant dependent only on the structure<br>of the drug and the structure of the receptor bin pharmacologists that the affinity of a drug for its receptor<br>is a physical constant dependent only on the structure<br>of the drug and the structure of the receptor binding site.<br>The local tissue environment in which the rec is a physical constant dependent only on the structure<br>of the drug and the structure of the receptor binding site.<br>The local tissue environment in which the receptor is<br>found will, of course, affect the ability of the rece of the drug and the structure of the receptor binding site.<br>The local tissue environment in which the receptor is<br>found will, of course, affect the ability of the receptor to<br>initiate a response. However, this factor has The local tissue environment in which the receptor is<br>found will, of course, affect the ability of the receptor to<br>initiate a response. However, this factor has been thought<br>to have little effect on the affinity of the rec found will, of course, affect the ability of the receptor to<br>initiate a response. However, this factor has been thought<br>to have little effect on the affinity of the receptor in<br>binding drugs. Only covalent modifications of initiate a response. However, this factor has been thought<br>to have little effect on the affinity of the receptor in<br>binding drugs. Only covalent modifications of receptor<br>structure would be expected to affect the kinetics to have little effect on the affinity of the receptor in binding drugs. Only covalent modifications of receptor structure would be expected to affect the kinetics of interactions between drugs and their receptor binding si interactions between drugs and their receptor binding<br>sites. This assumption has been well tested with antag-<br>onists. The binding constant for an antagonist has been<br>generally shown to be the same for a particular receptor sites. This assumption has been well tested with antagonists. The binding constant for an antagonist has been<br>generally shown to be the same for a particular receptor<br>type, regardless of the tissue in which it is found (8, 182).<br>In fact, differences in antagonist affinity con generally shown to be the same for a particular receptor<br>type, regardless of the tissue in which it is found (8, 182).<br>In fact, differences in antagonist affinity constants are<br>considered to be diagnostic of differences in type, regardless of the tissue in which it is found (8, 182).<br>In fact, differences in antagonist affinity constants are<br>considered to be diagnostic of differences in receptor<br>subtypes. Recently, with the application of bio In fact, differences in antagonist affinity constants are<br>considered to be diagnostic of differences in receptor<br>subtypes. Recently, with the application of biochemical<br>techniques to the study of receptors, it has been sho considered to be diagnostic of differences in receptor<br>subtypes. Recently, with the application of biochemical<br>techniques to the study of receptors, it has been shown<br>that the affinity of a receptor for an antagonist is no subtypes. Recently, with the application of biochemical techniques to the study of receptors, it has been shown

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104 The situation with agonists is much more complex. contra<br>
104 First, determination of agonist affinity constants in iso-MINE<br>The situation with agonists is much more complex.<br>First, determination of agonist affinity constants in iso-<br>lated tissues is much more difficult and dependent on MINNEMAN<br>The situation with agonists is much more complex. con<br>First, determination of agonist affinity constants in iso-<br>lated tissues is much more difficult and dependent on<br>assumptions about the specificity of alkylatin The situation with agonists is much more complex.<br>First, determination of agonist affinity constants in isolated tissues is much more difficult and dependent on<br>assumptions about the specificity of alkylating agents<br>and th The situation with agonists is much more complex.<br>First, determination of agonist affinity constants in isolated tissues is much more difficult and dependent on<br>assumptions about the specificity of alkylating agents<br>and th First, determination of agonist affinity constants in is<br>lated tissues is much more difficult and dependent as<br>assumptions about the specificity of alkylating agen<br>and the relationship of occupancy to response (18<br>which ha lated tissues is much more difficult and dependent on cease assumptions about the specificity of alkylating agents used and the relationship of occupancy to response (182) for which have been subjected to little experiment assumptions about the specificity of alkylating agents us<br>and the relationship of occupancy to response (182) for<br>which have been subjected to little experimental verifi-<br>fucation. Therefore there is still uncertainty abou and the relationship of occupancy to response (182<br>which have been subjected to little experimental verification. Therefore there is still uncertainty about the<br>accuracy and molecular interpretation of agonist affinity<br>con cation. Therefore there is still uncertainty about the accuracy and molecular interpretation of agonist affinity constants determined in this manner. It is equally difficult and complicated to determine agonist affinity co cation. Therefore there is still uncertainty about the accuracy and molecular interpretation of agonist affinity constants determined in this manner. It is equally difficult and complicated to determine agonist affinity co constants determined in this manner. It is equally difficult and complicated to determine agonist affinity constants in direct radioligand binding assays. The affinities of agonists in radioligand binding experiments are c constants determined in this manner. It is equally difficult and complicated to determine agonist affinity constants in direct radioligand binding assays. The affinities of agonists in radioligand binding experiments are c cult and complicated to determine agonist affinity constants in direct radioligand binding assays. The affinities more agonists in radioligand binding experiments are com-<br>monly found to be dependent on the experimental co stants in direct radioligand binding assays. The affinities more agonists in radioligand binding experiments are com-<br>monly found to be dependent on the experimental con-<br>ditions under which the binding is monitored. Much of agonists in radioligand binding experiments are com-<br>monly found to be dependent on the experimental con-<br>ditions under which the binding is monitored. Much of<br>this complexity is probably caused by the nature of<br>agonist monly found to be dependent on the experimental combitions under which the binding is monitored. Much this complexity is probably caused by the nature agonist-receptor interactions, since the agonist must ronly bind to the ditions under which the binding is monitored. Much<br>this complexity is probably caused by the nature<br>agonist-receptor interactions, since the agonist must n<br>only bind to the receptor, but must also induce a confor<br>mational this complexity is probably caused by the nature of agonist-receptor interactions, since the agonist must not only bind to the receptor, but must also induce a conformational change and activate a response. Many receptors, agonist-receptor interactions, since the agonist must not<br>only bind to the receptor, but must also induce a confor-<br>mational change and activate a response. Many recep-<br>tors, when occupied by agonist, associate with G prot only bind to the receptor, but must also induce a confor-<br>mational change and activate a response. Many recep-<br>tors, when occupied by agonist, associate with G proteins<br>within the membrane (see above), and the association mational change and activate a response. Many receptors, when occupied by agonist, associate with G proteins her within the membrane (see above), and the association of the agonist-bound receptor with the G protein greatly tors, when occupied by agonist, associate with G proteins<br>within the membrane (see above), and the association of<br>the agonist-bound receptor with the G protein greatly<br>reduces the dissociation rate of the agonist. GTP caus within the membrane (see above), and the association of note agonist-bound receptor with the G protein greatly for reduces the dissociation rate of the agonist. GTP causes the dissociation of the complex and speeds up ago the agonist-bound receptor with the G protein greatly<br>reduces the dissociation rate of the agonist. GTP causes<br>a dissociation of the complex and speeds up agonist<br>dissociation kinetics (114). Thus the apparent affinity of<br> reduces the dissociation rate of the agonist. GTP causes tiss<br>a dissociation of the complex and speeds up agonist con<br>dissociation kinetics (114). Thus the apparent affinity of (24<br>agonists can be influenced by the presenc a dissociation of the complex and speeds up agon<br>dissociation kinetics (114). Thus the apparent affinity<br>agonists can be influenced by the presence of G protein<br>guanine nucleotides, and other substances which c<br>influence association kinetics (114). Thus the apparent affinity onists can be influenced by the presence of G protein anine nucleotides, and other substances which calluence these interactions such as divalent cations.<br> $\alpha_1$ -Adre agonists can be influenced by the presence of G proteins, epotynine nucleotides, and other substances which can an influence these interactions such as divalent cations. as  $\alpha_1$ -Adrenergic receptors clearly exist in mul

guanine nucleotides, and other substances which can<br>influence these interactions such as divalent cations.<br> $\alpha_1$ -Adrenergic receptors clearly exist in multiple affinity<br>states an membrane preparations, and these affinity influence these interactions such as divalent cations. as  $\alpha_1$ -Adrenergic receptors clearly exist in multiple affin-<br>ity states in membrane preparations, and these affinity in<br>states are interconverted by nucleotides an  $\alpha_1$ -Adrenergic receptors clearly exist in multiple affin-<br>ity states in membrane preparations, and these affinity in o<br>states are interconverted by nucleotides and cations (38, It<br>66, 123, 160, 215, 311, 319, 335). It ity states in membrane preparations, and these affinity in states are interconverted by nucleotides and cations (38, 66, 123, 160, 215, 311, 319, 335). It is possible that these prodifferent affinity states are differentia states are interconverted by nucleotides and cations (38, 66, 123, 160, 215, 311, 319, 335). It is possible that these pidifferent affinity states are differentially involved in ta contractile responses in different tissue 66, 123, 160, 215, 311, 319, 335). It is possible that these different affinity states are differentially involved in contractile responses in different tissues. However, the differences between the high and low affinity different affinity states are differentially involved in taze<br>contractile responses in different tissues. However, the differences between the high and low affinity binding bind<br>states are usually less than 50-fold, subst contractile responses in different tissues. However, the differences between the high and low affinity binding states are usually less than 50-fold, substantially smaller than the differences in apparent  $K_{\alpha}$  values ob differences between the high and low affinity binding b<br>states are usually less than 50-fold, substantially smaller a<br>than the differences in apparent  $K_a$  values observed in I<br>different arteries (28). It is also difficul states are usually less than 50-fold, substantially smaller<br>than the differences in apparent  $K_a$  values observed in<br>different arteries (28). It is also difficult to understand<br>how the effect of receptor activation might than the differences in apparent  $K_a$  values observed in l<br>different arteries (28). It is also difficult to understand in<br>how the effect of receptor activation might be mediated<br>by different receptor affinity states in di different arteries (28). It is also difficult to understand how the effect of receptor activation might be mediate by different receptor affinity states in different tissue Our current understanding of the different affini how the effect of receptor activation might be mediated appeare<br>by different receptor affinity states in different tissues. agonist<br>Our current understanding of the different affinity states condition<br>is that they represen by different receptor affinity states in different tissues. ag<br>Our current understanding of the different affinity states<br>is that they represent free receptor (rapid agonist disso-<br>protein, low affinity) or receptor comple Our current understanding of the different affinity states<br>is that they represent free receptor (rapid agonist disso-<br>ciation, low affinity) or receptor complexed with a G<br>tiprotein (slow agonist dissociation, high affinit is that they represent free receptor (rapid agonist disso-<br>ciation, low affinity) or receptor complexed with a G<br>ion<br>protein (slow agonist dissociation, high affinity). Since of i<br>the interaction between the receptor and t ciation, low affinity) or receptor complexed with a  $G$  tion of specific <sup>126</sup>IBE binding to membrane preparations<br>protein (slow agonist dissociation, high affinity). Since of rat cerebral cortex. Scatchard analysis of <sup>1</sup> protein (slow agonist dissociation, high affinity). Since of rather interaction between the receptor and the G protein ing is probably the initial event in signal transduction, and petial activated receptors presumably hav the interaction between the receptor and the G protein is<br>is probably the initial event in signal transduction, and<br>all activated receptors presumably have to complex with<br>G proteins to activate their response, it is diffi is probably the initial event in signal transduct<br>all activated receptors presumably have to comp<br>G proteins to activate their response, it is dif<br>understand how this will differ in different tissue<br>either the receptor or *2. Complex with* proteins to activate their response, it is difficult to derstand how this will differ in different tissues unless ther the receptor or the G protein is different.<br>3. Comparison with binding studies. In fa G proteins to activate their response, it is difficult to understand how this will differ in different tissues unless either the receptor or the G protein is different.<br>3. Comparison with binding studies. In fact, when ag

either the receptor or the G protein is different.<br>3. Comparison with binding studies. In fact, when ag-<br>onist affinity constants have been compared using radi-<br>oligand binding methods, there has been little evidence<br>to s onist affinity constants have been compared using radi-<br>oligand binding methods, there has been little evidence<br>to support the differences in affinity between the  $\alpha_1$ -<br>adrenergic receptors in different tissues discusse oligand binding methods, there has been little evidence otlet of support the differences in affinity between the  $\alpha_1$ - no adrenergic receptors in different tissues discussed above. the Because of tissue limitations it i

contractile responses are examined. However, in large MAN<br>contractile responses are examined. However, in large<br>muscles like aorta, such studies can sometimes be suc-<br>cessful, particularly if high specific activity probes are MAN<br>contractile responses are examined. However, in large<br>muscles like aorta, such studies can sometimes be suc-<br>cessful, particularly if high specific activity probes are<br>used to label the receptors. The extremely high af contractile responses are examined. However, in large muscles like aorta, such studies can sometimes be successful, particularly if high specific activity probes are used to label the receptors. The extremely high affinity contractile responses are examined. However, in large<br>muscles like aorta, such studies can sometimes be suc-<br>cessful, particularly if high specific activity probes are<br>used to label the receptors. The extremely high affini muscles like aorta, such studies can sometimes be successful, particularly if high specific activity probes are used to label the receptors. The extremely high affinity for norepinephrine, which has been observed in many f cessful, particularly if high specific activity probes and to label the receptors. The extremely high affinit for norepinephrine, which has been observed in man functional studies on rabbit aorta (24, 276, 281, 313, 334) used to label the receptors. The extremely high affinity<br>for norepinephrine, which has been observed in many<br>functional studies on rabbit aorta (24, 276, 281, 313, 334),<br>has not been confirmed with radioligand binding tec functional studies on rabbit aorta (24, 276, 281, 313, 334),<br>has not been confirmed with radioligand binding tech-<br>niques. Two studies have reported direct labeling of  $\alpha_1$ -<br>adrenergic receptors with the high affinity r functional studies on rabbit aorta (24, 2'<br>has not been confirmed with radioliga<br>niques. Two studies have reported dire<br>adrenergic receptors with the high affi<br>antagonist  $^{125}I$ -{2-[ $\beta$ -(4-hydroxypher<br>methyl]tetralone} has not been confirmed with radioligand binding techniques. Two studies have reported direct labeling of  $\alpha_1$ -<br>adrenergic receptors with the high affinity radiolabeled<br>antagonist  $^{125}I$ -{2-{ $\beta$ -(4-hydroxyphenyl)ethyl niques. Two studies have reported direct labeling of  $\alpha_1$ <br>adrenergic receptors with the high affinity radiolabele<br>antagonist <sup>125</sup>I-{2-[ $\beta$ -(4-hydroxyphenyl)ethylamino<br>methyl]tetralone} (<sup>125</sup>IBE) (346, 365). Norepinep adrenergic receptors with the high affinity radiolabeled<br>antagonist <sup>125</sup>I-{2-[ $\beta$ -(4-hydroxyphenyl)ethylamino-<br>methyl]tetralone} (<sup>125</sup>IBE) (346, 365). Norepinephrine<br>shows apparent  $K_d$  values of 4  $\mu$ M and 11.5  $\mu$ M antagonist <sup>125</sup>I-{2-[ $\beta$ -(4-hydroxyphenyl)ethylamino-<br>methyl]tetralone} (<sup>125</sup>IBE) (346, 365). Norepinephrine<br>shows apparent  $K_d$  values of 4  $\mu$ M and 11.5  $\mu$ M in com-<br>peting for these binding sites (346, 365). This shows apparent  $K_d$  values of  $4 \mu M$  and 11.5  $\mu M$  in com-<br>pering for these binding sites (346, 365). This reflects a<br>substantially lower affinity than the  $K_d$  values which<br>have been determined in functional studies. It shows apparent  $K_d$  values of 4  $\mu$ M and 11.5  $\mu$ M in competing for these binding sites (346, 365). This reflects a substantially lower affinity than the  $K_a$  values which have been determined in functional studies. It peting for these binding sites (346, 365). This reflects a substantially lower affinity than the  $K_a$  values which have been determined in functional studies. It is also much closer to the  $K_a$  values reported in rabbit e substantially lower affinity than the  $K_a$  values which<br>have been determined in functional studies. It is also<br>much closer to the  $K_a$  values reported in rabbit ear artery<br>(4  $\mu$ M; 277) and many other tissues (244) than have been determined in functional studies. It is also<br>much closer to the  $K_a$  values reported in rabbit ear artery<br>(4  $\mu$ M; 277) and many other tissues (244) than in rabbit<br>aorta (0.1  $\mu$ M; 277). The  $K_a$  value for nor much closer to the  $K_a$  values reported in rabbit ear artery (4  $\mu$ M; 277) and many other tissues (244) than in rabbit aorta (0.1  $\mu$ M; 277). The  $K_d$  value for norepinephrine in binding to  $\alpha_1$ -adrenergic receptors i (4  $\mu$ M; 277) and many other tissues (244) than in rabbit<br>aorta (0.1  $\mu$ M; 277). The  $K_d$  value for norepinephrine in<br>binding to  $\alpha_1$ -adrenergic receptors in rabbit aorta is also<br>not substantially different from the aorta (0.1  $\mu$ M; 277). The  $K_d$  value for norepinephrine is binding to  $\alpha_1$ -adrenergic receptors in rabbit aorta is als not substantially different from the  $K_d$  values reporte for norepinephrine from binding studies i binding to  $\alpha_1$ -adrenergic receptors in rabbit aorta is also<br>not substantially different from the  $K_d$  values reported<br>for norepinephrine from binding studies in many other<br>tissues, taking into account differences in ex not substantially different from the  $K_d$  values reported<br>for norepinephrine from binding studies in many other<br>tissues, taking into account differences in experimental<br>conditions such as temperature, nucleotides, and cat tissues, taking into account differences in experimental<br>conditions such as temperature, nucleotides, and cations<br>(244). Similarly, differences in functional  $K_a$  values for<br>epinephrine between rabbit aorta (0.03  $\mu$ M) a tissues, taking into account differences in experimental<br>conditions such as temperature, nucleotides, and cations<br>(244). Similarly, differences in functional  $K_a$  values for<br>epinephrine between rabbit aorta (0.03  $\mu$ M) a conditions such as temperature, nucleotides, and cational  $K_a$  values<br>epinephrine between rabbit aorta  $(0.03 \mu)$  and<br>artery  $(6 \mu)$ ; 277) are also not observed in direct bind<br>assays of membranes from rabbit aorta, where (244). Similarly, differences in functional  $K_a$  values for epinephrine between rabbit aorta (0.03  $\mu$ M) and ear artery (6  $\mu$ M; 277) are also not observed in direct binding assays of membranes from rabbit aorta, where artery (6  $\mu$ M; 277) are also not observed in direct binding<br>assays of membranes from rabbit aorta, where epineph-<br>rine had a  $K_d$  of 4  $\mu$ M (346) or 9  $\mu$ M (365), similar to that<br>in other tissues (244).<br>It would be of tery (6  $\mu$ M; 277) are also not observed in direct binding<br>says of membranes from rabbit aorta, where epineph-<br>ne had a  $K_d$  of 4  $\mu$ M (346) or 9  $\mu$ M (365), similar to that<br>other tissues (244).<br>It would be of great in

either the receptor or the G protein is different. binding sites with different affinities for oxymetazoline 3. Comparison with binding studies. In fact, when ag-<br>onist affinity constants have been compared using radi-<br>on assays of membranes from rabbit aorta, where epine<br>
rine had a  $K_d$  of 4  $\mu$ M (346) or 9  $\mu$ M (365), similar to th<br>
in other tissues (244).<br>
It would be of great interest to determine the bindi<br>
properties of imidazolin rine had a  $K_d$  of 4  $\mu$ M (346) or 9  $\mu$ M (365), similar to that<br>in other tissues (244).<br>It would be of great interest to determine the binding<br>properties of imidazolines such as clonidine and oxyme-<br>tazoline at the  $\alpha$ in other tissues (244).<br>It would be of great interest to determine the binding<br>properties of imidazolines such as clonidine and oxyme-<br>tazoline at the  $\alpha_1$ -adrenergic receptor binding sites in<br>different smooth muscles, It would be of great interest to determine the binding<br>properties of imidazolines such as clonidine and oxyme-<br>tazoline at the  $\alpha_1$ -adrenergic receptor binding sites in<br>different smooth muscles, particularly rat aorta. properties of imidazolines such as clonidine and oxymetazoline at the  $\alpha_1$ -adrenergic receptor binding sites in different smooth muscles, particularly rat aorta. Direct binding studies on rat aorta have been reported (8 tazoline at the  $\alpha_1$ -adrenergic receptor binding sites in different smooth muscles, particularly rat aorta. Direct binding studies on rat aorta have been reported (82, 173), although the affinities for imidazolines were different smooth muscles, particularly rat aorta. Direct<br>binding studies on rat aorta have been reported (82, 173),<br>although the affinities for imidazolines were not studied.<br>In examining the properties of  $\alpha_1$ -adrenerg binding studies on rat aorta have been reported (82, 173),<br>although the affinities for imidazolines were not studied.<br>In examining the properties of  $\alpha_1$ -adrenergic receptors<br>in rat brain labeled by <sup>125</sup>IBE, however, o although the affinities for imidazolines were not studied.<br>In examining the properties of  $\alpha_1$ -adrenergic receptors<br>in rat brain labeled by  $^{125}$ IBE, however, oxymetazoline<br>appeared to behave differently than any of t In examining the properties of  $\alpha_1$ -adrenergic receptors<br>in rat brain labeled by <sup>125</sup>IBE, however, oxymetazoline<br>appeared to behave differently than any of the other<br>agonists or antagonists studied (239). Under the bin in rat brain labeled by  $^{125}$ IBE, however, oxymetazoli<br>appeared to behave differently than any of the oth<br>agonists or antagonists studied (239). Under the bindi<br>conditions used, all agonists and antagonists except of<br>ym appeared to behave differently than any of the other<br>agonists or antagonists studied (239). Under the binding<br>conditions used, all agonists and antagonists except ox-<br>ymetazoline had Hill coefficients close to 1.0 for inh agonists or antagonists studied (239). Under the bindin<br>conditions used, all agonists and antagonists except or<br>ymetazoline had Hill coefficients close to 1.0 for inhib-<br>tion of specific  $^{125}$ IBE binding to membrane pre conditions used, all agonists and antagonists except ox<br>ymetazoline had Hill coefficients close to 1.0 for inhibi<br>tion of specific <sup>125</sup>IBE binding to membrane preparation<br>of rat cerebral cortex. Scatchard analysis of <sup>125</sup> ymetazoline had Hill coefficients close to 1.0 for inhibition of specific <sup>125</sup>IBE binding to membrane preparations of rat cerebral cortex. Scatchard analysis of <sup>125</sup>IBE binding in the presence of different concentrations tion of specific  $^{125}$ IBE binding to membrane preparations<br>of rat cerebral cortex. Scatchard analysis of  $^{125}$ IBE bind-<br>ing in the presence of different concentrations of com-<br>peting drugs showed that, although other of rat cerebral cortex. Scatchard analysis of <sup>125</sup>IBE bind-<br>ing in the presence of different concentrations of com-<br>peting drugs showed that, although other agonists and<br>antagonists caused a purely competitive inhibition, ing in the presence of different concentrations of competing drugs showed that, although other agonists and antagonists caused a purely competitive inhibition, the inhibition caused by oxymetazoline appeared to consist of antagonists caused a purely competitive inhibition, the antagonists caused a purely competitive inhibition, the inhibition caused by oxymetazoline appeared to consist<br>of two components (fig. 7), consistent with two different<br>binding sites with different affinities for oxymetazo inhibition caused by oxymetazoline appeared to consist<br>of two components (fig. 7), consistent with two different<br>binding sites with different affinities for oxymetazoline<br>(239). Similar results were obtained in binding stu (239). Similar results were obtained in binding studies binding sites with different affinities for oxymetazoline (239). Similar results were obtained in binding studies on membranes from rat vas deferens (245). However, other imidazolines such as clonidine and tramazoline did (239). Similar results were obtained in binding studies<br>on membranes from rat vas deferens (245). However,<br>other imidazolines such as clonidine and tramazoline did<br>not show such differences (239, 245). The relationship of on membranes from rat vas deferens  $(245)$ . However<br>other imidazolines such as clonidine and tramazoline di<br>not show such differences  $(239, 245)$ . The relationship o<br>these differences to the different  $K_a$  values found i other imidazolines such as clonidine and tramazoline did<br>not show such differences (239, 245). The relationship of<br>these differences to the different  $K_a$  values found in<br>different smooth muscles remains to be determined.

**a**spet



**the antagonist indoramin and the agonist norepinephrine show simple competitive behavior, while oxymetazoline distinguishes between two<br>binding sites with different affinities.**  $B/F$ **, bound/free. From Minneman (239) with** FIG. 7. Complex behavior of oxymetazoline in competing for specific <sup>125</sup>IBE binding sites in membranes from rat cerebral cortex. Note that the antagonist indoramin and the agonist norepinephrine show simple competitive be FIG. 7. Complex behavior of oxymetazoline in competing for sp<br>the antagonist indoramin and the agonist norepinephrine show si<br>binding sites with different affinities.  $B/F$ , bound/free. From Minn<br>types of  $\alpha_1$ -adrenergic

FIG. *I*. Complex behavior of oxymetazointe in competities the antagonist indoramin and the agonist norepinephrino<br>binding sites with different affinities.  $B/F$ , bound/free. Free types of  $\alpha_1$ -adrenergic receptor bindin ethyl)aminomethyl-1,4-benzodioxane HCl (WB 4101)<br>discussed below.<br>discussed by the antagonist 2-(2,6-dimethoxyphenoxy-<br>ethyl)aminomethyl-1,4-benzodioxane HCl (WB 4101)<br>discussed below. types of  $\alpha_1$ -adree<br>guished by the ethyl)aminomethy<br>discussed below.<br>Colucci et al. (6 bes of  $\alpha_1$ -adrenergic receptor binding sites dist<br>ished by the antagonist 2-(2,6-dimethoxypheno<br>hyl)aminomethyl-1,4-benzodioxane HCl (WB 41<br>scussed below.<br>Colucci et al. (66) raised the possibility that contrac-<br>on of

ethyl)aminomethyl-1,4-benzodioxane HCl (WB 4101)<br>discussed below.<br>Colucci et al. (66) raised the possibility that contrac-<br>tion of rabbit aorta might be mediated by the high agonist<br>affinity binding state of the receptor ( ethyl)aminomethyl-1,4-benzodioxane HCI (WB 4101<br>discussed below.<br>Colucci et al. (66) raised the possibility that contraction of rabbit aorta might be mediated by the high agonis<br>affinity binding state of the receptor (pres discussed below.<br>
Colucci et al. (66) raised the possibility that contrac-<br>
tion of rabbit aorta might be mediated by the high agonist<br>
affinity binding state of the receptor (presumably com-<br>
plexed with a G protein). Th Colucci et al. (66) raised the possibility that contraction of rabbit aorta might be mediated by the high agonist<br>affinity binding state of the receptor (presumably com-<br>plexed with a G protein). These authors showed that tion of rabbit aorta might be mediated by the high agonist<br>
affinity binding state of the receptor (presumably com-<br>
plexed with a G protein). These authors showed that the<br>
binding of norepinephrine to membranes from cul affinity binding state of the receptor (presumably com-<br>plexed with a G protein). These authors showed that the<br>binding of norepinephrine to membranes from cultured<br>rabbit aorta smooth muscle cells was best described by a binding of norepinephrine to membranes from cultured<br>binding of norepinephrine to membranes from cultured<br>rabbit aorta smooth muscle cells was best described by a<br>two-site model in which about half of the sites had a  $K_d$ membranes) and stimulation of <sup>45</sup>Ca efflux (determined intriguing differences between the affinities and efficarabbit aorta smooth muscle cells was best described by a<br>two-site model in which about half of the sites had a  $K_d$ <br>of 0.1  $\mu$ M and the other half had a  $K_d$  of 7  $\mu$ M. The<br>relationship between receptor occupancy (deter two-site model in which about half of the sites had a  $K_d$ <br>of 0.1  $\mu$ M and the other half had a  $K_d$  of 7  $\mu$ M. The<br>relationship between receptor occupancy (determined in<br>membranes) and stimulation of <sup>45</sup>Ca efflux (det of 0.1  $\mu$ **M** and the other half had a  $K_d$  of 7  $\mu$ M. The relationship between receptor occupancy (determined in membranes) and stimulation of <sup>45</sup>Ca efflux (determined in whole cells) was linear for the high affinity relationship between receptor occupancy (determined in The membranes) and stimulation of <sup>45</sup>Ca efflux (determined intr in whole cells) was linear for the high affinity sites, but convex for the low affinity sites. However membranes) and stimulation of <sup>4</sup>°Ca efflux (determined<br>in whole cells) was linear for the high affinity sites, but<br>convex for the low affinity sites. However, these authors<br>also showed that, following receptor alkylation in whole cells) was linear for the high affinity sites, but<br>
convex for the low affinity sites. However, these authors<br>
also showed that, following receptor alkylation by<br>
fur<br>
phenoxybenzamine, there was a large loss of convex for the low affinity sites. However, these author also showed that, following receptor alkylation b<br>phenoxybenzamine, there was a large loss of receptot<br>binding sites but little loss of receptor-stimulated <sup>45</sup>C<br>eff phenoxybenzamine, there was a large loss of receptor<br>binding sites but little loss of receptor-stimulated <sup>45</sup>Ca<br>efflux, indicating a receptor reserve for this phenomenon.<br>In the presence of a receptor reserve, the occupan binding sites but little loss of receptor-stimulated <sup>45</sup>Ca tor inactivation with highly reactive and potentially non-<br>efflux, indicating a receptor reserve for this phenomenon.<br>In the presence of a receptor reserve, the binding sites but little loss of receptor-stimula<br>efflux, indicating a receptor reserve for this phen<br>In the presence of a receptor reserve, the occeptors<br>response relationships will be convex (182, 29<br>the linear relation efflux, indicating a receptor reserve for this phenomenon. sp<br>In the presence of a receptor reserve, the occupancy-<br>response relationships will be convex (182, 292). Thus di<br>the linear relationship between norepinephrine-In the presence of a receptor reserve, the occupancy-<br>response relationships will be convex (182, 292). Thus<br>the linear relationship between norepinephrine-stimu-<br>lated  $Ca^{2+}$  efflux and occupation of the high affinity s response relationships will be convex (182, 292). Thus disc<br>the linear relationship between norepinephrine-stimu-<br>lated  $Ca^{2+}$  efflux and occupation of the high affinity state differ<br>of the receptor (66) may be fortuitou the linear relation<br>lated Ca<sup>2+</sup> efflux an<br>of the receptor (6<br>hand, there may be<br>not yet understand<br>Differences in th

Differences in the potencies and efficacies of agonists<br>in promoting  $\alpha_1$ -adrenergic receptor-mediated accumu-<br>lation of different second messenger substances have also hand, there may be some mechanistic relationship we do<br>
not yet understand.<br>
Differences in the potencies and efficacies of agonists<br>
in promoting  $\alpha_1$ -adrenergic receptor-mediated accumu-<br>
lation of different second me not yet understand.<br>
Differences in the potencies and efficacies of agonists<br>
in promoting  $\alpha_1$ -adrenergic receptor-mediated accumu-<br>
lation of different second messenger substances have also<br>
been reported. In liver an Differences in the potencies and efficacies of agonists<br>in promoting  $\alpha_1$ -adrenergic receptor-mediated accumulation of different second messenger substances have also<br>been reported. In liver and brain,  $\alpha_1$ -adrenergic in promoting  $\alpha_1$ -adrenergic receptor-mediated accumulation of different second messenger substances have also<br>been reported. In liver and brain,  $\alpha_1$ -adrenergic receptor<br>activation increases cyclic AMP accumulation a lation of different second messenger substances have also<br>been reported. In liver and brain,  $\alpha_1$ -adrenergic receptor<br>activation increases cyclic AMP accumulation and po-<br>tentiates the cyclic AMP response to activation been reported. In liver and brain,  $\alpha_1$ -adrenergic receptor<br>activation increases cyclic AMP accumulation and po-<br>tentiates the cyclic AMP response to activation of other<br>receptors, as well as increasing inositol phospha activation increases cyclic AMP accumulation and po-<br>tentiates the cyclic AMP response to activation of other<br>receptors, as well as increasing inositol phosphates (58,<br>76, 168, 302, 307). Morgan et al. (252) showed that t receptors, as well as increasing inositol phosphates (58, 76, 168, 302, 307). Morgan et al. (252) showed that there were some pharmacological differences between the  $\alpha_1$ -adrenergic receptors controlling cyclic AMP accu

THE binding sites in membranes from rat cerebral cortex. Note the<br>competitive behavior, while oxymetazoline distinguishes between to<br>(239) with permission.<br>tion and phosphorylase activation in rat liver. Similarly<br>Johnson differences between the analysis of the analysis of the anti-<br>
differences between the  $\alpha_1$ -adrenergic receptors increasing inositol phosphate and cyclic AMP accumulation From and phosphorylase activation in rat liver. Similarly,<br>Johnson and Minneman (168) showed pharmacological<br>differences between the  $\alpha_1$ -adrenergic receptors increas-<br>ing inositol phosphate and cyclic AMP accumulation tion and phosphorylase activation in rat liver. Similarly,<br>Johnson and Minneman (168) showed pharmacological<br>differences between the  $\alpha_1$ -adrenergic receptors increas-<br>ing inositol phosphate and cyclic AMP accumulation Johnson and Minneman (168) showed pharmacological<br>differences between the  $\alpha_1$ -adrenergic receptors increas-<br>ing inositol phosphate and cyclic AMP accumulation in<br>slices of rat cerebral cortex. In particular, the synthe differences between the  $\alpha_1$ -adrenergic receptors increasing inositol phosphate and cyclic AMP accumulation in slices of rat cerebral cortex. In particular, the synthetic phenethylamine agonists phenylephrine and methox ing inositol phosphate and cyclic AMP accumulation in<br>slices of rat cerebral cortex. In particular, the synthetic<br>phenethylamine agonists phenylephrine and methox-<br>amine had substantially higher intrinsic activities in<br>ac slices of rat cerebral cortex. In particular, the synthetiphenethylamine agonists phenylephrine and methoz<br>amine had substantially higher intrinsic activities i<br>activating inositol phosphate accumulation (50 to 60?<br>of nore phenethylamine agonists phenylephrine and metho<br>amine had substantially higher intrinsic activities<br>activating inositol phosphate accumulation (50 to 60<br>of norepinephrine) than in activating cyclic AMP acc<br>mulation (7 to 1 amine had substantially higher intrinsic activities is<br>activating inositol phosphate accumulation (50 to 60<br>of norepinephrine) than in activating cyclic AMP accumulation (7 to 19% of norepinephrine). Only one imid<br>zoline a activating inositol phosphate accumulation (50 to 60% of norepinephrine) than in activating cyclic AMP accumulation (7 to 19% of norepinephrine). Only one imidazoline agonist was studied, St 587, which had no measurable in (168). **EXERT BOUNDER SET image in membranes from rat crebral cortex. Note that "SpE binding sites in membranes from rat crebral cortex. Note that computitive behavior, while oxymetazoline distinguishes between two (239) with pe** 

of the receptor (66) may be fortuitous. On the other<br>hand, there may be some mechanistic relationship we do<br>not yet understand.<br>Differences in the potencies and efficacies of agonists<br>in promoting  $\alpha_1$ -adrenergic recept zoline agonist was studied, St 587, which had no measurable intrinsic activity for stimulating either response (168).<br>In their totality, these data suggest that there are intriguing differences between the affinities and cies of agonists at  $\alpha_1$ -adrenergic receptors in different (168).<br>In their totality, these data suggest that there are<br>intriguing differences between the affinities and effica-<br>cies of agonists at  $\alpha_1$ -adrenergic receptors in different<br>tissues. Most such data have so far been o In their totality, these data suggest that there are<br>intriguing differences between the affinities and effica-<br>cies of agonists at  $\alpha_1$ -adrenergic receptors in different<br>tissues. Most such data have so far been obtained intriguing differences between the affinities and efficies of agonists at  $\alpha_1$ -adrenergic receptors in differe tissues. Most such data have so far been obtained fro functional studies, where both  $K_a$  and efficacy value cies of agonists at  $\alpha_1$ -adrenergic receptors in differentissues. Most such data have so far been obtained from functional studies, where both  $K_a$  and efficacy values are dependent on experiments performed after partia tissues. Most such data have so far been obtained from<br>functional studies, where both  $K_a$  and efficacy values are<br>dependent on experiments performed after partial recep-<br>tor inactivation with highly reactive and potentia functional studies, where both  $K_a$  and efficacy values are dependent on experiments performed after partial receptor inactivation with highly reactive and potentially non-specific alkylating agents. The most likely expla dependent on experiments performed after partial receptor inactivation with highly reactive and potentially nonspecific alkylating agents. The most likely explanations<br>for the observed differences include  $(a)$  the existence of<br>discrete receptor subtypes,  $(b)$  modulation of receptor<br>affinity by tissue microenvironment,  $(c)$  partici for the observed differences include  $(a)$  the existence discrete receptor subtypes,  $(b)$  modulation of receptor affinity by tissue microenvironment,  $(c)$  participation of different affinity states of a single receptor in discrete receptor subtypes, (b) modulation of receptor<br>affinity by tissue microenvironment, (c) participation of<br>different affinity states of a single receptor in responses<br>in different tissues, or (d) technical or theoret affinity by tissue microenvironment,  $(c)$  participation of<br>different affinity states of a single receptor in responses<br>in different tissues, or  $(d)$  technical or theoretical prob-<br>lems in calculating  $K_a$  and efficacy val different affinity states of a single receptor in responses<br>in different tissues, or  $(d)$  technical or theoretical prob-<br>lems in calculating  $K_a$  and efficacy values in functional<br>experiments. So far, the small amount of affinity for agonists which have been reported in funclems in calculating  $K_a$  and efficacy values in functione experiments. So far, the small amount of data available from radioligand binding assays which addresses this problem does not support the differences in recepto af experiments. So far, the small amount of data available<br>from radioligand binding assays which addresses this<br>problem does not support the differences in receptor<br>affinity for agonists which have been reported in func-<br>tion from radioligand binding assays which addresses this problem does not support the differences in receptor affinity for agonists which have been reported in functional studies. However, further work is clearly needed in thi problem does not support the differences in recept affinity for agonists which have been reported in fundional studies. However, further work is clearly need in this area to distinguish between these possibilities and to r differences. *C. Differentiation using Selective Antagonists*<br>*C. Differentiation using Selective Antagonists*<br>*C. Differentiation using Selective Antagonists*<br>Subclassification of receptors using selective resolve these potentially important pharmacologi<br>fferences.<br>Differentiation using Selective Antagonists<br>Subclassification of receptors using selective anta<br>sts is generally much less difficult to interpret the

C. Differentiation using Selective Antagonists<br>Subclassification of receptors using selective antagonists is generally much less difficult to interpret than

M<br>subclassification using selective agonists. Since antagoists<br>nists bind to the receptor but do not activate it, they nists bind to the receptor agonists. Since antago-<br>nists bind to the receptor but do not activate it, they are sel<br>characterized only on the basis of their affinity constants. The MIN<br>subclassification using selective agonists. Since antago-<br>nists bind to the receptor but do not activate it, they are<br>characterized only on the basis of their affinity constants.<br>There is no complication with differenc subclassification using selective agonists. Since antagonists bind to the receptor but do not activate it, they are characterized only on the basis of their affinity constants. There is no complication with differences in subclassification using selective agonists. Since antagonists bind to the receptor but do not activate it, they are characterized only on the basis of their affinity constants. There is no complication with differences in characterized only on the basis of their affinity constants.<br>There is no complication with differences in efficacy.<br>Also, the degree of receptor blockade is absolutely pro-<br>portional to the degree of receptor occupancy by characterized only on the basis of their affinity constants. m<br>There is no complication with differences in efficacy.<br>Also, the degree of receptor blockade is absolutely pro-<br>portional to the degree of receptor occupancy b There is no complication with differences in efficacy. fer<br>Also, the degree of receptor blockade is absolutely pro-<br>portional to the degree of receptor occupancy by a com-<br>petitive antagonist, and therefore the actual bind Also, the degree of receptor blockade is absolutely pro-<br>portional to the degree of receptor occupancy by a com-<br>petitive antagonist, and therefore the actual binding<br>constant of the antagonist for the receptor under stud portional to the degree of receptor occupancy by a competitive antagonist, and therefore the actual binding 1 constant of the antagonist for the receptor under study more can be determined relatively easily. If appropriat petitive antagonist, and therefore the actual binding constant of the antagonist for the receptor under study can be determined relatively easily. If appropriate precautions are taken and certain criteria fulfilled, the constant of the antagonist for the receptor under study m<br>can be determined relatively easily. If appropriate pre-<br>cautions are taken and certain criteria fulfilled, the pA<sub>2</sub> cl<br>for an antagonist in blocking the response can be determined relatively easil cautions are taken and certain criterior an antagonist in blocking the resolution of to the receptor site  $(8, 182, 292)$ .<br>When the  $pA_2$  values for antagonic utions are taken and certain criteria fulfilled, the  $pA_2$  clear and antagonist in blocking the response to an agonist to could be an accurate indication of its affinity in binding d the receptor site  $(8, 182, 292)$ .<br>Wh for an antagonist in blocking the response to an agonist<br>should be an accurate indication of its affinity in binding<br>to the receptor site  $(8, 182, 292)$ .<br>When the  $pA_2$  values for antagonists in blocking  $\alpha_1$ -<br>adrener

should be an accurate indication of its affinity in binding<br>to the receptor site  $(8, 182, 292)$ .<br>When the  $pA_2$  values for antagonists in blocking  $\alpha_1$ -<br>adrenergic receptor-mediated responses have been com-<br>pared to t to the receptor site (8, 182, 292). existen<br>When the pA<sub>2</sub> values for antagonists in blocking  $\alpha_1$ -<br>adrenergic receptor-mediated responses have been com-<br>pared to their  $K_d$  values in competing for  $\alpha_1$ -adrenergic hav When the pA<sub>2</sub> values for antagonists in blocking  $\alpha_1$ -<br>adrenergic receptor-mediated responses have been com-<br>pared to their  $K_d$  values in competing for  $\alpha_1$ -adrenergic<br>receptor binding sites in membrane preparations adrenergic receptor-mediated responses have been co<br>pared to their  $K_d$  values in competing for  $\alpha_1$ -adrener<br>receptor binding sites in membrane preparations fr<br>the same (151, 231, 243, 245, 247, 301, 305) or differ<br>(140 pared to their  $K_d$  values in competing for  $\alpha_1$ -adrend<br>receptor binding sites in membrane preparations if<br>the same (151, 231, 243, 245, 247, 301, 305) or differ<br>(140, 239, 336) tissues, the correlation has been imp<br>siv receptor binding sites in membrane preparations from dthe same (151, 231, 243, 245, 247, 301, 305) or different p<br>(140, 239, 336) tissues, the correlation has been impressive (fig. 8). These data have supported the interp the same (151, 231, 243, 245, 247, 301, 305) or different prazosin was about 10-fold more potent in blocking nor-<br>(140, 239, 336) tissues, the correlation has been impres-<br>epinephrine-mediated contractions of rat aorta (p sive (fig. 8). These data have supported the interpretations that (*a*) the affinity of  $\alpha_1$ -adrenergic receptors for antagonists is not altered by homogenizing tissues and making membrane preparations; and (*b*) the pharmacological properties of  $\alpha_1$ -adrenergic receptors tions that  $(a)$  then<br>antagonists is no<br>making membra<br>logical propertie<br>in most tissues.<br>However, appa tagonists is not altered by homogenizing tissues and<br>aking membrane preparations; and (b) the pharmaco-<br>igical properties of  $\alpha_1$ -adrenergic receptors are similar<br>most tissues.<br>However, apparent differences between pA<sub>2</sub> making membrane preparations; and (b) the pharmaco-<br>logical properties of  $\alpha_1$ -adrenergic receptors are similar<br>in most tissues.<br>However, apparent differences between  $pA_2$  values for<br>antagonists have been observed at

logical properties of  $\alpha_1$ -adrenergic receptors are similar<br>in most tissues.<br>However, apparent differences between  $pA_2$  values for<br>antagonists have been observed at  $\alpha_1$ -adrenergic recep-<br>tors in different tissues. in most tissues.<br>
However, apparent differences between  $pA_2$  values for<br>
the antagonists have been observed at  $\alpha_1$ -adrenergic recep-<br>
tors in different tissues. As mentioned above, Sheys and<br>
Green (313) noted that t However, apparent differences between pA<sub>2</sub> values f<br>antagonists have been observed at  $\alpha_1$ -adrenergic rece<br>tors in different tissues. As mentioned above, Sheys a<br>Green (313) noted that the pA<sub>2</sub> for phentolamine differ antagonists have been observed at  $\alpha_1$ -adrenergic receptors in different tissues. As mentioned above, Sheys and Creen (313) noted that the pA<sub>2</sub> for phentolamine differed (pby 2- to 3-fold in different tissues. More dra tors in different tissues. As mentioned above, Sheys and<br>Green (313) noted that the  $pA_2$  for phentolamine differed<br>by 2- to 3-fold in different tissues. More dramatic differ-<br>ences were observed when  $pA_2$  values for y Green (313) noted that the pA<sub>2</sub> for phentolamine differed<br>by 2- to 3-fold in different tissues. More dramatic differ-<br>ences were observed when pA<sub>2</sub> values for yohimbine were<br>compared in aortae from different species (29 by 2- to 3-fold in different tissues. More dramatic differences were observed when  $pA_2$  values for yohimbine were<br>compared in aortae from different species (297), although<br>this was originally thought to be due to differ

![](_page_19_Figure_4.jpeg)

FIG. 8. Similarity of pA<sub>2</sub> and *pK<sub>d</sub>* values for antagonists in rat vas deferens. These data suggest that the pharmacological properties of receptor binding sites in membranes do not differ from those in intact **race in the property of parts in the property.** FIG. 8. Similarity of  $pA_2$  and  $pK_d$  values for antagonists in rat vas deferens. These data suggest that the pharmacological properties of receptor binding sites in membr FIG. 8. Similarity of  $pA_2$  and  $pK_d$  values for antagonists in rat vas<br>deferens. These data suggest that the pharmacological properties of<br>receptor binding sites in membranes do not differ from those in intact<br>tissues, permission.

now seems likely that differences in affinity for  $\alpha_2$ -<br>selective antagonists could reveal differences in the phar-MAN<br>now seems likely that differences in affinity for  $\alpha$ <br>selective antagonists could reveal differences in the phar<br>macological properties of  $\alpha_1$ -adrenergic receptors in di MAN<br>now seems likely that differences in affinity for  $\alpha_2$ -<br>selective antagonists could reveal differences in the phar-<br>macological properties of  $\alpha_1$ -adrenergic receptors in dif-<br>ferent tissues, although the potentia mow seems likely that differences in affinity for  $\alpha_2$ -<br>selective antagonists could reveal differences in the phar-<br>macological properties of  $\alpha_1$ -adrenergic receptors in dif-<br>ferent tissues, although the potential fo now seems likely that differences in affinity for  $\alpha_2$ -<br>selective antagonists could reveal differences in the phar-<br>macological properties of  $\alpha_1$ -adrenergic receptors in dif-<br>ferent tissues, although the potential fo selective antagonists<br>macological propertie<br>ferent tissues, althou<br>effects on  $\alpha_2$ -adrener<br>completely eliminate.<br>1. Prazosin. The use acological properties of  $\alpha_1$ -adrenergic receptors in dif-<br>rent tissues, although the potential for confounding<br>fects on  $\alpha_2$ -adrenergic receptors is always difficult to<br>mpletely eliminate.<br>1. Prazosin. The use of  $\alpha$ 

ferent tissues, although the potential for confounding<br>effects on  $\alpha_2$ -adrenergic receptors is always difficult to<br>completely eliminate.<br>1. Prazosin. The use of  $\alpha_1$ -selective antagonists is much<br>more straightforward. completely enhimate.<br>
1. Prazosin. The use of  $\alpha_1$ -selective antagonists is mu<br>
more straightforward. Since these drugs will block a<br>
adrenergic receptors in concentrations which can<br>
clearly shown to have no effect on 1. Prazosin. The use of  $\alpha_1$ -selective antagonists is much<br>more straightforward. Since these drugs will block  $\alpha_1$ -<br>adrenergic receptors in concentrations which can be<br>clearly shown to have no effect on  $\alpha_2$ -adrener more straightforward. Since these drugs will block  $\alpha_1$ -<br>adrenergic receptors in concentrations which can be<br>clearly shown to have no effect on  $\alpha_2$ -adrenergic recep-<br>tors, differences in apparent affinity for recepto adrenergic receptors in concentrations which can be clearly shown to have no effect on  $\alpha_2$ -adrenergic receptors, differences in apparent affinity for receptors in different tissues can more easily be attributed to the clearly shown to have no effect on  $\alpha_2$ -adrenergic receptors, differences in apparent affinity for receptors in different tissues can more easily be attributed to the existence of discrete subtypes of  $\alpha_1$ -adrenergic tors, differences in apparent affinity for receptors in different tissues can more easily be attributed to the existence of discrete subtypes of  $\alpha_1$ -adrenergic receptors. Several reports have appeared, suggesting that different tissues can more easily be attributed to the<br>existence of discrete subtypes of  $\alpha_1$ -adrenergic receptors.<br>Several reports have appeared, suggesting that the pro-<br>totype  $\alpha_1$ -adrenergic receptor antagonist pr existence of discrete subtypes of  $\alpha_1$ -adrenergic receptors.<br>Several reports have appeared, suggesting that the prototype  $\alpha_1$ -adrenergic receptor antagonist prazosin might<br>have different affinities for  $\alpha_1$ -adrener Several reports have appeared, suggesting that the pro-<br>totype  $\alpha_1$ -adrenergic receptor antagonist prazosin might<br>have different affinities for  $\alpha_1$ -adrenergic receptors in<br>different tissues. Digges and Summers (88) s totype  $\alpha_1$ -adrenergic receptor antagonist prazosin might<br>have different affinities for  $\alpha_1$ -adrenergic receptors in<br>different tissues. Digges and Summers (88) showed that<br>prazosin was about 10-fold more potent in blo have different affinities for  $\alpha_1$ -adrenergic receptors in different tissues. Digges and Summers (88) showed that prazosin was about 10-fold more potent in blocking nor-epinephrine-mediated contractions of rat aorta (pA different tissues. Digges and Summers (88) showed that<br>prazosin was about 10-fold more potent in blocking nor-<br>epinephrine-mediated contractions of rat aorta (pA<sub>2</sub> of<br>9.4) than rat portal vein (8.4). Interestingly, simil prazosin was about 10-fold more poten<br>epinephrine-mediated contractions of<br>9.4) than rat portal vein (8.4). Interest<br>fold differences were observed for most<br>tested  ${2-[{\beta-(4-hydroxyphenyl)ethylar}}$ <br>lone (BE 2254), phentolamine, and rat epinephrine-mediated contractions of rat aorta (pA<sub>2</sub> of 9.4) than rat portal vein (8.4). Interestingly, similar 10-<br>fold differences were observed for most other antagonists<br>tested {2-[ $\beta$ -(4-hydroxyphenyl)ethylaminomet 9.4) than rat portal vein (8.4). Interestingly, similar 10-<br>fold differences were observed for most other antagonists<br>tested  $\{2-[\beta-(4-hydroxyphenyl)ethylaminomethyl]tetra-  
lone (BE 2254), phentolamine, and rawolscine} except,   
surprisingly, for yohimbine. In studying contractions of  
rabbit main pulmonary artery, Holck et al. (147) found$ fold differences were observed for most other antagonists<br>tested {2-[ $\beta$ -(4-hydroxyphenyl)ethylaminomethyl]tetra-<br>lone (BE 2254), phentolamine, and rauwolscine} except,<br>surprisingly, for yohimbine. In studying contraction tested  ${2-[{\beta-(4-hydroxyphenyl)ethylaminomethyl]}tetrad-  
lone (BE 2254), phentolamine, and rauwolscine} except,  
surprisingly, for yohimbine. In studying contractions of  
rabbit main pulmonary artery, Holck et al. (147) found  
that prazosin competitively blocked contractions caused  
by both clonidine and methoxamine, but was signifi$ lone (BE 2254), phentolamine, and rauwolscine) exce<br>surprisingly, for yohimbine. In studying contractions<br>rabbit main pulmonary artery, Holck et al. (147) fou<br>that prazosin competitively blocked contractions caus<br>by both c surprisingly, for yohimbine. In studying contractions of rabbit main pulmonary artery, Holck et al.  $(147)$  found that prazosin competitively blocked contractions caused by both clonidine and methoxamine, but was signific rabbit main pulmonary artery, Holck et al.  $(147)$  found<br>that prazosin competitively blocked contractions caused<br>by both clonidine and methoxamine, but was signifi-<br>cantly more potent in blocking responses to clonidine<br> $(p$ that prazosin competitively blocked contractions caused<br>by both clonidine and methoxamine, but was signifi-<br>cantly more potent in blocking responses to clonidine<br> $(pA_2$  of 9.4) than methoxamine (8.4). In this case, simila by both clonidine and methoxamine, but was significantly more potent in blocking responses to clonidine ( $pA_2$  of 9.4) than methoxamine (8.4). In this case, similar differences were found for yohimbine ( $pA_2$  of 6.6 aga cantly more potent in blocking responses to clonidine ( $pA_2$  of 9.4) than methoxamine (8.4). In this case, similar differences were found for yohimbine ( $pA_2$  of 6.6 against clonidine and 5.8 against methoxamine). Since  $(pA_2$  of 9.4) than methoxamine (8.4). In this case, similar differences were found for yohimbine ( $pA_2$  of 6.6 against clonidine and 5.8 against methoxamine). Since clonidine is a relatively  $\alpha_2$ -selective agonist whi differences were found for yohimbine (pA<sub>2</sub> of 6.6 against clonidine and 5.8 against methoxamine). Since clonidine is a relatively  $\alpha_2$ -selective agonist while methoxamine is relatively  $\alpha_1$  selective, it was surprisi clonidine and 5.8 against methoxamine). Since clonidine<br>is a relatively  $\alpha_2$ -selective agonist while methoxamine is<br>relatively  $\alpha_1$  selective, it was surprising that the  $\alpha_1$ -<br>selective antagonist prazosin was more is a relatively  $\alpha_2$ -selective agonist while methoxamine is<br>relatively  $\alpha_1$  selective, it was surprising that the  $\alpha_1$ -<br>selective antagonist prazosin was more potent against<br>clonidine than methoxamine. Conversely, M relatively  $\alpha_1$  selective, it was surprising that the  $\alpha_1$ -<br>selective antagonist prazosin was more potent against<br>clonidine than methoxamine. Conversely, Medgett and<br>Langer (232) reported that prazosin was about 10-fo selective antagonist prazosin was more potent against<br>clonidine than methoxamine. Conversely, Medgett and<br>Langer (232) reported that prazosin was about 10-fold<br>more potent in blocking contractile responses of rat tail<br>arte clonidine than methoxamine. Conversely, Medgett and Langer (232) reported that prazosin was about 10-fold more potent in blocking contractile responses of rat tail artery to methoxamine [log concentration of antagonist sh more potent in blocking contractile responses of rat tail<br>artery to methoxamine [log concentration of antagonist<br>shifting agonist dose-response curve 2-fold ( $pK_B$ ) of 9.7]<br>than norepinephrine (8.9). In examining the lite more potent in biocking contractie responses of rat tail<br>artery to methoxamine [log concentration of antagonist<br>shifting agonist dose-response curve 2-fold (p $K_B$ ) of 9.7]<br>than norepinephrine (8.9). In examining the liter artery to methoxamine [log concentration of antagonist<br>shifting agonist dose-response curve 2-fold (p $K_B$ ) of 9.7]<br>than norepinephrine (8.9). In examining the literature,<br>Medgett and Langer (232) and Agrawal et al. (2) no shifting agonist dose-response curve 2-fold (p $K_B$ ) of 9.7]<br>than norepinephrine (8.9). In examining the literature,<br>Medgett and Langer (232) and Agrawal et al. (2) noted<br>that there was a very wide range in the p $A_2$  valu than norepinephrine (8.9). In examining the literature,<br>Medgett and Langer (232) and Agrawal et al. (2) noted<br>that there was a very wide range in the  $pA_2$  values<br>reported for prazosin in different tissues. The values<br>ra Medgett and Langer (232) and Agrawal et al. (2) noted<br>that there was a very wide range in the  $pA_2$  values<br>reported for prazosin in different tissues. The values<br>ranged from a low of 11.2 in rat aorta (78) to a high of<br>7 that there was a very wide range in the  $pA_2$  values<br>reported for prazosin in different tissues. The values<br>ranged from a low of 11.2 in rat aorta (78) to a high of<br>7.2 in rabbit renal artery (71). Although in some cases reported for prazosin in different tissues. The value ranged from a low of 11.2 in rat aorta (78) to a high 7.2 in rabbit renal artery (71). Although in some cas there may have been some noncompetitive actions prazosin (2 ranged from a low of 11.2 in rat aorta (78) to a high of 7.2 in rabbit renal artery (71). Although in some cases there may have been some noncompetitive actions of prazosin (282) or the involvement of  $\alpha_2$ -adrenergic re 7.2 in rabbit renal artery (71). Although in some cases<br>there may have been some noncompetitive actions of<br>prazosin (282) or the involvement of  $\alpha_2$ -adrenergic recep-<br>tors, in general the variations appear to reflect tr there may have been some noncompetitive actions of<br>prazosin (282) or the involvement of  $\alpha_2$ -adrenergic recep-<br>tors, in general the variations appear to reflect true<br>differences between the receptors in different tissue prazosin (282) or the involvement of  $\alpha_2$ -adrenergic receptors, in general the variations appear to reflect true differences between the receptors in different tissues. On the other hand, much of the variation comes fro tors, in general the variations appear to reflect true<br>differences between the receptors in different tissues. On<br>the other hand, much of the variation comes from a<br>single tissue, rat aorta, where the affinity of prazosin<br> differences between the receptors in different tissues. On the other hand, much of the variation comes from a single tissue, rat aorta, where the affinity of prazosin appears to be about 10-fold higher than in most other t 244). ngle tissue, rat aorta, where the affinity of prazosin<br>pears to be about 10-fold higher than in most other<br>sues (16, 78, 216, 282) (see data compilation in ref.<br>4).<br>Drew (95) suggested that  $pA_2$  values reported for yo-<br> appears to be about 10-fold higher than in most other tissues (16, 78, 216, 282) (see data compilation in ref. 244).<br>
Drew (95) suggested that  $pA_2$  values reported for yo-<br>
himbine in blocking responses in various isola

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 $\alpha_1$ -ADRENERGIC RECEPT<br>which were highly sensitive to prazosin blockade and "hi<br>therefore presumably mediated by  $\alpha_1$ -adrenergic recep- $\alpha_1$ -ADRENERGIC<br>which were highly sensitive to prazosin blockade antherefore presumably mediated by  $\alpha_1$ -adrenergic rece<br>tors, could be divided into different subgroups. He su  $\alpha_1$ -ADRENERGIC F<br>which were highly sensitive to prazosin blockade and<br>therefore presumably mediated by  $\alpha_1$ -adrenergic recep-<br>tors, could be divided into different subgroups. He sug-<br>gested that there might exist two which were highly sensitive to prazosin blockade and "lefter therefore presumably mediated by  $\alpha_1$ -adrenergic receptors, could be divided into different subgroups. He suggested that there might exist two different subty which were highly sensitive to prazosin blockade and<br>therefore presumably mediated by  $\alpha_1$ -adrenergic recep-<br>tors, could be divided into different subgroups. He sug-<br>gested that there might exist two different subtypes therefore presumably mediated by  $\alpha_1$ -adrenergic recep-<br>tors, could be divided into different subgroups. He sug-<br>gested that there might exist two different subtypes of<br>the<br> $\alpha_1$ -adrenergic receptors differentiated by tors, could be divided into different subgroups. He suggested that there might exist two different subtypes of the  $\alpha_1$ -adrenergic receptors differentiated by their affinities other loboratories, Flavahan and Vanhoutte  $\alpha_1$ -adrenergic receptors differentiated by their affinities other tissues (2, 105, 244). Two binding studies have<br>for yohimbine. In reviewing data from their own and been performed on rat aorta. Descombes and Stoclet ( for yohimbine. In reviewing data from their own and been performed on rat aorta. Descombes and Stoclet (82) other laboratories, Flavahan and Vanhoutte (105) noted found that [<sup>3</sup>H]prazosin labeled  $\alpha_1$ -adrenergic recept for yohimbine. In reviewing data from their own and beed other laboratories, Flavahan and Vanhoutte (105) noted fourth that the wide variation in affinity for prazosin reported bin in functional studies in different tissue other laboratories, Flavahan and Vanhoutte (105) noted for that the wide variation in affinity for prazosin reported bin functional studies in different tissues was reflected by singular wide variation in affinity for yoh that the wide variation in affinity for prazosin reported<br>in functional studies in different tissues was reflected by<br>a similar wide variation in affinity for yohimbine, even<br>though none of the tissues studied appeared to postjunctional  $\alpha_2$ -adrenergic receptors (fig. 9). They proposed that the data they had compiled suggested that there were two distinct subtypes of  $\alpha_1$ -adrenergic recepa similar wide variation in affinity for yohimbine, even though none of the tissues studied appeared to conta postjunctional  $\alpha_2$ -adrenergic receptors (fig. 9). They prosed that the data they had compiled suggested ther though none of the tissues studied appeared to contain spostjunctional  $\alpha_2$ -adrenergic receptors (fig. 9). They pro-<br>posed that the data they had compiled suggested that between two distinct subtypes of  $\alpha_1$ -adrenergi posed that the data they had compiled suggested that buffer, but that this value was increased to 10.6 in there were two distinct subtypes of  $\alpha_1$ -adrenergic recep-<br>tors which could be distinguished by their affinities posed that the data they had compiled suggested that b<br>there were two distinct subtypes of  $\alpha_1$ -adrenergic recep-<br>tors which could be distinguished by their affinities for<br>doth prazosin and yohimbine. One subtype had a there were two distinct subtypes of  $\alpha_1$ -adrenergic recep-<br>tors which could be distinguished by their affinities for<br>both prazosin and yohimbine. One subtype had a high<br>affinity for both drugs (pA<sub>2</sub>s greater than 9 for tors which could be distinguished by their affinities for both prazosin and yohimbine. One subtype had a high affinity for both drugs (pA<sub>2</sub>s greater than 9 for prazosin and greater than 6.4 for yohimbine), and the other respectively). finity for both drugs (pA<sub>2</sub>s greater than 9 for prazosin<br>d greater than 6.4 for yohimbine), and the other had<br>low affinity for both drugs (pA<sub>2</sub>s less than 9 and 6.2,<br>spectively).<br>Binding studies have generally provided

and greater than 6.4 for yohimbine), and the other had<br>a low affinity for both drugs (pA<sub>2</sub>s less than 9 and 6.2,<br>respectively).<br>Binding studies have generally provided little support<br>for this proposal. Radioligand bindin a low affinity for both drugs (pA<sub>2</sub>s less than 9 and 6.2, respectively).<br>
Binding studies have generally provided little support<br>
for this proposal. Radioligand binding studies using [<sup>3</sup>H]<br>
prazosin have usually suggest respectively).<br>
Binding studies have generally provided little support<br>
for this proposal. Radioligand binding studies using [<sup>3</sup>H]<br>
prazosin have usually suggested that prazosin has similar<br>
affinities for  $\alpha_1$ -adrener Binding studies have generally provided little support<br>for this proposal. Radioligand binding studies using  $[^{3}H]$  (prazosin have usually suggested that prazosin has similar<br>affinities for  $\alpha_1$ -adrenergic receptors in for this proposal. Radioligand binding studies using  $[{}^3H]$  (11)<br>prazosin have usually suggested that prazosin has similar prep<br>affinities for  $\alpha_1$ -adrenergic receptors in all tissues ex-<br>amined. Bylund (48) recently prazosin have usually suggested that prazosin has similar<br>affinities for  $\alpha_1$ -adrenergic receptors in all tissues ex-<br>amined. Bylund (48) recently compiled  $K_d$  values for  $[^{3}H]$ <br>prazosin (p $K_d$ ) in binding to  $\alpha_1$ affinities for  $\alpha_1$ -adrenergic receptors in all tissues ex-<br>amined Bylund (48) recently compiled  $K_d$  values for [<sup>3</sup>H] sul<br>prazosin (p $K_d$ ) in binding to  $\alpha_1$ -adrenergic receptors in<br>25 different tissues from five di amined. Bylund (48) recently compiled  $K_d$  values for [<sup>3</sup>H] prazosin (p $K_d$ ) in binding to  $\alpha_1$ -adrenergic receptors in 25 different tissues from five different species. p $K_d$  values were generally around 9.3 to 9.7, s were generally around  $9.3$  to  $9.7$ , similar to the high of these tissues since Scatchard plots were generally affinity subtype proposed above. There was little evi-<br>dence for the existence of a low affinity subtype in any<br>of these tissues since Scatchard plots were generally<br>linear, indicative of a single class of binding sites. dence for the existence of a fow all intity subtype in any the of these tissues since Scatchard plots were generally linear, indicative of a single class of binding sites. Calculation of binding constants by kinetic analy

![](_page_20_Figure_6.jpeg)

**Bind and Secrets**<br> **EXECUTE:** ONE CONTRESS CONTRESS CONTRESS OF THE SERVICE PROPERTIES OF PRESS CONTRESS CONTRACTIONS IN 180-<br>
Lated blood vessels. The grouping of the data into two general sets may **EXECUTE:** The group of the grouping of the data into two general sets may be given blocking  $\alpha_1$ -adrenergic receptor-mediated contractions in iso-<br>lated blood vessels. The grouping of the data into two general sets may FIG. 9. Correlation between the potencies of prazosin and yohim-<br>bine in blocking  $\alpha_1$ -adrenergic receptor-mediated contractions in iso-<br>lated blood vessels. The grouping of the data into two general sets may<br>suggest th which is become<br>lated blood ves<br>suggest the exaffinities for b<br>with permission.

EPTOR SUBTYPES<br>"high affinity" subtype would predominate in most tis-<br>sues, while functional studies suggest that this subtype EPTOR SUBTYPES<br>"high affinity" subtype would predominate in most tis-<br>sues, while functional studies suggest that this subtype<br>occurs mainly in rat aorta and mesenteric artery, and EPTOR SUBTYPES 107<br>
"high affinity" subtype would predominate in most tis-<br>
sues, while functional studies suggest that this subtype<br>
occurs mainly in rat aorta and mesenteric artery, and<br>
that the "low affinity" subtype p "high affinity" subtype would predominate in most tis-<br>sues, while functional studies suggest that this subtype<br>occurs mainly in rat aorta and mesenteric artery, and<br>that the "low affinity" subtype predominates in most<br>oth "high affinity" subtype would predominate in most tissues, while functional studies suggest that this subtype occurs mainly in rat aorta and mesenteric artery, and that the "low affinity" subtype predominates in most othe sues, while functional studies suggest that this subtype<br>occurs mainly in rat aorta and mesenteric artery, and<br>that the "low affinity" subtype predominates in most<br>other tissues (2, 105, 244). Two binding studies have<br>bee occurs mainly in rat aorta and mesenteric artery, and<br>that the "low affinity" subtype predominates in most<br>other tissues (2, 105, 244). Two binding studies have<br>been performed on rat aorta. Descombes and Stoclet (82)<br>foun other tissues  $(2, 105, 244)$ . Two binding studies have other tissues (2, 105, 244). Two binding studies have<br>been performed on rat aorta. Descombes and Stoclet (82)<br>found that [<sup>3</sup>H]prazosin labeled  $\alpha_1$ -adrenergic receptor<br>binding sites in rat aorta with a p $K_d$  of 9.4, wh been performed on rat aorta. Descombes and Stoclet (82)<br>found that [<sup>3</sup>H]prazosin labeled  $\alpha_1$ -adrenergic receptor<br>binding sites in rat aorta with a p $K_d$  of 9.4, which was<br>similar to its affinity for the receptors in b found that [<sup>3</sup>H]prazosin labeled  $\alpha_1$ -adrenergic receptor<br>binding sites in rat aorta with a p $K_d$  of 9.4, which was<br>similar to its affinity for the receptors in bovine aorta,<br>as well as in most other tissues (48). Jone binding sites in rat aorta with a p $K_d$  of 9.4, which was<br>similar to its affinity for the receptors in bovine aorta,<br>as well as in most other tissues (48). Jones et al. (173)<br>showed that [<sup>3</sup>H]prazosin labeled  $\alpha_1$ -adre similar to its affinity for the receptors in bovine aorta,<br>as well as in most other tissues (48). Jones et al. (173)<br>showed that [<sup>3</sup>H]prazosin labeled  $\alpha_1$ -adrenergic receptors<br>in membranes from rat aorta with a p $K_d$  as well as in most other tissues (48). Jones et al. (173)<br>showed that [<sup>3</sup>H]prazosin labeled  $\alpha_1$ -adrenergic receptors<br>in membranes from rat aorta with a p $K_d$  of 9.7 in Tris<br>buffer, but that this value was increased to showed that [<sup>3</sup>H]prazosin labeled  $\alpha_1$ -adrenergic receptors<br>in membranes from rat aorta with a p $K_d$  of 9.7 in Tris<br>buffer, but that this value was increased to 10.6 in<br>glycylglycine buffer. Similar data were obtained in membranes from rat aorta with a p $K_d$  of 9.7 in Tris<br>buffer, but that this value was increased to 10.6 in<br>glycylglycine buffer. Similar data were obtained in the<br>dog aorta (173). Thus these binding studies do not sup-<br> buffer, but that this value was increased to 10.6 in glycylglycine buffer. Similar data were obtained in the dog aorta (173). Thus these binding studies do not support the proposition that the  $\alpha_1$ -adrenergic receptors glycylglycine buffer. Similar data were obtained in the dog aorta (173). Thus these binding studies do not support the proposition that the  $\alpha_1$ -adrenergic receptors in rat aorta have a substantially higher affinity for

prazosin (p $K_d$ ) in binding to  $\alpha_1$ -adrenergic receptors in affinity p $K_d$ s of 10.3 and 9, respectively. Few conclusions 25 different tissues from five different species. p $K_d$  values could be drawn about the low affini Recently, however, two reports have appeared which<br>support the existence of two distinct affinity constants port the proposition that the  $\alpha_1$ -adrenergic receptors in rat aorta have a substantially higher affinity for prazosin than the  $\alpha_1$ -adrenergic receptors in many other tissues.<br>Recently, however, two reports have appe rat aorta have a substantially higher affinity for prazosin<br>than the  $\alpha_1$ -adrenergic receptors in many other tissues.<br>Recently, however, two reports have appeared which<br>support the existence of two distinct affinity con than the  $\alpha_1$ -adrenergic receptors in many other tissues.<br>Recently, however, two reports have appeared which<br>support the existence of two distinct affinity constants<br>for prazosin in radioligand binding studies. Babich e Recently, however, two reports have appeared which<br>support the existence of two distinct affinity constants<br>for prazosin in radioligand binding studies. Babich et al.<br>(11) examined the binding of  $[^3H]$ prazosin to microso support the existence of two distinct affinity constants<br>for prazosin in radioligand binding studies. Babich et al.<br>(11) examined the binding of [<sup>3</sup>H]prazosin to microsomal<br>preparations from rabbit aorta. They reported a for prazosin in radioligand binding studies. Babich et al. (11) examined the binding of [<sup>3</sup>H]prazosin to microsomal preparations from rabbit aorta. They reported a slight curvature in the Scatchard plot. Computer analysi preparations from rabbit aorta. They reported a slight curvature in the Scatchard plot. Computer analysis resulted in a significant two-site fit, with low and high curvature in the Scatchard plot. Computer analysis recurvature in the Scatchard plot. Computer analysis resulted in a significant two-site fit, with low and high affinity  $pK_d s$  of 10.3 and 9, respectively. Few conclusions could be drawn about the low affinity site, however affinity p $K_d$ s of 10.3 and 9, respectively. Few conclusions<br>could be drawn about the low affinity site, however, since<br>the highest  $[^3H]$ prazosin concentration examined was<br>1.2 nM, which would result in only about a 50% could be drawn about the low affinity site, however, since<br>the highest  $[^3H]$ prazosin concentration examined was<br>1.2 nM, which would result in only about a 50% satura-<br>tion of this site. Jagadeesh and Deth (160) recently<br> the highest [<sup>3</sup>H]prazosin concentration examined was 1.2 nM, which would result in only about a 50% saturation of this site. Jagadeesh and Deth (160) recently reported that competition of unlabeled prazosin for [<sup>3</sup>H] pr 1.2 nM, which would result in only about a 50% saturation of this site. Jagadeesh and Deth (160) recentlereported that competition of unlabeled prazosin for  $[^{3}F$ prazosin binding sites in purified membranes from ration tion of this site. Jagadeesh and Deth (160) recently<br>reported that competition of unlabeled prazosin for [<sup>3</sup>H]<br>prazosin binding sites in purified membranes from rat<br>aorta was characterized by a low Hill coefficient. Com-<br> reported that competition of unlabeled prazosin for  $[^3H]$ <br>prazosin binding sites in purified membranes from rat<br>aorta was characterized by a low Hill coefficient. Com-<br>puter modeling suggested the existence of two differ prazosin binding sites in purified membranes from rat<br>aorta was characterized by a low Hill coefficient. Com-<br>puter modeling suggested the existence of two different<br>affinity states for prazosin, although with less than 1 aorta was characterized by a low Hill coefficient. Computer modeling suggested the existence of two different affinity states for prazosin, although with less than 10 fold affinity differences (p $K_d$ s of 9.8 and 10.6). Ho puter modeling suggested the existence of two different affinity states for prazosin, although with less than 1<br>fold affinity differences (p $K_d$ s of 9.8 and 10.6). Howeve<br>extensive direct saturation analysis of  $[^3H]$ praz affinity states for prazosin, although with less than 10-<br>fold affinity differences ( $pK_d$ s of 9.8 and 10.6). However<br>extensive direct saturation analysis of [<sup>3</sup>H]prazosin bind-<br>ing showed no evidence for binding site he fold affinity differences (p $K_d$ s of 9.8 and 10.6). However,<br>extensive direct saturation analysis of [<sup>3</sup>H]prazosin bind-<br>ing showed no evidence for binding site heterogeneity.<br>The Scatchard plot was linear from 5 to 98% extensive direct saturation analysis of [<sup>3</sup>H]prazosin bind-<br>ing showed no evidence for binding site heterogeneity.<br>The Scatchard plot was linear from 5 to 98% occupancy,<br>with a correlation coefficient of 0.997 (160). The ing showed no evidence for binding site heterogeneity.<br>The Scatchard plot was linear from 5 to 98% occupancy,<br>with a correlation coefficient of 0.997 (160). The authors<br>suggested that the relatively low specific activity The Scatchard plot was linear from 5 to 98% occupancy,<br>with a correlation coefficient of 0.997 (160). The authors<br>suggested that the relatively low specific activity of  $[^{3}H]$ <br>prazosin might have prevented detection of with a correlation coefficient of 0.997 (160). The authors<br>suggested that the relatively low specific activity of [<sup>3</sup>H]<br>prazosin might have prevented detection of high affinity<br>binding sites. This could also be explained suggested that the relatively low specific activity of [<sup>3</sup>H] prazosin might have prevented detection of high affinit binding sites. This could also be explained if [<sup>3</sup>H] prazosin differed from unlabeled prazosin. Howeve prazosin might have prevented detection of high affinity<br>binding sites. This could also be explained if  $[^3H]$ prazosin<br>differed from unlabeled prazosin. However, the potency<br>of prazosin in competing for  $\alpha_1$ -adrenergic binding sites. This could also be explained if  $[^{3}H]$  prazosin differed from unlabeled prazosin. However, the potency of prazosin in competing for  $\alpha_1$ -adrenergic receptor binding sites labeled by either  $[^{3}H]$  praz differed from unlabeled prazosin. However, the potention of prazosin in competing for  $\alpha_1$ -adrenergic receptor bin<br>ing sites labeled by either [<sup>3</sup>H]prazosin or <sup>125</sup>IBE all<br>does not vary substantially between different of prazosin in competing for  $\alpha_1$ -adrenergic receptor bind-<br>ing sites labeled by either [<sup>3</sup>H]prazosin or <sup>125</sup>IBE also<br>does not vary substantially between different tissues (48,<br>244), and  $K_i$  values are very similar t ing sites labeled by either  $[^{3}H]$ prazosin or  $^{125}$ IBE also<br>does not vary substantially between different tissues (48,<br>244), and  $K_i$  values are very similar to  $K_d$  values deter-<br>mined for  $[^{3}H]$ prazosin directly b 244), and  $K_i$  values are very similar to  $K_d$  values determined for [<sup>3</sup>H]prazosin directly by Scatchard analysis.<br>In addition, the two affinity constants reported in these studies (11, 160) for prazosin do not agree wit 244), and  $K_i$  values are very similar to  $K_d$  values deter-<br>mined for [<sup>3</sup>H]prazosin directly by Scatchard analysis.<br>In addition, the two affinity constants reported in these<br>studies (11, 160) for prazosin do not agree w mined for [<sup>3</sup>H]prazosin directly by Scatchard analysis.<br>In addition, the two affinity constants reported in these<br>studies (11, 160) for prazosin do not agree with the data<br>from functional studies. The low affinity bindin In addition, the two affinity constants reported in these<br>studies (11, 160) for prazosin do not agree with the data<br>from functional studies. The low affinity binding site<br> $(pK_d 9.0 \text{ to } 9.5)$  is similar to the high affinit from functional studies. The low affinity binding site (p $K_d$  9.0 to 9.5) is similar to the high affinity functional receptor (pA<sub>2</sub> greater than 9.0; 105) and different from the low affinity functional receptor (pA<sub>2</sub> le  $(pK_d 9.0 \text{ to } 9.5)$  is similar to the high affinity functional<br>receptor  $(pA_2 \text{ greater than } 9.0; 105)$  and different from<br>the low affinity functional receptor  $(pA_2 \text{ less than } 9.0)$ .<br>Thus, the available radioligand binding data provid

108<br>little support for the existence of subtypes of  $\alpha_1$ -adre<br>gic receptors with different affinities for prazosin. 108<br>little support for the existence of subtypes of  $\alpha_1$ -ad<br>gic receptors with different affinities for prazosin.<br>2. WB 4101. On the other hand, radioligand bi

**2. MINNEM.**<br> **2. WB 4101.** On the other hand, radioligand binding provided direct evidence for subdivision of (9.1)<br>
2. WB 4101. On the other hand, radioligand binding provided direct evidence for subdivision of (9.1) Little support for the existence of subtypes of  $\alpha_1$ -adrener-<br>gic receptors with different affinities for prazosin. [<sup>3</sup><br>2. WB 4101. On the other hand, radioligand binding pistudies have provided direct evidence for sub gic receptors with different affinities for prazosin.<br>2. WB 4101. On the other hand, radioligand binding studies have provided direct evidence for subdivision  $\alpha_1$ -adrenergic receptor binding sites based on their affini gic receptors with different affinities for prazosin.<br>2. WB 4101. On the other hand, radioligand bindir<br>studies have provided direct evidence for subdivision<br> $\alpha_1$ -adrenergic receptor binding sites based on their affin<br>i 2. WB 4101. On the other hand, radioligand binding prostudies have provided direct evidence for subdivision of (9  $\alpha_1$ -adrenergic receptor binding sites based on their affin-<br>ities for the antagonists WB 4101 and phento  $\alpha_1$ -adrenergic receptor binding sites based on their affin-<br>ities for the antagonists WB 4101 and phentolamine. an<br>Battaglia et al. (13) first reported that inhibition of [<sup>3</sup>H] bin<br>prazosin binding in rat frontal cort Battaglia et al.  $(13)$  first reported that inhibition of  $[^{3}H]$  prazosin binding in rat frontal cortex by both WB 4101 and phentolamine was characterized by low Hill coefficients. This was in contrast to a variety of o Battaglia et al. (13) first reported that inhibition of [<sup>3</sup>H] bir<br>prazosin binding in rat frontal cortex by both WB 4101 band<br>phentolamine was characterized by low Hill coefficients. This was in contrast to a variety of o prazosin binding in rat frontal cortex by both WB 4101 basis and phentolamine was characterized by low Hill coeffi-<br>cients. This was in contrast to a variety of other antag-<br>low<br>onists, including both prazosin and yohimbin and phentolamine was characterized by low Hill coeffi-<br>cients. This was in contrast to a variety of other antag-<br>low<br>onists, including both prazosin and yohimbine, where the<br>381<br>Hill coefficients were approximately 1.0. I cients. This was in contrast to a variety of other ant<br>onists, including both prazosin and yohimbine, where<br>Hill coefficients were approximately 1.0. It was also<br>contrast to the inhibition of  $[^{3}H]$ prazosin binding<br>porc onists, including both prazosin and yohimbine, where the<br>Hill coefficients were approximately 1.0. It was also in<br>contrast to the inhibition of  $[^{3}H]$  prazosin binding in<br>porcine pituitary, where both WB 4101 and phento Hill coefficients were approximately 1.0. It was also in contrast to the inhibition of  $[^3H]$  prazosin binding in porcine pituitary, where both WB 4101 and phentol-<br>amine had Hill coefficients close to 1.0, just like the contrast to the inhibition of  $[^{3}H]$ prazosin binding is porcine pituitary, where both WB 4101 and phentol amine had Hill coefficients close to 1.0, just like the othe antagonists. Interestingly, WB 4101 was approximatel porcine pituitary, where both WB 4101 and phent<br>amine had Hill coefficients close to 1.0, just like the ot<br>antagonists. Interestingly, WB 4101 was approximat<br>15-fold more potent in competing for [<sup>3</sup>H]prazosin bi<br>ing sites amine had Hill coefficients close to 1.0, just like the other reatagonists. Interestingly, WB 4101 was approximately profile-fold more potent in competing for  $[^{3}H]$ prazosin binding sites in pituitary than in cortex, al antagonists. Interestingly, WB 4101 was approximatel 15-fold more potent in competing for  $[^3H]$ prazosin bind<br>ing sites in pituitary than in cortex, although phento<br>amine had similar potencies in both tissues (13). Thes<br>a 15-fold more potent in competing for  $[^{3}H]$  prazosin bind-<br>ing sites in pituitary than in cortex, although phentol-<br>amine had similar potencies in both tissues (13). These<br>authors raised the possibility that there might ing sites in pituitary than in<br>amine had similar potencies in<br>authors raised the possibility<br>macological differences in th<br>binding sites in these tissues.<br>These observations were co minime had similar potencies in both tissues (15). These not<br>authors raised the possibility that there might be phar-<br>macological differences in the  $\alpha_1$ -adrenergic receptor der<br>binding sites in these tissues. In and<br>Th

macological differences in the  $\alpha_1$ -adrenergic receptor derivations with these tissues. In a receptor of these observations were confirmed by Morrow et al. rece (253), who showed that the curves for WB 4101 and accupate binding sites in these tissues.<br>
These observations were confirmed by Morrow et al.<br>
(253), who showed that the curves for WB 4101 and<br>
phentolamine in competing for  $[^{3}H]$  prazosin binding in<br>
membranes from rat cerebr These observations were confirmed by Morrow et al. (253), who showed that the curves for WB 4101 and phentolamine in competing for  $[^3H]$  prazosin binding in membranes from rat cerebral cortex were significantly better fi phentolamine in competing for [<sup>3</sup>H]prazosin binding in<br>membranes from rat cerebral cortex were significantly<br>better fit by a two-site rather than a one-site model (fig.<br>10). These authors suggested that there were two su phenolal and a competing for  $\lfloor$  Hiprazosin binding in membranes from rat cerebral cortex were significantly better fit by a two-site rather than a one-site model (fig. 10). These authors suggested that there were two s better fit by a two-site rather than a one-site model (fig.<br>10). These authors suggested that there were two sub-<br>types of  $\alpha_1$ -adrenergic receptor binding sites in rat cere-<br>bral cortex, with equal affinities for prazo 10). These authors suggested that there were two sub-<br>types of  $\alpha_1$ -adrenergic receptor binding sites in rat cere-<br>bral cortex, with equal affinities for prazosin and most<br>applement affinities for WB<br>4101 and phentolami types of  $\alpha_1$ -adrenergic receptor binding sites in rat cerebral cortex, with equal affinities for prazosin and most cother antagonists, but with different affinities for WB  $\uparrow$ 14101 and phentolamine. WB 4101 was sligh bral cortex, with equal affinities for prazosin and most<br>other antagonists, but with different affinities for WB<br>4101 and phentolamine. WB 4101 was slightly more<br>selective than phentolamine, with p $K_d$ s of 9.2 and 7.6 at<br> other antagonists, but with different affinities for WI<br>4101 and phentolamine. WB 4101 was slightly more<br>selective than phentolamine, with  $pK_d s$  of 9.2 and 7.6 a<br>the two different binding sites (253). Morrow and Crees<br>(2 4101 and phentolamine. WB 4101 was slightly m<br>selective than phentolamine, with  $pK_d s$  of 9.2 and 7.<br>the two different binding sites (253). Morrow and Cr<br>(254) compared the binding of  $[^3H]$ prazosin to the bing of  $[^3H]$ W selective than phentolamine, with p $K_d$ s of 9.2 and 7.6 at<br>the two different binding sites (253). Morrow and Creese<br>(254) compared the binding of [<sup>3</sup>H]prazosin to the bind-<br>ing of [<sup>3</sup>H]WB 4101 in membranes from rat hipp the two different binding sites (253). Morrow and Creese (254) compared the binding of  $[^{3}H]$ JPT azosin to the binding of  $[^{3}H]WB$  4101 in membranes from rat hippocampus. They showed, as had been shown previously by ot (204) compared the binding of  $\lceil$  H)prazosin to the binding of  $\lceil$ <sup>3</sup>H)WB 4101 in membranes from rat hippocampus. They showed, as had been shown previously by others (286), that  $\lceil$ <sup>3</sup>H)WB 4101 labeled two binding s

![](_page_21_Figure_4.jpeg)

Profile in  $-11$   $-10$   $-9$   $-8$   $-7$   $-6$   $-5$   $-4$ <br>  $log(COMPEIING DRUS)$  (N)  $-11$   $-16$   $-5$   $-4$ <br>  $log(COMPEIING DRUS)$ FIG. 10. Heterogeneity in the competition of antagonists for [<sup>3</sup>H] prazosin binding sites in membranes from rat cerebral cortex. Only WB 4101 ( $\square$ ) and to a lesser extent phentolamine ( $\bigcirc$ ) show evidence for two affini permission.

MAN<br>in nature. When this site was eliminated, the density of<br>[<sup>3</sup>H]WB 4101 binding sites was about half that of [<sup>3</sup>H] MAN<br>in nature. When this site was eliminated, the density of<br>[<sup>3</sup>H]WB 4101 binding sites was about half that of [<sup>3</sup>H]<br>prazosin binding sites, and the p $K_d$  for [<sup>3</sup>H]WB 4101 MAN<br>in nature. When this site was eliminated, the density of<br>[<sup>3</sup>H]WB 4101 binding sites was about half that of [<sup>3</sup>H]<br>prazosin binding sites, and the pK<sub>d</sub> for [<sup>3</sup>H]WB 4101<br>(9.5) was similar to that for the high affinit in nature. When this site was eliminated, the density of  $[{}^3H]WB$  4101 binding sites was about half that of  $[{}^3H]$ <br>prazosin binding sites, and the p $K_d$  for  $[{}^3H]WB$  4101<br>(9.5) was similar to that for the high affinit if HJWB 4101 binding sites was eliminated, the defisity of  $[{}^3H]WB$  4101 binding sites, and the p $K_d$  for  $[{}^3H]WB$  4101 (9.5) was similar to that for the high affinity binding site discussed above (254). Reviewing the l [11] WB 4101 binding sites was about han that of [11]<br>prazosin binding sites, and the p $K_d$  for [<sup>3</sup>H]WB 4101<br>(9.5) was similar to that for the high affinity binding site<br>discussed above (254). Reviewing the literature, M (3.5) was similar to that for the right arrinty binding site<br>discussed above (254). Reviewing the literature, Morrow<br>and Creese (254) suggested that  $\alpha_1$ -adrenergic receptor<br>binding sites and responses could be subdivid and Creese (254) suggested that  $\alpha_1$ -adrenergic receptor<br>binding sites and responses could be subdivided on the<br>basis of the ratio of their relative affinities for the antag-<br>onists phentolamine and prazosin. These rang binding sites and responses could be subdivided on the basis of the ratio of their relative affinities for the antagonists phentolamine and prazosin. These ranged from a low of 3.1 in rat submandibular gland (49) to a high basis of the ratio of their relative affinities for the antag-<br>onists phentolamine and prazosin. These ranged from a<br>low of 3.1 in rat submandibular gland (49) to a high of<br>381 in guinea pig heart (178) with a wide range onists phentolamine and prazosin. These ranged from a low of 3.1 in rat submandibular gland (49) to a high of 381 in guinea pig heart (178) with a wide range of intermediate values. Morrow and Creese (254) suggested that low of 3.1 in rat submandibular gland (49) to a high of 381 in guinea pig heart (178) with a wide range of intermediate values. Morrow and Creese (254) suggested that the two types of  $\alpha_1$ -adrenergic receptor binding si 381 in guinea pig heart (178) with a wide range of intermediate values. Morrow and Creese (254) suggested that the two types of  $\alpha_1$ -adrenergic receptor binding sites should be called  $\alpha_{1A}$  and  $\alpha_{1B}$ . Jagadeesh an that the two types of  $\alpha_1$ -adrenergic receptor binding sites<br>should be called  $\alpha_{1A}$  and  $\alpha_{1B}$ . Jagadeesh and Deth (160)<br>reported similar heterogeneity in the inhibition of [<sup>3</sup>H]<br>prazosin by WB 4101 in membranes f at the two types of  $\alpha_1$ -autenergic receptor binding sites<br>ould be called  $\alpha_{1A}$  and  $\alpha_{1B}$ . Jagadeesh and Deth (160)<br>ported similar heterogeneity in the inhibition of [<sup>3</sup>H]<br>azosin by WB 4101 in membranes from bovi

should be called  $\alpha_{1A}$  and  $\alpha_{1B}$ . Jagadeesh and Deth (160)<br>reported similar heterogeneity in the inhibition of [<sup>3</sup>H]<br>prazosin by WB 4101 in membranes from bovine aorta.<br>Using a different approach which eventually c reported similar neterogenerty in the infinition of  $\begin{bmatrix} H \end{bmatrix}$ <br>prazosin by WB 4101 in membranes from bovine aorta.<br>Using a different approach which eventually converged<br>with the above results, Johnson and Minneman (1 prazosin by WB 4101 in membranes from bovine aorta.<br>Using a different approach which eventually converged<br>with the above results, Johnson and Minneman (169)<br>noted differences in the sensitivity of  $\alpha_1$ -adrenergic re-<br>ce Using a different approach which eventually converged<br>with the above results, Johnson and Minneman (169)<br>noted differences in the sensitivity of  $\alpha_1$ -adrenergic re-<br>ceptor binding sites to inactivation by the alkylating with the above results, Johnson and Minneman (169)<br>noted differences in the sensitivity of  $\alpha_1$ -adrenergic re-<br>ceptor binding sites to inactivation by the alkylating<br>derivative of clonidine, chlorethylclonidine (202) (C noted differences in the sensitivity of  $\alpha_1$ -adrenergic receptor binding sites to inactivation by the alkylating derivative of clonidine, chlorethylclonidine (202) (CEC). In attempting to differentiate between the  $\alpha_1$ ceptor binding sites to inactivation by the alkylating<br>derivative of clonidine, chlorethylclonidine (202) (CEC).<br>In attempting to differentiate between the  $\alpha_1$ -adrenergic<br>receptors increasing cyclic AMP and inositol ph In attempting to differentiate between the  $\alpha_1$ -adrenergic<br>receptors increasing cyclic AMP and inositol phosphate<br>accumulation in rat cerebral cortex, these authors noted<br>that pretreatment of membranes with CEC dose-dep receptors increasing cyclic AMP and inositol phosphate<br>accumulation in rat cerebral cortex, these authors noted<br>that pretreatment of membranes with CEC dose-depend-<br>ently inactivated only approximately half of the  $\alpha_1$ receptors increasing cyclic AMP and inositol phosphate<br>accumulation in rat cerebral cortex, these authors noted<br>that pretreatment of membranes with CEC dose-depend-<br>ently inactivated only approximately half of the  $\alpha_1$ accumulation in rat cerebral cortex, these authors noted<br>that pretreatment of membranes with CEC dose-depend-<br>ently inactivated only approximately half of the  $\alpha_1$ -<br>adrenergic receptor binding sites. Further increasing ently inactivated only approximately half of the  $\alpha_1$ -<br>adrenergic receptor binding sites. Further increasing the<br>concentration of CEC by 100-fold caused no further<br>inactivation. This was in contrast to other alkylating<br> ently inactivated only approximately half of the  $\alpha_1$ -<br>adrenergic receptor binding sites. Further increasing the<br>concentration of CEC by 100-fold caused no further<br>inactivation. This was in contrast to other alkylating<br> adrenergic receptor binding sites. Further increasing to<br>concentration of CEC by 100-fold caused no furth<br>inactivation. This was in contrast to other alkylation<br>agents, including phenoxybenzamine, dibenamine, a<br>benextrami concentration of CEC by 100-fold caused no furth<br>inactivation. This was in contrast to other alkylati-<br>agents, including phenoxybenzamine, dibenamine, an<br>benextramine, which completely inactivated all  $\alpha_1$ -adi-<br>nergic r inactivation. This was in contrast to other alkylating<br>agents, including phenoxybenzamine, dibenamine, and<br>benextramine, which completely inactivated all  $\alpha_1$ -adre-<br>nergic receptor binding sites in this tissue in a mono agents, including phenoxybenzamine, dibenamine, benextramine, which completely inactivated all  $\alpha_1$ -adenergic receptor binding sites in this tissue in a mo<br>phasic manner (169, 240). Examination of the effec<br>CEC on other benextramine, which completely inactivated all  $\alpha_1$ -adre<br>nergic receptor binding sites in this tissue in a mono<br>phasic manner (169, 240). Examination of the effect c<br>CEC on other brain regions showed that CEC pretreat<br>m mergic receptor binding sites in this tissue in a mono-<br>phasic manner (169, 240). Examination of the effect of<br>CEC on other brain regions showed that CEC pretreat-<br>ment did not inactivate any  $\alpha_1$ -adrenergic receptor bi Dependent of the superior of the effect of CEC on other brain regions showed that CEC pretreatment did not inactivate any  $\alpha_1$ -adrenergic receptor binding sites in membranes from hippocampus (169). These results suggest ment did not inactivate any  $\alpha_1$ -adrenergic receptor bind-<br>ing sites in membranes from hippocampus (169). These<br>results suggested that there were two distinct types of<br> $\alpha_1$ -adrenergic receptor binding sites in rat cer ing sites in membranes from hippocampus (169). The<br>results suggested that there were two distinct types<br> $\alpha_1$ -adrenergic receptor binding sites in rat cerebral co<br>tex, only one of which could be inactivated by CEC. R<br>hip  $\alpha_1$ -adrenergic receptor binding sites in rat cerebral cor-<br>tex, only one of which could be inactivated by CEC. Rat<br>hippocampus appeared to contain only the type of recep-<br>tor insensitive to CEC inactivation. Comparing  $\alpha_1$ -adrenergic receptor-stimulated by CEC. Rat<br>hippocampus appeared to contain only the type of recep-<br>tor insensitive to CEC inactivation. Comparing the effect<br>of CEC on  $\alpha_1$ -adrenergic receptor-stimulated inositol<br> hippocampus appeared to contain only the type of receptor insensitive to CEC inactivation. Comparing the effect of CEC on  $\alpha_1$ -adrenergic receptor-stimulated inositol phosphate and cyclic AMP accumulation in cerebral co of CEC on  $\alpha_1$ -adrenergic receptor-stimulated inositol<br>phosphate and cyclic AMP accumulation in cerebral<br>cortex, however, gave inconclusive results (169). High phosphate and cyclic AMP accumulation in cerebral cortex, however, gave inconclusive results (169). High concentrations of CEC (100  $\mu$ M) were necessary to obtain significant inactivation in slice preparations. This high phosphate and cyclic AMP accumulation in cerebral<br>cortex, however, gave inconclusive results (169). High<br>concentrations of CEC (100  $\mu$ M) were necessary to obtain<br>significant inactivation in slice preparations. This high cortex, however, gave inconclusive results (169). High<br>concentrations of CEC (100  $\mu$ M) were necessary to obtain<br>significant inactivation in slice preparations. This high<br>concentration of CEC partially blocked the cyclic significant inactivation in slice preparations. This high concentration of CEC partially blocked the cyclic AMP response but had no significant effect on the inositol phosphate response. Although these results raised the significant inactivation in site preparations. This high<br>concentration of CEC partially blocked the cyclic AMP<br>response but had no significant effect on the inositol<br>phosphate response. Although these results raised the<br>po response but had no significant effect on the inositol<br>phosphate response. Although these results raised the<br>possibility that the receptors mediating these two re-<br>sponses might be differentially affected by CEC, since<br>onl phosphate response. Although these results raised the possibility that the receptors mediating these two responses might be differentially affected by CEC, since only small effects were seen at high concentrations, they w ssibility that the receptors mediating these two re-<br>onses might be differentially affected by CEC, since<br>ly small effects were seen at high concentrations, they<br>re difficult to interpret conclusively.<br>If different subtyp sponses might be differentially affected by CEC, since<br>only small effects were seen at high concentrations, they<br>were difficult to interpret conclusively.<br>If different subtypes of  $\alpha_1$ -adrenergic receptors were<br>differen

only small effects were seen at high concentrations, they<br>were difficult to interpret conclusively.<br>If different subtypes of  $\alpha_1$ -adrenergic receptors were<br>differentially sensitive to CEC, then it might be possible<br>to f

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 $\alpha_1$ -ADRENERGIC RECI<br>subtype. In screening a variety of tissues, Han et al. (130) t<br>showed that pretreatment of membranes from rat liver<br>or spleen with 10  $\mu$ M CEC caused a 70 to 80% loss of  $\alpha_1$ -ADRENERGIC RECE<br>subtype. In screening a variety of tissues, Han et al. (130) to<br>showed that pretreatment of membranes from rat liver<br>or spleen with 10  $\mu$ M CEC caused a 70 to 80% loss of T<br>specific <sup>125</sup>IBE bindin subtype. In screening a variety of tissues, Han et al.  $(130)$  ten<br>showed that pretreatment of membranes from rat liver sit<br>or spleen with 10  $\mu$ M CEC caused a 70 to 80% loss of Th<br>specific <sup>125</sup>IBE binding sites, but th Showed that pretreatment of membranes from rat five<br>or spleen with 10  $\mu$ M CEC caused a 70 to 80% loss of<br>specific <sup>125</sup>IBE binding sites, but that this treatment has<br>no effect on <sup>125</sup>IBE binding sites in membranes from specific  $^{125}$ IBE binding sites, but that this treatment had<br>no effect on  $^{125}$ IBE binding sites in membranes from rat<br>hippocampus or vas deferens. Interestingly, binding stud-<br>ies showed that CEC did not appear to ha specific <sup>125</sup>IBE binding sites, but that this treatment had<br>no effect on <sup>125</sup>IBE binding sites in membranes from rat<br>hippocampus or vas deferens. Interestingly, binding stud-<br>ies showed that CEC did not appear to have di the difference appeared to line ability of the difference appeared to lies showed that CEC did not appear to have different affinities in binding to the receptors in these different issues; the difference appeared to lie mppocampus or vas deferents. Interestingly, binding studies showed that CEC did not appear to have different with affinities in binding to the receptors in these different H tissues; the difference appeared to lie in the diminities in binding to the receptors in these different<br>tissues; the difference appeared to lie in the ability<br>CEC to inactivate the receptors (130). These resu<br>suggested that rat liver and spleen contained main<br>"CEC-se called that rat liver and spleared with it is ability.<br>CEC to inactivate the receptors (130). These resuggested that rat liver and spleen contained method.<br>"CEC-sensitive"  $\alpha_1$ -adrenergic receptors, while has campus and CEC to inactivate the receptors (130). These results pocaggested that rat liver and spleen contained mainly oge "CEC-sensitive"  $\alpha_1$ -adrenergic receptors, while hippo- (13 campus and vas deferens contained mainly "CEC-i exaggested that rat liver and spiesn contained mainly<br>
"CEC-sensitive"  $\alpha_1$ -adrenergic receptors, while hippo-<br>
campus and vas deferens contained mainly "CEC-insensitive" receptors. These findings were important for two "CEC-sensitive"  $\alpha_1$ -adrenergic receptors, while hippo- (130). This was in apparent contradiction to the almost campus and vas deferens contained mainly "CEC-insen-<br>sitive" receptors. These findings were important for t sitive" receptors. These findings were important for two deferens). These mainly were important for two tors in reasons. First, contractile responses to  $\alpha_1$ -adrenergic receptor stimulation could be measured in one of each of ian comparison the CEC-sensitive (spleen) and CECreasons. First, contractie responses to  $a_1$ -autenergic receptor stimulation could be measured in one of each of indiverse to the CEC-sensitive (spleen) and CEC-insensitive (vas sudeferens) tissues, allowing comparison of the CEC-sensitive (spieen) and CEC-insensitive (vectorians) tissues, allowing comparison of results from radioligand binding studies to functional studies on receptor activation. The selectivity of CEC in bindistudies was deferently ussues, allowing comparison of results from pure<br>radioligand binding studies to functional studies on receptor activation. The selectivity of CEC in binding vio<br>studies was shown to clearly extend to functional radioligand binding studies to functional studies on receptor activation. The selectivity of CEC in binding studies was shown to clearly extend to functional receptor activation. Pretreatment of intact tissues with 100  $\mu$ ceptor activation. The selectivity of CEC in binding viestudies was shown to clearly extend to functional recep-<br>tor activation. Pretreatment of intact tissues with 100 si<br> $\mu$ M CEC for 30 min greatly reduced the contract studies was shown to clearly extend to functional receptor activation. Pretreatment of intact tissues with  $100 \mu$ M CEC for 30 min greatly reduced the contractile response to norepinephrine in rat spleen, without affectin  $\mu$ M CEC for 30 min greatly reduced the contractile response to norepinephrine in rat spleen, without affecting<br>the response in vas deferens (fig. 11) (130). In addition,<br>these tissues could be used to easily screen for pharmacological differences between the proposed recep-<br>pharmacological differences between the proposed recep-<br>pharmacological differences between the proposed rece-<br>tor subtypes, particularly the affinities of competitio the response in vas deferens (fig. 11) (130). In addition, these tissues could be used to easily screen for other pharmacological differences between the proposed receptor subtypes, particularly the affinities of competiti antagonists. Exercises could be used to easily screen for other generational afferences between the proposed recep-<br>
r subtypes, particularly the affinities of competitive spices of a variety of agonists and<br>
In comparing the potencie

pharmacological differences between the proposed recep-<br>tor subtypes, particularly the affinities of competitive<br>antagonists.<br>In comparing the potencies of a variety of agonists and<br>antagonists in competing for  $^{125}$ IBE Franklynes, particularly the all inities of competitive antagonists.<br>
In comparing the potencies of a variety of agonists and a<br>
antagonists in competing for  $^{125}$ IBE binding sites in<br>
CEC-sensitive (liver) and insensit In comparing the potencies of a variety of agonists and<br>antagonists in competing for  $^{125}$ IBE binding sites in<br>CEC-sensitive (liver) and insensitive (hippocampus) tis-<br>sues, Han et al. (130) showed that several drugs ap antagonists in competing for <sup>125</sup>IBE binding sites in red<br>CEC-sensitive (liver) and insensitive (hippocampus) tis-<br>sues, Han et al. (130) showed that several drugs appeared<br>to have different potencies at the putative rec LEC-sensitive (iiver) and insensitive (inplocampus) tis-<br>sues, Han et al. (130) showed that several drugs appeared<br>to have different potencies at the putative receptor sub-<br>types. The most selective compound appeared to b by may different potenties at the putative receptor sub-<br>types. The most selective compound appeared to be the<br>imidazoline agonist oxymetazoline, which was 9-fold<br>more potent in hippocampus than liver.<br>6- to 7-fold more p imidazoline agonist oxymetazoline, which was 9-fold<br>more potent in hippocampus than liver, followed closely<br>by WB 4101 and its congener benoxathian, which were<br>in the<br>6- to 7-fold more potent in hippocampus than liver.<br>Ph more potent in hippocampus than liver, followed closely<br>by WB 4101 and its congener benoxathian, which were<br>6- to 7-fold more potent in hippocampus than liver.<br>Phentolamine also showed small (3-fold) differences in po-<br>pot

![](_page_22_Figure_6.jpeg)

- Log Norepinephrine (M)<br>FIG. 11. Effect of CEC on norepinephrine-induced contractions of<br>rat vas deferens  $(\alpha_{1a})$  and spleen  $(\alpha_{1b})$ . The selective antagonism of the **rature 1.1.** Effect of CEC on norepine<br>phrine-induced contractions of pratices deferens  $(\alpha_{1a})$  and spleen  $(\alpha_{1b})$ . The selective antagonism of the contractile response in spleen supports the selectivity of this drug i **contraction is a response <b>contraction**  $\mathbf{r}_1$ . Fro. 11. Effect of CEC on norepine<br>phrine-induced contractions of general vas deferens  $(\alpha_{1a})$  and spleen  $(\alpha_{1b})$ . The selective antagonism of the contractile response FIG. 11. Effect of CEC on norepine<br>phrine-induced contractions of rat vas deferens  $(\alpha_{1a})$  and spleen  $(\alpha_{1b})$ . The selective antagonism of the contractile response in spleen supports the selectivity of this drug in inac contractile response in spleen supports the selectivity of this drug in inactivating the  $\alpha_1$ -adrenergic receptors observed in radioligand binding **assays**. From Han et al. (130) with permission.

 $\alpha_1$ -ADRENERGIC RECEPTOR SUBTYPES<br>subtype. In screening a variety of tissues, Han et al. (130) tency were observed when  $\alpha_1$ -adrenergic receptor binding<br>showed that pretreatment of membranes from rat liver sites in sp EPTOR SUBTYPES<br>tency were observed when  $\alpha_1$ -adrenergic receptor binding EPTOR SUBTYPES 109<br>tency were observed when  $\alpha_1$ -adrenergic receptor binding<br>sites in spleen and vas deferens were compared (130).<br>The Hill coefficients for these apparently selective com-<br>petitive antagonists were clos tency were observed when  $\alpha_1$ -adrenergic receptor binding<br>sites in spleen and vas deferens were compared (130).<br>The Hill coefficients for these apparently selective com-<br>petitive antagonists were close to 1.0 in liver a consistent with the existence of a single receptor of a single sites in spleen and vas deferens were compared (130).<br>The Hill coefficients for these apparently selective competitive antagonists were close to 1.0 in liver a shees in spieen and vas deferens were compared (100).<br>The Hill coefficients for these apparently selective com-<br>petitive antagonists were close to 1.0 in liver and spleen,<br>consistent with the existence of a single receptor The Tim coefficients for these apparently selective com-<br>petitive antagonists were close to 1.0 in liver and spleen,<br>consistent with the existence of a single receptor subtype<br>predicted by the almost complete inactivation petitive antagonists were close to 1.0 in liver and spiceonsistent with the existence of a single receptor sub-<br>predicted by the almost complete inactivation observith CEC in these tissues. Surprisingly, however,<br>Hill coef trively and the substantially less than 1.0 in hip-<br>predicted by the almost complete inactivation observed<br>with CEC in these tissues. Surprisingly, however, the<br>Hill coefficients for the selective (but not the nonselec-<br>ti which CEC in these tissues. Surprisingly, however, the<br>Hill coefficients for the selective (but not the nonselec-<br>tive) antagonists were substantially less than 1.0 in hip-<br>pocampus and vas deferens, suggesting a possible Finit coefficients for the selective (but not the holiselective) antagonists were substantially less than 1.0 in hip-<br>pocampus and vas deferens, suggesting a possible heter-<br>ogeneity in the receptor populations in these ti cive) antagonists were substantiany less than 1.0 If in<br>pocampus and vas deferens, suggesting a possible het<br>ogeneity in the receptor populations in these tissu<br>(130). This was in apparent contradiction to the almo<br>complet pocampus and vas de<br>ogeneity in the reco<br>(130). This was in a<br>complete insensitivit<br>tors in these tissues.<br>Computer-assisted Computer-assisted analysis of WB 4101 and benoxath-<br>
ian computer-assisted analysis of WB 4101 and benoxath-<br>
ian computer-assisted analysis of WB 4101 and benoxath-<br>
ian competition curves showed that a two-site fit was<br>

complete insensitivity to CEC mactivation by the reflors in these tissues.<br>Computer-assisted analysis of WB 4101 and benox<br>ian competition curves showed that a two-site fit<br>substantially better than a one-site fit in the h computer-assisted analysis of WB 4101 and benoxath-<br>ian competition curves showed that a two-site fit was<br>substantially better than a one-site fit in the hippocam-<br>pus and vas deferens (131) with both sites existing in<br>ap Computer-assisted analysis of WB 4101 and behoxati-<br>ian competition curves showed that a two-site fit was<br>substantially better than a one-site fit in the hippocam-<br>pus and vas deferens (131) with both sites existing in<br>app substantially better than a one-site fit in the hippocam-<br>pus and vas deferens (131) with both sites existing in<br>approximately equal proportions, in agreement with pre-<br>vious results in the cerebral cortex and hippocampus pus and vas deferens (151) with both sites existing in<br>approximately equal proportions, in agreement with pre-<br>vious results in the cerebral cortex and hippocampus<br>(253, 254). Liver and spleen appeared to contain only a<br>si vious results in the cerebral cortex and hippocampus  $(253, 254)$ . Liver and spleen appeared to contain only a single type of binding site, and the affinity of both WB 4101 and benoxathian for this site in liver and splee (200, 204). Liver and spiesn appeared to contain only a<br>single type of binding site, and the affinity of both WE<br>4101 and benoxathian for this site in liver and spleer<br>agreed well with the affinity for the relatively low a 4101 and benoxathian for this site in liver and spleen<br>agreed well with the affinity for the relatively low affinity<br>site in hippocampus and vas deferens. These data sug-<br>gested that hippocampus and vas deferens contained agreed well with the affinity for the relatively low affinity<br>site in hippocampus and vas deferens. These data suggested that hippocampus and vas deferens contained<br>both  $\alpha_{1a}$ - and  $\alpha_{1b}$ -type binding sites, while li agreed well with the affinity for the relatively low affinity<br>site in hippocampus and vas deferens. These data suggested that hippocampus and vas deferens contained<br>both  $\alpha_{1a}$ - and  $\alpha_{1b}$ -type binding sites, while li site in hippocampus and vas deferens. These data suffered that hippocampus and vas deferens contain both  $\alpha_{1a}$ - and  $\alpha_{1b}$ -type binding sites, while liver as spleen had only the  $\alpha_{1b}$ - subtype, as defined by Morro both  $\alpha_{1a}$ - and  $\alpha_{1b}$ -type binding sites, while liver and spleen had only the  $\alpha_{1b}$ - subtype, as defined by Morrov and Creese (254). To determine whether these differences in binding sites were reflected in the f both  $\alpha_{1a}$ - and  $\alpha_{1b}$ -type binding sites, while liver and  $\omega_a$ <br>spleen had only the  $\alpha_{1b}$ - subtype, as defined by Morrow<br>and Creese (254). To determine whether these differ-<br>ences in binding sites were reflected and Creese (254). To determine whether these differences in binding sites were reflected in the functional receptors, the potencies of these antagonists in blocking  $\alpha_1$ -adrenergic receptor-mediated contractile response ences in binding sites were reflected in the functional<br>receptors, the potencies of these antagonists in blocking<br> $\alpha_1$ -adrenergic receptor-mediated contractile responses in<br>rat spleen and vas deferens were determined. B receptors, the potencies of these antagomists in blocking<br>  $\alpha_1$ -adrenergic receptor-mediated contractile responses in<br>
rat spleen and vas deferens were determined. Both WB<br>
4101 and benoxathian were 10- to 20-fold more For speed and vas deterent were determined. Both WB<br>4101 and benoxathian were 10- to 20-fold more potent<br>in blocking contractions of vas deferens (containing both<br>subtypes) than in blocking contractions of spleen (con-<br>ta Fivid and behold all with the 10<sup>-1</sup>  $\omega$  20-101d libre potent in blocking contractions of vas deferens (containing both subtypes) than in blocking contractions of spleen (containing only the  $\alpha_{1b}$ -subtype). The pA<sub>2</sub> subtypes) than in blocking contractions of spleen (containing only the  $\alpha_{1b}$ -subtype). The pA<sub>2</sub> values calculated<br>in the vas deferens agreed well with the pK<sub>d</sub> values for<br>the  $\alpha_{1a}$ -subtype, while pA<sub>2</sub> values obta the vasile d<sub>1b</sub>-subtype). The p<sub>A2</sub> values calculation the vas deferens agreed well with the p $K_d$  values the  $\alpha_{1a}$ -subtype, while pA<sub>2</sub> values obtained in the splagreed well with the p $K_d$  values for the  $\alpha_{1b}$ -sub It the vas determis agreed went with the  $p_{\text{H}_d}$  values for the  $\alpha_{1a}$ -subtype, while  $p_{\text{H}_d}$  values for the  $\alpha_{1b}$ -subtype (131). These results suggested that the binding sites differentiated by WB 4101 repre agreed well with the p $K_d$  values for the  $\alpha_{1b}$ -subtype (131).  $\sum_{i=1}^{\infty}$  agreed well with the p $K_d$  values for the  $\alpha_{1b}$ -subtype (131). These results suggested that the binding sites differentiated by WB 4101 r These results suggested that the binding sites differentiated by WB 4101 represented true receptor subtypes, and that activation of both subtypes could activate contractile responses in different tissues. Although binding and that activation of both subtypes could activate corractile responses in different tissues. Although bindistudies showed that the rat vas deferens contained botypes of receptors, only the  $\alpha_{1a}$  subtype appeared to i tractile responses in different tissues. Although binding<br>studies showed that the rat vas deferens contained both<br>types of receptors, only the  $\alpha_{1a}$  subtype appeared to be<br>involved in the contractile response to norepi studies showed that the rat vas deferens contained both<br>types of receptors, only the  $\alpha_{1a}$  subtype appeared to be<br>involved in the contractile response to norepinephrine.<br>The contractile response of rat spleen to norepi involved in the contractile response to norepinephrine.<br>The contractile response of rat spleen to norepinephrine<br>was mediated by the  $\alpha_{1b}$ -subtype, which was the only<br>subtype found in the tissue with binding studies.

Taken together, the similarity between the results The contractile response of rat spleen to norepinephrine<br>was mediated by the  $\alpha_{1b}$ -subtype, which was the only<br>subtype found in the tissue with binding studies.<br>Taken together, the similarity between the results<br>from b was mediated by the  $\alpha_{1b}$ -subtype, which was the only subtype found in the tissue with binding studies.<br>Taken together, the similarity between the results from both binding and functional studies strongly suggested the ratent together, the similarity between the results<br>from both binding and functional studies strongly suggested the existence of two subtypes of  $\alpha_1$ -adrenergic<br>receptors with different sensitivities to CEC and differ-<br>

110 **MINNEMAN**<br>tion between CEC sensitivity and the proportion of low for WI<br>affinity WB 4101 binding sites  $(\alpha_{1b})$  in each tissue, there an EC<sub>c</sub> 110 **and ST and ST and ST and ST and ST and ST affinity WB 4101 binding sites**  $(\alpha_{1b})$  **in each tissue, there a was not quantitative agreement between these two ap-<br>proaches. In all tissues, a substantially greater proport** tion between CEC sensitivity and the proportion of low<br>affinity WB 4101 binding sites  $(\alpha_{1b})$  in each tissue, there<br>was not quantitative agreement between these two ap-<br>proaches. In all tissues, a substantially greater p tion between CEC sensitivity and the proportion of low<br>affinity WB 4101 binding sites  $(\alpha_{1b})$  in each tissue, there<br>was not quantitative agreement between these two ap-<br>proaches. In all tissues, a substantially greater p affinity WB 4101 binding sites  $(\alpha_{1b})$  in each tissue, the was not quantitative agreement between these two proaches. In all tissues, a substantially greater propor of the receptors had a low affinity for WB 4101 tould b was not quantitative agreement between these two<br>proaches. In all tissues, a substantially greater proport<br>of the receptors had a low affinity for WB 4101 tl<br>could be inactivated by CEC. Although both hippoce<br>pus and vas d proacnes. In an ussues, a substantianty greater proportion of the receptors had a low affinity for WB 4101 than yould be inactivated by CEC. Although both hippocam-<br>pus and vas deferens appeared to contain equal propor-<br>ti sites in these tissues (130). Similarly, although liver and was deferent appeared to contain equal propor-<br>tions of the two subtypes defined with WB 4101 (131), there was no effect of CEC inactivation on the binding im<br>si pus and vas deferents appeared to contain equal proportions of the two subtypes defined with WB 4101 (131), there was no effect of CEC inactivation on the binding sites in these tissues (130). Similarly, although liver an there was no effect of CEC inactivation on the binding is<br>sites in these tissues (130). Similarly, although liver and<br>spleen appeared to contain only the  $\alpha_{1b}$ -subtype as de-<br>fined with WB 4101 (131), 20 to 30% of the there was no enect of CEC mactivation on the ontain<br>sites in these tissues (130). Similarly, although liver an<br>spleen appeared to contain only the  $\alpha_{1b}$ -subtype as do<br>fined with WB 4101 (131), 20 to 30% of the binding

spleen appeared to contain only the  $\alpha_{1b}$ -subtype as de-<br>fined with WB 4101 (131), 20 to 30% of the binding sites we<br>were resistant to inactivation by CEC (130).<br>Further studies showed that this discrepancy was prob-<br>a water-soluble compound, under the conditions studied (246). When membranes from rat hippocampus were  $\frac{1}{2}$  (246). When membranes from rat hippocampus were  $\frac{1}{2}$ were resistant to inactivation by CEC (150).<br>Further studies showed that this discrepancy was prob-<br>ably caused by incomplete inactivation by CEC, a highly<br>water-soluble compound, under the conditions studied<br>(246). When Further studies showed that this discrepancy was probably caused by incomplete inactivation by CEC, a highly<br>water-soluble compound, under the conditions studied<br>(246). When membranes from rat hippocampus were<br>repetitivel water-soluble compound, under the conditions studied<br>
(246). When membranes from rat hippocampus were<br>
repetitively exposed to four separate incubations with 10<br>  $\mu$ M CEC, 25% of the binding sites were inactivated. These (246). When membranes from rat inppocampus were<br>repetitively exposed to four separate incubations with 10<br>results suggested that CEC might not be able to gain<br>access to all the  $\alpha_1$ -adrenergic receptors in a single in-<br>  $\mu$ M CEC, 25% of the binding sites were inactivated. These<br>results suggested that CEC might not be able to gain<br>access to all the  $\alpha_1$ -adrenergic receptors in a single in-<br>cubation period. All CEC inactivation experime results suggested that CEC imglit flot be able to gain<br>access to all the  $\alpha_1$ -adrenergic receptors in a single in-<br>cubation period. All CEC inactivation experiments had<br>been performed in phosphate-buffered saline which access to an the d<sub>1</sub>-adientryc receptors in a single in-<br>cubation period. All CEC inactivation experiments had<br>been performed in phosphate-buffered saline which is<br>routinely used for <sup>125</sup>IBE binding experiments. Since<br>su been performed in phosphate-buffered saline which is<br>routinely used for <sup>125</sup>IBE binding experiments. Since<br>such isotonic conditions promote resealing of vesicles<br>following tissue homogenization, the high water solubil-<br>i bilayers to gain access to binding sites in a hypotonic buffer (10 mM sodium<br>
binding sites in a hypotonic buffer (10 mM sodium<br>
bilayers to gain access to binding sites enclosed in such and proportional contraction of sm following tissue homogenization, the high water solubil-<br>ity of CEC might have prevented it from crossing lipid<br>bilayers to gain access to binding sites enclosed in such<br>vesicles. Therefore the ability of CEC to inactivat binding ussue homogenization, the high water solubility of CEC might have prevented it from crossing lipid<br>bilayers to gain access to binding sites enclosed in such vesicles. Therefore the ability of CEC to inactivate  $^{1$ bilayers to gain access to binding sites enclosed in successicles. Therefore the ability of CEC to inactivate  $^{125}$ IB binding sites in a hypotonic buffer (10 mM sodium Hepes) which would promote vesicle lysis was tested vesicles. Therefore the ability of CEC to inactivate  $^{125}$ IBE<br>binding sites in a hypotonic buffer (10 mM sodium<br>Hepes) which would promote vesicle lysis was tested.<br>CEC caused a much greater inactivation of  $^{125}$ IBE b binding sites in a hypotonic buffer (10 mM sodium<br>Hepes) which would promote vesicle lysis was tested.<br>CEC caused a much greater inactivation of <sup>125</sup>IBE bind-<br>ing sites under such hypotonic conditions in all tissues<br>exam Hepes) which would promote vesicle lysis was tested.<br>CEC caused a much greater inactivation of <sup>125</sup>IBE binding sites under such hypotonic conditions in all tissues<br>examined than had been observed under the isotonic<br>condi CEC caused a much greater inactivation of <sup>125</sup>IBE bind-<br>ing sites under such hypotonic conditions in all tissues<br>examined than had been observed under the isotonic<br>conditions used previously (246). In the presence of<br>iso ing sites under such hypotonic conditions in all tissuexamined than had been observed under the isotor conditions used previously (246). In the presence isotonic NaCl, 10  $\mu$ M CEC had no effect on the density of sites in conditions used previously  $(246)$ . In the presence of isotonic NaCl, 10  $\mu$ M CEC had no effect on the density of sites in hippocampus, while under hypotonic conditions this treatment caused a 41% loss in binding sites. conductions used previously (240). In the presence of ever, neither WB 4101 nor CEC was examined in these<br>isotonic NaCl, 10  $\mu$ M CEC had no effect on the density<br>of sites in hippocampus, while under hypotonic condi-<br>tion other tissues (246). When the proportion of  $\alpha_1$ -adrenergic<br>receptor binding sites with a low affinity for WB 4101 of sites in hippocampus, while under hypotonic condi-<br>tions this treatment caused a 41% loss in binding sites.<br>Similar increases in inactivation were observed in all<br>other tissues (246). When the proportion of  $\alpha_1$ -adre tions this treatment caused a 41% loss in binding sites<br>Similar increases in inactivation were observed in all<br>other tissues (246). When the proportion of  $\alpha_1$ -adrenergi<br>receptor binding sites with a low affinity for WB Similar increases in inactivation were observed in a other tissues (246). When the proportion of  $\alpha_1$ -adrenerg receptor binding sites with a low affinity for WB 410 was compared to the proportion sensitive to CEC inativ other tissues (246). When the proportion of  $\alpha_1$ -adrenergic<br>receptor binding sites with a low affinity for WB 4101<br>was compared to the proportion sensitive to CEC inac-<br>tivation under hypotonic conditions, an excellent leceptor binding sites with a low allmity for WB 4101 in<br>was compared to the proportion sensitive to CEC inac-<br>tivation under hypotonic conditions, an excellent corre-<br>lation was observed. The best fit line was close to t was compared to the proportion sensitive to CEC mac-<br>tivation under hypotonic conditions, an excellent corre-<br>lation was observed. The best fit line was close to the<br>line of identity, suggesting that these two methods are<br> Evation under hypotome conditions, an excellent correlation was observed. The best fit line was close to the line of identity, suggesting that these two methods are distinguishing the same subpopulations of binding sites. line of identity, suggesting that these two methods are CEC (130, 131). Conversely, norepinephrine-mediated distinguishing the same subpopulations of binding sites.<br>Finally, when WB 4101 inhibition curves were examined by Finally, when WB 4101 inhibition curves were examined<br>following pretreatment of membranes from hippocampus<br>or vas deferens with CEC, the apparent low affinity sites<br>had been eliminated (246).<br>These results suggest that tw These results suggest that two subtypes of a1-adrenerfollowing pretreatment of membranes from hippocampus<br>or vas deferens with CEC, the apparent low affinity sites<br>had been eliminated (246).<br>These results suggest that two subtypes of  $\alpha_1$ -adrener-<br>gic receptors can be dif

and been eliminated (246).<br>
and been eliminated (246).<br>
These results suggest that two subtypes of  $\alpha_1$ -adrener-<br>
gic receptors can be differentiated by the competitive<br>
antagonist WB 4101 and the alkylating agent CEC. These results suggest that two subtypes of  $\alpha_1$ -adrener-<br>gic receptors can be differentiated by the competitive spon<br>antagonist WB 4101 and the alkylating agent CEC. The dipi<br> $\alpha_{1a}$  subtype has a high affinity for WB gic receptors can be differentiated by the competitive sponse of spleen  $(\alpha_{1b})$  (fig. 12). In the presence of nife-<br>antagonist WB 4101 and the alkylating agent CEC. The dipine, a residual contractile response was observe

MAN<br>for WB 4101 (p $K_d$  8.0) and is inactivated by CEC with<br>an EC<sub>50</sub> around 1  $\mu$ M. The relationship of these receptor<br>subtypes to those differentiated by prazosin, yohimbine, MAN<br>for WB 4101 (p $K_d$  8.0) and is inactivated by CEC wit<br>an EC<sub>50</sub> around 1  $\mu$ M. The relationship of these recepto<br>subtypes to those differentiated by prazosin, yohimbine<br>or selective agonists is not yet clear. Both pr for WB 4101 (p $K_d$  8.0) and is inactivated by CEC with<br>an EC<sub>50</sub> around 1  $\mu$ M. The relationship of these receptor<br>subtypes to those differentiated by prazosin, yohimbine,<br>or selective agonists is not yet clear. Both pra an EC<sub>50</sub> around 1  $\mu$ M. The relationship of these receptor subtypes to those differentiated by prazosin, yohimbine, or selective agonists is not yet clear. Both prazosin and yohimbine appear to have similar affinities f or selective agonists is not yet clear. Both prazosin and yohimbine appear to have similar affinities for both of these subtypes (131) (p $K_d$ s of 9 and 6, respectively). Although oxymetazoline appears to distinguish betwe subtypes to those differentiated by prazosin, yohimbine,<br>or selective agonists is not yet clear. Both prazosin and<br>yohimbine appear to have similar affinities for both of<br>these subtypes (131) (p $K_d$ s of 9 and 6, respectiv or selective agonists is not yet clear. Both prazosin and<br>yohimbine appear to have similar affinities for both of<br>these subtypes (131) (p $K_{d}s$  of 9 and 6, respectively).<br>Although oxymetazoline appears to distinguish betw yonimoine appear to have similar armitties for both of<br>these subtypes (131) (p $K_d$ s of 9 and 6, respectively).<br>Although oxymetazoline appears to distinguish between<br>these receptors (p $K_d$ s of 8 and 6.8), clonidine and oth these subtypes. (131) ( $pA_d$ s or  $\theta$  and  $\theta$ , respectively).<br>Although oxymetazoline appears to distinguish between<br>these receptors ( $pK_d$ s of 8 and 6.8), clonidine and other<br>imidazolines appear to have similar affinitie Atthough oxymetazoine appears to distinguish betwee<br>these receptors ( $pK_d s$  of 8 and 6.8), clonidine and oth<br>imidazolines appear to have similar affinities for bo<br>subtypes. The actual interrelationships between the<br>studie work. imidazolines appear to have similar affinities for both<br>subtypes. The actual interrelationships between these<br>studies will need to be clarified by further experimental<br>work.<br>XI. Relationship to Inositol Phospholipid<br>Metabo

## **XI. Relationship to Inositol Phospholipid**

Once strong evidence for pharmacologically distinct **XI. Relationship to Inositol Phospholipid**<br>Metabolism and  $Ca^{2+}$  Influx<br>Once strong evidence for pharmacologically distinct<br> $\alpha_1$ -adrenergic receptor subtypes was obtained, one of the<br>first interesting questions to be **Metabolism and Ca<sup>2+</sup> Influx**<br>Once strong evidence for pharmacologically distinct<br> $\alpha_1$ -adrenergic receptor subtypes was obtained, one of the<br>first interesting questions to be answered is whether they<br>utilize the same s Once strong evidence for pharmacologically distinct  $\alpha_1$ -adrenergic receptor subtypes was obtained, one of the first interesting questions to be answered is whether they utilize the same signal transduction mechanism. T Once strong evidence for pharmacologically distinct  $\alpha_1$ -adrenergic receptor subtypes was obtained, one of the first interesting questions to be answered is whether they utilize the same signal transduction mechanism. T Inst interesting questions to be answered is whether they<br>utilize the same signal transduction mechanism. The<br>availability of specific and well-characterized drugs<br>which clearly distinguish between different receptor sub-<br> that different receptor subtypes are linked to the alternate receptor subtypes makes it relatively easy to examine the possibilities that different receptor subtypes are linked to the alternate signal transduction mechanis types makes it relatively easy to examine the possibilities<br>that different receptor subtypes are linked to the alter-

Lular Ca<sup>2+</sup> for  $\alpha_1$ -adrenergic receptor-mediated contraction of smooth muscle raise the obvious possibility in the importance of extrac-mediated contrac-mediated contrac-mediated contrac-mediated contrac-mediated cont that different receptor subtypes are inked to the alternate signal transduction mechanisms discussed above.<br>The marked variations in the importance of extracel-<br>lular Ca<sup>2+</sup> for  $\alpha_1$ -adrenergic receptor-mediated contrac nate signal transduction mechanisms discussed above.<br>
The marked variations in the importance of extracel-<br>
lular Ca<sup>2+</sup> for  $\alpha_1$ -adrenergic receptor-mediated contrac-<br>
tion of smooth muscle raise the obvious possibilit fular Ca for  $\alpha_1$ -adrenergic receptor-mediated contraction of smooth muscle raise the obvious possibility that<br>one receptor subtype might release intracellular Ca<sup>2+</sup>,<br>while the other might promote Ca<sup>2+</sup> influx (147, 2 one receptor subtype might release intracellular  $Ca^{2+}$ while the other might promote  $Ca^{2+}$  influx (147, 228)<br>(see above). As discussed above, Korstanje et al. (191)<br>and Beckeringh et al. (16) showed that several competi-<br>tive antagonists had similar potencies in blocking bo while the other might promote  $Ca^{2+}$  influx (147, 228) (see above). As discussed above, Korstanje et al. (191) and Beckeringh et al. (16) showed that several competitive antagonists had similar potencies in blocking both (see above). As discussed above, Korstanje et al. (191) and Beckeringh et al. (16) showed that several competitive antagonists had similar potencies in blocking both Ca<sup>2+</sup> influx-dependent and independent responses to  $\$ and Beckeringh et al. (16) showed that several competitive antagonists had similar potencies in blocking both  $Ca^{2+}$  influx-dependent and independent responses to  $\alpha_1$ -adrenergic receptor agonists, concluding that the Ca<sup>-1</sup> initux-dependent and independent responses to  $\alpha_1$ <br>adrenergic receptor agonists, concluding that the same<br>receptor subtypes were involved in both processes. How<br>ever, neither WB 4101 nor CEC was examined in these adrenergic receptor agonists, concluding that the same<br>receptor subtypes were involved in both processes. How-<br>ever, neither WB 4101 nor CEC was examined in these<br>studies. When both binding and functional studies sug-<br>ges receptor subtypes were involved in both processes. However, neither WB 4101 nor CEC was examined in these studies. When both binding and functional studies suggested the existence of  $\alpha_{1a}$ - and  $\alpha_{1b}$ -adrenergic rece ever, nether WB 4101 nor CEC was examined in these<br>studies. When both binding and functional studies sug-<br>gested the existence of  $\alpha_{1a}$ - and  $\alpha_{1b}$ -adrenergic receptors<br>differentiated by these two compounds, it was o studies. When both binding and functional studings<br>gested the existence of  $\alpha_{1a}$ - and  $\alpha_{1b}$ -adrenergic redifferentiated by these two compounds, it was of i<br>to examine the role of  $Ca^{2+}$  influx in the con<br>responses gested the existence of  $\alpha_{1a}$ - and  $\alpha_{1b}$ -adrenergic receptors<br>differentiated by these two compounds, it was of interest<br>to examine the role of  $Ca^{2+}$  influx in the contractile<br>responses initiated by each subtype. N differentiated by these two compounds, it was of interest<br>to examine the role of  $Ca^{2+}$  influx in the contractile<br>responses initiated by each subtype. Norepinephrine-<br>induced contractions of rat vas deferens appear to be Once strong evidence for pharmacologically distinct<br>  $\alpha_1$ -adrenergic receptor subtypes was obtained, one of the<br>
first interesting questions to be answered is whether they<br>
trilize the same signal transduction mechanism  $pA<sub>2</sub>$  for WB 4101 is about 9.3 and the contractile response is completely unaffected by pretreatment with 100  $\mu$ M is completely unaffected by pretreatment with 100  $\mu$ M<br>CEC (130, 131). Conversely, norepinephrine-mediated<br>contractions of rat spleen appear to be mediated solely<br>by  $\alpha_{1b}$ -adrenergic receptors, since they are blocked CEC (130, 131). Conversely, norepinephrine-mediated<br>contractions of rat spleen appear to be mediated solely<br>by  $\alpha_{1b}$ -adrenergic receptors, since they are blocked by<br>WB 4101 with a pA<sub>2</sub> of 8.0 and are markedly antagoni contractions or rat spieen appear to be mediated solety<br>by  $\alpha_{1b}$ -adrenergic receptors, since they are blocked by<br>WB 4101 with a pA<sub>2</sub> of 8.0 and are markedly antagonized<br>by CEC pretreatment. Han et al. (131) showed tha by  $\alpha_{1b}$ -adrenergic receptors, since they are blocked by<br>WB 4101 with a pA<sub>2</sub> of 8.0 and are markedly antagonized<br>by CEC pretreatment. Han et al. (131) showed that 1  $\mu$ M<br>nifedipine markedly reduced the contractile re WB 4101 with a pA<sub>2</sub> of 8.0 and are markedly antagonizee<br>by CEC pretreatment. Han et al. (131) showed that 1  $\mu$ N<br>nifedipine markedly reduced the contractile response o<br>vas deferens ( $\alpha_{1a}$ ) but did not affect the cont by CEC pretreatment. Han et al. (131) showed that 1  $\mu$ M<br>nifedipine markedly reduced the contractile response of<br>vas deferens  $(\alpha_{1a})$  but did not affect the contractile re-<br>sponse of spleen  $(\alpha_{1b})$  (fig. 12). In the pr nire<br>applies markedly reduced the contractile response of<br>vas deferens  $(\alpha_{1a})$  but did not affect the contractile re-<br>sponse of spleen  $(\alpha_{1b})$  (fig. 12). In the presence of nife-<br>dipine, a residual contractile response vas dererens  $(\alpha_{1a})$  out did not arrect the contractile re-<br>sponse of spleen  $(\alpha_{1b})$  (fig. 12). In the presence of nife-<br>dipine, a residual contractile response was observed in<br>vas deferens, but this response was much l

ъM .<br>Nifediaine

![](_page_24_Figure_1.jpeg)

 $\alpha_{14}$ -anoneight receptors may aller the permeability of diffusion. Bars<br>sensitive Ca<sup>2+</sup> channels. From Han et al. (131) with permission. Bars<br>SE.<br>show to exist in this tissue, can mediate contraction<br>when the other su SE.<br>show to exist in this tissue, can mediate contraction<br>when the other subtype is functionally neutralized. Sim-<br>ilarly, chelation of extracellular Ca<sup>2+</sup> with EGTA almost<br>abolished the contractile response of vas defere show to exist in this tissue, can mediate contraction<br>when the other subtype is functionally neutralized. Similarly, chelation of extracellular  $Ca^{2+}$  with EGTA almost<br>abolished the contractile response of vas deferens, show to exist in this tissue,<br>when the other subtype is func<br>ilarly, chelation of extracellula<br>abolished the contractile respo<br>had no effect in spleen (131).<br>These studies clearly resurre nen the other subtype is functionally neutralized. Singly, chelation of extracellular  $Ca^{2+}$  with EGTA alm olished the contractile response of vas deferens, d no effect in spleen (131).<br>These studies clearly resurrect th

 $1.0$ 

 $0.5$ 

marry, cheration of extracemular Ca<sup>2</sup> with EGTA almost abolished the contractile response of vas deferens, but had no effect in spleen (131).<br>
These studies clearly resurrect the intriguing possibility that Ca<sup>2+</sup> influx had no effect in spleen (131).<br>These studies clearly resurrect the intriguing possibil-<br>ity that Ca<sup>2+</sup> influx-dependent and independent con-<br>tractile responses to  $\alpha_1$ -adrenergic receptor activation<br>are mediated by pha These studies clearly resurrect the intriguing possibility that  $Ca^{2+}$  influx-dependent and independent contractile responses to  $\alpha_1$ -adrenergic receptor activation are mediated by pharmacologically distinct receptor s riese status clearly resulted the intriguing possiblical isotophate formation in brain and other tissues (124,<br>ity that Ca<sup>2+</sup> influx-dependent and independent con-<br>tractile responses to  $\alpha_1$ -adrenergic receptor activat  $\alpha_{1b}$ -adrenergic receptors may cause release of stored inare mediated by pharmacologically distinct receptor sub-<br>types. We hypothesized that activation of  $\alpha_{1a}$ -adrenergic<br>receptors may primarily activate  $Ca^{2+}$  influx through<br>dihydropyridine-sensitive channels, while acti types. We hypothesized that activation of  $\alpha_{1a}$ -adrenergic<br>receptors may primarily activate  $Ca^{2+}$  influx through<br>dihydropyridine-sensitive channels, while activation of<br> $\alpha_{1b}$ -adrenergic receptors may cause release receptors may primarily activate  $Ca^{2+}$  influx through<br>dihydropyridine-sensitive channels, while activation of<br> $\alpha_{1b}$ -adrenergic receptors may cause release of stored in-<br>tracellular  $Ca^{2+}$  (131). However, many more t dihydropyridine-sensitive channels, while activation of  $\alpha_{1b}$ -adrenergic receptors may cause release of stored in-<br>tracellular Ca<sup>2+</sup> (131). However, many more tissues need<br>to be examined before unequivocal conclusions  $\alpha_{1b}$ -adrenergic receptors may cause release of stored in-<br>tracellular Ca<sup>2+</sup> (131). However, many more tissues need<br>to be examined before unequivocal conclusions can be<br>drawn. Unfortunately, we have found that in many to be examined before unequivocal conclusions can be<br>
drawn. Unfortunately, we have found that in many tis-<br>
sues contractile responses to norepinephrine appear to<br>
involve both  $\alpha_1$ -adrenergic receptor subtypes to diff to be examined before unequivocal conclusions can be<br>drawn. Unfortunately, we have found that in many tis-<br>sues contractile responses to norepinephrine appear to<br>involve both  $\alpha_1$ -adrenergic receptor subtypes to differi drawn. Unfortunately, we have found that in many tis-<br>sues contractile responses to norepinephrine appear to<br>involve both  $\alpha_1$ -adrenergic receptor subtypes to differing<br>degrees. We seem to have been fortunate in happeni sues contractile responses to norepinephrine appear to involve both  $\alpha_1$ -adrenergic receptor subtypes to differing creating degrees. We seem to have been fortunate in happening mediated by only a gic single receptor sub involve both  $\alpha_1$ -adrenergic receptor subtypes to differing creasure degrees. We seem to have been fortunate in happening more upon the clear differentiation between vas deferens and spleen, where responses appear to be degrees. We seem to have been fortunate in happening<br>upon the clear differentiation between vas deferens and<br>spleen, where responses appear to be mediated by only a<br>single receptor subtype. In general, this appears to be t upon the clear differentiation bespleen, where responses appear to single receptor subtype. In gener exception rather than the rule Minneman, unpublished data). If this hypothesis is correct, leen, where responses appear to be mediated by only a<br>ngle receptor subtype. In general, this appears to be the<br>ception rather than the rule (P. W. Abel and K. P.<br>inneman, unpublished data).<br>If this hypothesis is correct,

single receptor subtype. In general, this appears to be the exception rather than the rule (P. W. Abel and K. P. W. Minneman, unpublished data).<br>If this hypothesis is correct, one would predict that ponly  $\alpha_{1b}$ -adrener Minneman, unpublished data).<br>
If this hypothesis is correct, one would predict that<br>
only  $\alpha_{1b}$ -adrenergic receptors would be linked to hydrol-<br>
ysis of PIP<sub>2</sub> and formation of Ins(1,4,5)P<sub>3</sub>, since it is this<br>
latter If this hypothesis is correct, one would predict that P<br>only  $\alpha_{1b}$ -adrenergic receptors would be linked to hydrol-<br>ysis of PIP<sub>2</sub> and formation of Ins(1,4,5)P<sub>3</sub>, since it is this this<br>latter compound that releases sto only  $\alpha_{1b}$ -adrenergic receptors would be linked to hydrol-<br>ysis of  $\text{PIP}_2$  and formation of  $\text{Ins}(1,4,5)P_3$ , since it is this<br>latter compound that releases stored intracellular  $\text{Ca}^{2+}$ .<br>The evidence we have obta ysis of PIP<sub>2</sub> and formation of Ins(1,4,5)P<sub>3</sub>, since it is this that the latter compound that releases stored intracellular Ca<sup>2+</sup>. <sup>U</sup><br>The evidence we have obtained to date supports this chypothesis. Han et al. (131) de increases such a intracement Ca.<br>The evidence we have obtained to date supports this<br>hypothesis. Han et al. (131) determined  $pA_2$  values for<br>WB 4101 in blocking norepinephrine-stimulated  $[^3H]$ <br>inositol phosphate accumu The evidence we have obtained to date supports this<br>hypothesis. Han et al. (131) determined  $pA_2$  values for<br>WB 4101 in blocking norepinephrine-stimulated [<sup>3</sup>H]<br>inositol phosphate accumulation in the presence of lith-<br>i hypothesis. Han et al. (131) determined p $A_2$  values for WB 4101 in blocking norepinephrine-stimulated [<sup>3</sup>H] inositol phosphate accumulation in the presence of lithium in tissues which, from radioligand binding assays, WB 4101 in blocking norepinephrine-stimulated [<sup>3</sup>H] inositol phosphate accumulation in the presence of lith-<br>ium in tissues which, from radioligand binding assays,<br>were known to contain both  $\alpha_1$ -adrenergic receptor su ium in tissues which, from radioligand binding assays,<br>were known to contain both  $\alpha_1$ -adrenergic receptor sub-<br>types. The pA<sub>2</sub> values ranged from 8 to 8.3 in all tissues<br>examined, suggesting that only  $\alpha_{1b}$ -adrener

EPTOR SUBTYPES 111<br>were activating this response. In fact, the pA<sub>2</sub> for WB<br>4101 in blocking norepinephrine-stimulated [<sup>3</sup>H]inositol EPTOR SUBTYPES<br>were activating this response. In fact, the  $pA_2$  for W1<br>4101 in blocking norepinephrine-stimulated [<sup>3</sup>H]inosito<br>phosphate accumulation in the rat vas deferens (108 EPTOR SUBTYPES 111<br>were activating this response. In fact, the pA<sub>2</sub> for WB<br>4101 in blocking norepinephrine-stimulated [<sup>3</sup>H]inositol<br>phosphate accumulation in the rat vas deferens (108)<br>was found to be 8.2, even though t were activating this response. In fact, the  $p_{12}$  for WB<br>4101 in blocking norepinephrine-stimulated [<sup>3</sup>H]inositol<br>phosphate accumulation in the rat vas deferens (108)<br>was found to be 8.2, even though the  $p_{12}$  for th A to I in blocking horepmephrime-sumulated [  $H$ ] inostion<br>phosphate accumulation in the rat vas deferens (108<br>was found to be 8.2, even though the  $pA_2$  for this drug is<br>blocking the contractile response in this tissue phosphate accumulation in the rat vas deterents (106)<br>was found to be 8.2, even though the  $pA_2$  for this drug in<br>blocking the contractile response in this tissue was 9.3<br>(131). Thus it appeared that, in this tissue whic blocking the contractile response in this tissue was 9.3 (131). Thus it appeared that, in this tissue which contained both receptor subtypes,  $\alpha_{1b}$ -adrenergic receptors were activating inositol phosphate formation but blocking the contractile response in this tissue was 9.3 (131). Thus it appeared that, in this tissue which contained both receptor subtypes,  $\alpha_{1b}$ -adrenergic receptors were activating inositol phosphate formation but (131). Thus it appeared that, in this tissue which tained both receptor subtypes,  $\alpha_{1b}$ -adrenergic receptors were activating inositol phosphate formation but adrenergic receptors were activating the contractile sponse tained both receptor subtypes,  $\alpha_{1b}$ -adrenergic recepto<br>were activating inositol phosphate formation but  $\alpha$ <br>adrenergic receptors were activating the contractile r<br>sponse by promoting  $Ca^{2+}$  influx through nifedipin<br> were activating inositol phosphate formation but  $\alpha_{1a}$ -<br>adrenergic receptors were activating the contractile re-<br>sponse by promoting  $Ca^{2+}$  influx through nifedipine-<br>sensitive channels. Similarly, CEC pretreatment ma atteneight receptors were activating the contractive response by promoting  $Ca^{2+}$  influx through nifedipinesensitive channels. Similarly, CEC pretreatment markedly reduced norepinephrine-stimulated  $[^{3}H]$ inositol phosp sensitive channels. Similarly, CEC pretreatment markedly reduced norepinephrine-stimulated  $[^{3}H]$ inositol phosphate accumulation in the rat vas deferens (246) without affecting the contractile response of this tissue (1 sensitive channels. Similarly, CEC pretreatment markedly reduced norepinephrine-stimulated  $[^3H]$ inositol<br>phosphate accumulation in the rat vas deferens (246)<br>without affecting the contractile response of this tissue<br>(130 edly reduced norepinephrine-stimulated [<sup>3</sup>H]inos<br>phosphate accumulation in the rat vas deferens (2<br>without affecting the contractile response of this tis<br>(130). Finally, CEC pretreatment of rat liver slices, wh<br>contain o phosphate accumulation in the rat vas defere<br>without affecting the contractile response of th<br>(130). Finally, CEC pretreatment of rat liver slice<br>contain only the  $\alpha_{1b}$  subtype, caused a parallel i<br>tion of receptor bin without ariseting the contractie response of this ussue<br>(130). Finally, CEC pretreatment of rat liver slices, which<br>contain only the  $\alpha_{1b}$  subtype, caused a parallel inactiva-<br>tion of receptor binding sites and norepin (150). Finally, CEC pretreatment of rat liver sitces, which<br>contain only the  $\alpha_{1b}$  subtype, caused a parallel inactiva-<br>tion of receptor binding sites and norepinephrine-stim-<br>ulated inositol phosphate accumulation (24 contain only the  $a_{1b}$  subtype, caused a parallel inactivation of receptor binding sites and norepinephrine-stim-<br>ulated inositol phosphate accumulation (246). These re-<br>sults are all consistent with the hypothesis that com of receptor binding sites and norepinephrine-sum-<br>ulated inositol phosphate accumulation (246). These re-<br>sults are all consistent with the hypothesis that only the<br> $\alpha_{1b}$ -adrenergic receptor subtypes are linked to

sults are all consistent with the hypothesis that only the  $\alpha_{1b}$ -adrenergic receptor subtypes are linked to inositol phosphate accumulation in these tissues.<br>It seems likely, however, that  $\alpha_{1a}$ -adrenergic receptor  $\alpha_{\rm b}$ -adrenergic receptor solutypes are inneed to intertion<br>phosphate accumulation in these tissues.<br>It seems likely, however, that  $\alpha_{\rm 1a}$ -adrenergic receptor<br>activation might also activate inositol phospholipid It seems likely, however, that  $\alpha_{1a}$ -adrenergic receptor<br>activation might also activate inositol phospholipid me-<br>tabolism in some tissues. The opening of dihydropyri-<br>dine-sensitive Ca<sup>2+</sup> channels, either by depolari activation might also activate inositol phospholipid metabolism in some tissues. The opening of dihydropyridine-sensitive Ca<sup>2+</sup> channels, either by depolarization or application of Ca<sup>2+</sup> channel agonist drugs, activates dine-sensitive Ca<sup>2+</sup> channels, either by depolarization or application of Ca<sup>2+</sup> channel agonist drugs, activates inositol phosphate formation in brain and other tissues (124, 185, 220, 291) (see above). If  $\alpha_{1a}$ -adre application of Ca channel agonst drugs, activates ino-<br>sitol phosphate formation in brain and other tissues (124,<br>185, 220, 291) (see above). If  $\alpha_{1a}$ -adrenergic receptor<br>activation promotes  $Ca^{2+}$  influx, either dire sion phosphate formation in brain and other tissues (124, 185, 220, 291) (see above). If  $\alpha_{1a}$ -adrenergic receptor activation promotes  $Ca^{2+}$  influx, either directly or indirectly, it is likely that this may also resu 160, 220, 251) (see above). If  $\alpha_{1a}$ -adrenergic receptor<br>activation promotes  $Ca^{2+}$  influx, either directly or indi-<br>rectly, it is likely that this may also result in breakdown<br>of inositol phospholipids (69). Possibly activation promotes  $Ca^{2+}$  influx, either directly or indi-<br>rectly, it is likely that this may also result in breakdown<br>of inositol phospholipids (69). Possibly, there might be<br>differential involvement of different inosi rectly, it is likely that this may also result in breakdow of inositol phospholipids (69). Possibly, there might differential involvement of different inositol phospha and/or diacylglycerol in signal transduction by the t of inositol phospholipids (69). Possibly, there might be<br>differential involvement of different inositol phosphates<br>and/or diacylglycerol in signal transduction by the two<br>subtypes. In particular, the differences between a and/or diacylglycerol in signal transduction by the two subtypes. In particular, the differences between activation of phospholipase C by G protein activation and by increasing  $Ca^{2+}$  (69, 121) (see above) raise the poss increasing  $Ca^{2+}$  (69, 121) (see above) raise the possibility mechanisms. that activation of different receptor subtypes might in-<br>crease inositol phospholipid metabolism by different<br>mechanisms.<br>Another interesting possibility is that the  $\alpha_1$ -adrener-<br>gic receptors activating phospholipase

crease inositol phospholipid metabolism by different<br>mechanisms.<br>Another interesting possibility is that the  $\alpha_1$ -adrener-<br>gic receptors activating phospholipase  $A_2$  activity in var-<br>ious cells (45, 46, 142, 318) may increase inositor phosphonpid metabolism by different<br>mechanisms.<br>Another interesting possibility is that the  $\alpha_1$ -adrener-<br>gic receptors activating phospholipase  $A_2$  activity in var-<br>ious cells (45, 46, 142, 318) may whole interesting possibility is that the  $a_1$ -autenti-<br>gic receptors activating phospholipase  $A_2$  activity in var-<br>ious cells (45, 46, 142, 318) may be of a different subtype<br>than those activating phospholipase C acti ghe receptors activating phosphonpase  $A_2$  activity in various cells (45, 46, 142, 318) may be of a different subtype than those activating phospholipase C activity. This would explain the differential sensitivities of t ious cells (45, 46, 142, 318) may be of a different subtype<br>than those activating phospholipase C activity. This<br>would explain the differential sensitivities of these two<br>processes to toxins and drugs (45). Also, if arach the cyclic AMP responses to activity. In would explain the differential sensitivities of these two processes to toxins and drugs (45). Also, if arachidon acid release and prostaglandin formation are involved is the cyclic would explain the differential sensitivities of these two<br>processes to toxins and drugs (45). Also, if arachidonic<br>acid release and prostaglandin formation are involved in<br>the cyclic AMP response to  $\alpha_1$ -adrenergic rece processes to toxins and drugs (45). Also, if arachidonic<br>acid release and prostaglandin formation are involved in<br>the cyclic AMP response to  $\alpha_1$ -adrenergic receptor stim-<br>ulation (98, 268, 304) in the brain, the involv acid release and prostagiand in formation are involved in<br>the cyclic AMP response to  $\alpha_1$ -adrenergic receptor stim-<br>ulation (98, 268, 304) in the brain, the involvement of<br>different receptors could explain the different che cyclic AMT response to  $\alpha_1$ -aurenergic receptor sum-<br>ulation (98, 268, 304) in the brain, the involvement of<br>different receptors could explain the different abilities of<br>agonists to activate inositol phosphate and c different receptors could explain the different abilities<br>agonists to activate inositol phosphate and cyclic AM<br>responses (168). All of these different processes, Ca<sup>i</sup><br>inositol phosphates, diacylglycerol, cyclic AMP, cycl agonists to activate mositor phosphate and cyclic AMP<br>responses (168). All of these different processes, Ca<sup>2</sup><br>inositol phosphates, diacylglycerol, cyclic AMP, cycl<br>GMP, arachidonic acid, membrane potential, and men<br>brane responses (100). An of these unferent processes, Ca<sup>-</sup>,<br>inositol phosphates, diacylglycerol, cyclic AMP, cyclic<br>GMP, arachidonic acid, membrane potential, and mem-<br>brane channels, are clearly interrelated in complex man-<br>n GMP, arachidonic acid, membrane potential, and membrane channels, are clearly interrelated in complex manners in living cells, and the unambiguous dissection of these systems presents an interesting challenge. Clearly,

**a**spet

112 MINNEMAN<br>much work remains to be done in this area to distinguish that  $\alpha_1$ <br>the various signal transduction mechanisms activated by tissues MINNEMAN<br>much work remains to be done in this area to distinguish that<br>the various signal transduction mechanisms activated by tissue<br>each receptor subtype. mec 112<br>much work remains to l<br>the various signal trans<br>each receptor subtype. **Example 15 to be done in this<br>ransduction mecha<br>pe.<br>XII. Conclusions**<br>tablished that acti Exercious signal transduction mechanisms activated<br>
ch receptor subtype.<br> **XII. Conclusions**<br>
It is now well established that activation of  $\alpha_1$ -adre<br>
gic receptors by norepinephrine or other agoni

each receptor subtype.<br> **XII. Conclusions**<br>
It is now well established that activation of  $\alpha_1$ -adre-<br>
nergic receptors by norepinephrine or other agonists<br>
increases hydrolysis of PIP<sub>2</sub>, probably through an inter-**XII. Conclusions**<br>It is now well established that activation of  $\alpha_1$ -adre<br>nergic receptors by norepinephrine or other agonist<br>increases hydrolysis of PIP<sub>2</sub>, probably through an inter-<br>mediary G protein. The resulting **EXECUTE ALL: CONCLUSIONS**<br>
It is now well established that activation of  $\alpha_1$ -adre-<br>
nergic receptors by norepinephrine or other agonists<br>
increases hydrolysis of PIP<sub>2</sub>, probably through an inter-<br>
mediary G protein. It is now well established that activation of  $\alpha_1$ -adre-<br>nergic receptors by norepinephrine or other agonists<br>increases hydrolysis of  $\text{PIP}_2$ , probably through an inter-<br>mediary G protein. The resulting release of  $\text$ mergic receptors by norepinephrine or other agonists<br>increases hydrolysis of  $\text{PIP}_2$ , probably through an inter-<br>mediary G protein. The resulting release of  $\text{Ins}(1,4,5)\text{P}_3$ <br>and diacylglycerol into the intracellular m mediary G protein. The resulting release of  $\text{Ins}(1,4,5)P_3$ <br>and diacylglycerol into the intracellular milieu mobilizes<br> $\text{Ca}^{2+}$  stored in nonmitochondrial pools, such as the en-<br>doplasmic and sarcoplasmic reticulum, a mediary G protein. The resulting release of  $Ins(1,4,5)$ <br>and diacylglycerol into the intracellular milieu mobili:<br>Ca<sup>2+</sup> stored in nonmitochondrial pools, such as the  $\epsilon$ <br>doplasmic and sarcoplasmic reticulum, and activate and diacylglycerol into the intracellular milieu mobilizes  $Ca^{2+}$  stored in nonmitochondrial pools, such as the endoplasmic and sarcoplasmic reticulum, and activates protein kinase C. These primary events appear to be re Ca<sup>2+</sup> stored in nonmitochor<br>doplasmic and sarcoplasmic<br>tein kinase C. These primary<br>sible for many of the effec<br>activation in many tissues.<br>However, it is increasing plasmic and sarcoplasmic reticulum, and activates pro-<br>n kinase C. These primary events appear to be respon-<br>le for many of the effects of  $\alpha_1$ -adrenergic receptor<br>tivation in many tissues.<br>However, it is increasingly c

tein kinase C. These primary events appear to be responsible for many of the effects of  $\alpha_1$ -adrenergic receptor activation in many tissues.<br>However, it is increasingly clear that  $\alpha_1$ -adrenergic receptors are not pha sible for many of the effects of  $\alpha_1$ -adrenergic recepto<br>activation in many tissues.<br>However, it is increasingly clear that  $\alpha_1$ -adrenergic<br>receptors are not pharmacologically homogeneous. Evidence from radioligand bi However, it is increasingly clear that  $\alpha_1$ -adrenergic<br>receptors are not pharmacologically homogeneous. Evi-<br>dence from radioligand binding studies, functional stud-<br>ies of smooth muscle contractile responses, and studi receptors are not pharmacologically homogeneous. Evidence from radioligand binding studies, functional studies of smooth muscle contractile responses, and studies of receptor-mediated second messenger accumulation shows su dence from radiongand binding studies, functional studies<br>ies of smooth muscle contractile responses, and studies<br>of receptor-mediated second messenger accumulation<br>shows substantial differences in the affinities and effi of receptor-mediated second messenger accumulation the shows substantial differences in the affinities and effi-<br>cacies of agonists, and the affinities of antagonists for the existence of at least two discrete these diffe shows substantial differences in the affinities and effi-<br>cacies of agonists, and the affinities of antagonists for<br> $\alpha_1$ -adrenergic receptors in different tissues. Based on<br>these differences, the existence of at least t cacies of agonists, and the affinities of antagonists for tion-<br> $\alpha_1$ -adrenergic receptors in different tissues. Based on least<br>these differences, the existence of at least two discrete the<br>subtypes of  $\alpha_1$ -adrenergic  $\alpha_1$ -adrenergic receptors in different tissues. Based on these differences, the existence of at least two discrete subtypes of  $\alpha_1$ -adrenergic receptors seems clear. The best drugs currently available to distinguish b these differences, the existence of at least two discressiblypes of  $\alpha_1$ -adrenergic receptors seems clear. The bedrugs currently available to distinguish between the receptor types appear to be the competitive antagoni subtypes of  $\alpha_1$ -adrenergic receptors seems clear. The be drugs currently available to distinguish between the receptor types appear to be the competitive antagoni<br>WB 4101 and the irreversible alkylating agent chlore th drugs currently available to distinguish between these<br>receptor types appear to be the competitive antagonist<br>WB 4101 and the irreversible alkylating agent chlore-<br>thylclonidine. However, it also seems likely that differ-<br> WB 4101 and the irreversible alkylating agent chlore-<br>thylclonidine. However, it also seems likely that differ-<br>ences in the affinities and efficacies of imidazoline and<br>phenethylamine agonists will be found as the two rec thylclonidine. However, it also seems likely that differences in the affinities and efficacies of imidazoline and

![](_page_25_Figure_9.jpeg)

FIG. 13. Schematic diagram for different signal transduction mechanisms by two different  $\alpha_1$ -adrenergic receptor subtypes.  $\alpha_{1a}$ -Adrenergic receptors appear to activate phospholipase C (*PLC*) through a G **anisms** by two different  $\alpha_1$ -adrenergic receptor subtypes.  $\alpha_{1a}$ -Adrenergic 12. BALLA, T., GUILEMETT, G., BAUKAL, A. J., AND CATT, K. J.: Metabolism<br>**receptors** appear to activate phospholipase C (*PLC*) through a FIG. 13. Schematic diagram for different signal transduction mechanisms by two different  $\alpha_1$ -adrenergic receptor subtypes.  $\alpha_{1a}$ -Adrenergic receptors appear to activate phospholipase C (*PLC*) through a G protein (dimensity appear to activate phospholipase C (*PLC*) through a G protein  $(G_{\rho})$  to cause hydrolysis of PIP<sub>2</sub> to Ins(1,4,5)P<sub>3</sub> and diacylgly-<br>erol (*DAG*). This may indirectly stimulate Ca<sup>2+</sup> influx through non-<br>dihydr protein  $(G_{\rho})$  to cause hydrolysis of  $\text{PIP}_2$  to  $\text{Ins}(1,4,5)P_3$  and discylgly-<br>prol  $(DAG)$ . This may indirectly stimulate  $\text{Ca}^{2+}$  influx through non-<br>dihydropyridine-sensitive channels.  $\alpha_{1a}$ -Adrenergic recepto sensitive channels, possibly through a G protein through a G protein through dihydropyridine-sensitive channels.  $\alpha_{1a}$ -Adrenergic receptors meetly or indirectly, stimulate Ca<sup>2+</sup> influx through nifedipine (essibly chan iding *(CEC)* selective channels.  $\alpha_{1a}$ -Adrenergic receptors may, directly or indirectly, stimulate  $Ca^{2+}$  influx through nifedipine (*NIF*)-<br>tensitive channels, possibly through a G protein ( $G_R$ ). Chlorethylclon-<br>id mey by rindirectly, stimulate Ca<sup>2+</sup> influx the<br>sensitive channels, possibly through a G protection<br>idine (CEC) selectively inactivates only the<br>norepinephrine (NE) activates both subtypes

MAN<br>that  $\alpha_1$ -adrenergic receptor-mediated responses in some<br>tissues may be mediated through a signal transduction MAN<br>that  $\alpha_1$ -adrenergic receptor-mediated responses in some<br>tissues may be mediated through a signal transduction<br>mechanism unrelated to breakdown of PIP<sub>2</sub>. Increases MAN<br>that  $\alpha_1$ -adrenergic receptor-mediated responses in some<br>tissues may be mediated through a signal transduction<br>mechanism unrelated to breakdown of PIP<sub>2</sub>. Increases<br>in  $Ca^{2+}$  influx, arachidonic acid release, cycli that  $\alpha_1$ -adrenergic receptor-mediated responses in some<br>tissues may be mediated through a signal transduction<br>mechanism unrelated to breakdown of PIP<sub>2</sub>. Increases<br>in Ca<sup>2+</sup> influx, arachidonic acid release, cyclic AMP that  $\alpha_1$ -adrenergic receptor-mediated responses in some<br>tissues may be mediated through a signal transduction<br>mechanism unrelated to breakdown of PIP<sub>2</sub>. Increases<br>in Ca<sup>2+</sup> influx, arachidonic acid release, cyclic AMP tissues may be mediated through a signal transduction<br>mechanism unrelated to breakdown of  $\text{PIP}_2$ . Increases<br>in  $\text{Ca}^{2+}$  influx, arachidonic acid release, cyclic AMP<br>accumulation, and cyclic GMP accumulation have all mechanism unrelated to breakdown of  $\text{F1F}_2$ . Increases<br>in Ca<sup>2+</sup> influx, arachidonic acid release, cyclic AMP<br>accumulation, and cyclic GMP accumulation have all<br>been reported in response to  $\alpha_1$ -adrenergic receptor a accumulation, and cyclic GMP accumulation have all<br>been reported in response to  $\alpha_1$ -adrenergic receptor ac-<br>tivation, and some of these effects have been clearly<br>differentiated from activation of inositol phospholipid<br> been reported in response to  $\alpha_1$ -adrenergic receptor activation, and some of these effects have been clearly differentiated from activation of inositol phospholipid breakdown. The possibility that different  $\alpha_1$ -adre differentiated from activation of inositol phospholipic<br>differentiated from activation of inositol phospholipic<br>breakdown. The possibility that different  $\alpha_1$ -adrenergic<br>receptor subtypes utilize different signal transd breakdown. The possibility that different  $\alpha_1$ -adrenergic<br>receptor subtypes utilize different signal transduction<br>mechanisms is increasingly attractive. A hypothesis con-<br>sistent with most available data is that  $\alpha_{1a}$ breakdown. The possibility that different  $\alpha_1$ -adrenergic<br>receptor subtypes utilize different signal transduction<br>mechanisms is increasingly attractive. A hypothesis con-<br>sistent with most available data is that  $\alpha_{1a}$ receptor subtypes utinze unferent signal transduction<br>mechanisms is increasingly attractive. A hypothesis con-<br>sistent with most available data is that  $\alpha_{1a}$ -adrenergic<br>receptors primarily promote influx of extracellul sistent with most available data is that  $\alpha_{1a}$ -adrenergic<br>receptors primarily promote influx of extracellular Ca<sup>2+</sup><br>through dihydropyridine-sensitive channels, while  $\alpha_{1b}$ -<br>adrenergic receptors initiate signals thr ceptors primarily promote influx of extracellular Ca<sup>2+</sup><br>rough dihydropyridine-sensitive channels, while  $\alpha_{1b}$ -<br>renergic receptors initiate signals through the well-<br>aracterized inositol phospholipid pathway (fig. 13).

ies of smooth muscle contractile responses, and studies signal transduction mechanisms raises interesting ques-<br>of receptor-mediated second messenger accumulation tions concerning the basic mechanisms by which receptor<br>sh through dihydropyridine-sensitive channels, while  $\alpha_{1b}$ -<br>adrenergic receptors initiate signals through the well-<br>characterized inositol phospholipid pathway (fig. 13).<br>Overall, the existence of pharmacologically distin adrenergic receptors initiate signals through the well<br>characterized inositol phospholipid pathway (fig. 13).<br>Overall, the existence of pharmacologically distinc<br>subtypes of  $\alpha_1$ -adrenergic receptors linked to differen<br> characterized mostor phosphonpid pathway (iig. 15).<br>Overall, the existence of pharmacologically distinct<br>subtypes of  $\alpha_1$ -adrenergic receptors linked to different<br>signal transduction mechanisms raises interesting ques-<br> subtypes of  $\alpha_1$ -adrenergic receptors linked to different<br>signal transduction mechanisms raises interesting ques-<br>tions concerning the basic mechanisms by which receptor<br>activation controls the intracellular free Ca<sup>2+</sup> signal transduction mechanisms raises interesting ques-<br>tions concerning the basic mechanisms by which receptor<br>activation controls the intracellular free  $Ca^{2+}$  concentra-<br>tion. Further characterization of these subtype tions concerning the basic mechanisms by which receptor activation controls the intracellular free  $Ca^{2+}$  concentration. Further characterization of these subtypes may also lead to the development of more selective and u disorders.

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