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# Copyright © 1993/4502-0147\$03.00/0<br>
Pharmacological Reviews<br>
Copyright © 1993 by The American Society for Pharmacology and Experimental Therapeutics<br> **Cardiac a<sub>1</sub>-Adrenoceptors: An Overview\***<br>
ANDRÉ TERZIC,<sup>1,+</sup> MICHEL PU **Cardiac**  $\alpha_1$ **-Adrenoceptors: An Overview\***<br>ANDRE TERZIC,<sup>1,†</sup> MICHEL PUCEAT,<sup>2</sup> GUY VASSORT,<sup>2</sup> AND STEPHEN M. VOGEL<sup>3</sup><br><sup>1</sup>Division of Cardiovascular Diseases, Department of Internal Medicine, and Department of Pharmaco

**CAPCIAC**  $\alpha_1$ **-AGPENOCEDUOPS: AN UVEPVIEW**<br><sup>1</sup>Division of Cardiovascular Diseases, Department of Internal Medicine, and Department of Pharmacology, Mayo Clinic, Mayo Foundation,<br><sup>1</sup>Division of Cardiovascular Diseases, Dep *Rochester, Minnesota, 2Laboratoire, Minnesota, 2Cardiovascular Diseases, Department of Internal Medicine, and Department of Pharmacology, Mayo Clinic, Mayo Foundation,<br>Rochester, Minnesota, <sup>2</sup>Laboratoire de Physiologie C* ANDRÉ TERZIC,<sup>1,†</sup> MICHEL PUCÉAT,<sup>2</sup> GUY VASSORT,<sup>2</sup> AND STEPHEN M. VOGEL<sup>3</sup><br>3Department of Internal Medicine, and Department of Pharmacology, Mayo Clinic, Mayo F<br>3Departments of Anesthesiology and Pharmacology, College of <sup>3</sup>Departments of Anesthesiology and Pharmacology, College of Medicine, University of Illinois, Chicago, Illinois



The sympathetic nervous system is a major regulator conductances, cytosolic ionic activities, cellular meta<br>of myocardial function (for review, see Levy and Martin, conductances, cytosolic ionic activities, cellular meta<br> or myocardiac muscle. However, during the last two decades, and force of contraction. In addition of through which catecholamines exert their actions on physiological or pathophysiological conditions,  $\alpha_1$ -adrenoceptors 1989). For many years,  $\beta$ -adrenoceptors had been considerable.<br>
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I. Introduction<br>
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1989). For many years, The sympathetic nervous system is a major regulator<br>of myocardial function (for review, see Levy and Martin,<br>1989). For many years,  $\beta$ -adrenoceptors had been consid-<br>lism, and the  $Ca^{2+}$  sensitivity of contractile prot

Fundate muscle. However, during the last two decades, noceptors could regulate the cardiac rhythm, conduction, -adrenoceptors have also been identified in myocardial and force of contraction. In addition to these acute su  $\alpha_1$ -adrenoceptors have also been identified in myocardial and force of contraction. In addition to these acute tissue. Selective stimulation of animal and human  $\alpha_1$ - actions,  $\alpha_1$ -adrenoceptors also mediate severa a Grant-in-Aid from the American Heart Association (Minnesota Affiliate).<br>
A. T. is a recipient of the Award for Careers in Clinical Pharmacology from<br>
a Grant-in-Aid from the American Heart Association (Minnesota Affilia sue. Selective stimulation of animal and numan  $\alpha_1$ -<br>
\* Part of the work presented in this review was conducted under the ausp<br>
T. is a recipient of the Award for Careers in Clinical Pharmacology from the<br>
Strant-in-Aid

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effects which include the expression of genes responsible<br>
for cell growth.<br>
The purpose of recent investigations has been to un-<br>
cover the mechanisms that underlie the  $\alpha_1$ -adrenoceptoreffects which include the expression of genes respo<br>for cell growth.<br>The purpose of recent investigations has been<br>cover the mechanisms that underlie the  $\alpha_1$ -adrenoce<br>mediated regulation of cellular processes in the effects which include the expression of genes responsible<br>for cell growth.<br>The purpose of recent investigations has been to un-<br>cover the mechanisms that underlie the  $\alpha_1$ -adrenoceptor-<br>mediated regulation of cellular p for cell growth.<br>The purpose of recent investigations has been to un<br>cover the mechanisms that underlie the  $\alpha_1$ -adrenergic<br>mediated regulation of cellular processes in the heart<br>Although it has been described that  $\alpha_$ The purpose of recent investigations has been to uncover the mechanisms that underlie the  $\alpha_1$ -adrenoceptor-<br>mediated regulation of cellular processes in the heart.<br>Although it has been described that  $\alpha_1$ -adrenergic cover the mechanisms that underlie the  $\alpha_1$ -adrenoceptor-<br>mediated regulation of cellular processes in the heart.<br>Although it has been described that  $\alpha_1$ -adrenergic stim-<br>ulation modulates cardiac contractility in a mediated regulation of cellular processes in the heart.<br>Although it has been described that  $\alpha_1$ -adrenergic stimulation modulates cardiac contractility in a way that differs from conventional cardiotonic agents (Pucéat regulation modulates cardiac contractility in a way that<br>
differs from conventional cardiotonic agents (Pucéat et sub-<br>
al., 1992), many questions regarding the  $\alpha_1$ -adrenergic of the<br>
regulation of heart function remai

differs from conventional cardiotonic agents (Pucéat et al., 1992), many questions regarding the  $\alpha_1$ -adrenergic regulation of heart function remain unresolved.<br>The following overview provides an update relative to the al., 1992), many questions regarding the  $\alpha_1$ -adrenergic regulation of heart function remain unresolved.<br>The following overview provides an update relative to che  $\alpha_1$ -adrenoceptor-mediated effects on cardiac tissue. regulation of heart function remain unresolved.<br>The following overview provides an update relative to<br>the  $\alpha_1$ -adrenoceptor-mediated effects on cardiac tissue.<br>It is not intended to be exhaustive, and the interested<br>rea The following overview provides an update relative to<br>the  $\alpha_1$ -adrenoceptor-mediated effects on cardiac tissue.<br>It is not intended to be exhaustive, and the interested<br>reader is referred to earlier presentations of this the  $\alpha_1$ -adrenoceptor-mediated effects on cardiac tissue.<br>It is not intended to be exhaustive, and the interested<br>reader is referred to earlier presentations of this subject<br>for more detailed information (Brückner et al reader is referred to earlier presentations of this subject<br>for more detailed information (Brückner et al., 1985;<br>Osnes et al., 1985; Benfey, 1987; Nawrath, 1989; Endoh,<br>1991; Rosen et al., 1991). Osnes et al., 1985; Benfey, 1987; Nawrath, 1989; Endoh, 1991; Rosen et al., 1991).<br>**II. Characterization of Myocardial**  $\alpha_1$ -

### **Adrenoceptors**

## **I. Characterization of Myocardial**  $\alpha_1$ <br>**Adrenoceptors**<br>*A. Demonstration, Species Differences, and*<br>*Developmental Changes of Cardiac*  $\alpha_1$ -Adrenocept **II. Characterization of Myocardial**  $\alpha_1$ **-**<br>**Adrenoceptors**<br>*A. Demonstration, Species Differences, and<br>Developmental Changes of Cardiac*  $\alpha_1$ -*Adrenocepto*<br>The unequivocal identification of myocardial  $\alpha$

**Adrenoceptors**<br>
Demonstration, Species Differences, and<br>
velopmental Changes of Cardiac  $\alpha_1$ -Adrenoceptors<br>
The unequivocal identification of myocardial  $\alpha_1$ -ad<br>
cceptors was made during the last decade, when inv A. Demonstration, Species Differences, and<br>Developmental Changes of Cardiac  $\alpha_1$ -Adrenoceptors<br>The unequivocal identification of myocardial  $\alpha_1$ -adr<br>noceptors was made during the last decade, when inve<br>tigators were a A. Demonstration, species Differences, and<br>Developmental Changes of Cardiac  $\alpha_1$ -Adrenoceptors b<br>The unequivocal identification of myocardial  $\alpha_1$ -adre-<br>noceptors was made during the last decade, when inves-<br>tigators Developmental Changes of Caralac  $\alpha_1$ -Aarenoceptors<br>
The unequivocal identification of myocardial  $\alpha_1$ -adre-<br>
moceptors was made during the last decade, when inves-<br>
tigators were able to label these receptors with sp The unequivocal identification of myocardial  $\alpha_1$ -adre-<br>noceptors was made during the last decade, when inves-<br>tigators were able to label these receptors with specific<br>radioligands and subsequently to isolate and clone noceptors was made during the last decade, when invertigators were able to label these receptors with spectral<br>or radioligands and subsequently to isolate and clone<br>receptor molecule. In the late 1970s, it was demonstrat<br> drows were able to laber these receptors with specific<br>radioligands and subsequently to isolate and clone the<br>receptor molecule. In the late 1970s, it was demonstrated<br>that a tritiated  $\alpha$ -adrenoceptor antagonist ([<sup>3</sup>H] receptor molecule. In the late 1970s, it was demonstrated<br>that a tritiated  $\alpha$ -adrenoceptor antagonist ([<sup>3</sup>H]dihy-<br>droergocryptine) binds specifically and with high affinity<br>to a membrane fraction derived from myocardia that a tritiated  $\alpha$ -adrenoceptor antagonist ( $\alpha$  Hjdniy-droergocryptine) binds specifically and with high affinity to a membrane fraction derived from myocardial multicellular preparations (rat heart: Williams and Lefk to a membrane fraction derived from myocardial multi-<br>cellular preparations (rat heart: Williams and Lefkowitz,<br>1978; Guicheney et al., 1978; rabbit heart: Schümann<br>and Brodde, 1979). The tritiated ligand could be dis-<br>pl cellular preparations (rat heart: Williams and Lefkowitz, cellular preparations (rat heart: Williams and Lefkowitz, 1978; Guicheney et al., 1978; rabbit heart: Schümann add Brodde, 1979). The tritiated ligand could be dishabled from specific membrane-binding sites by unlabled  $\$ 1978; Guicheney et al., 1978; rabbit heart: Schümann<br>and Brodde, 1979). The tritiated ligand could be dis-<br>placed from specific membrane-binding sites by unla-<br>beled  $\alpha$ -adrenoceptor agonists and antagonists. More<br>recent and Brodde, 1979). The tritiated ligand could be oplaced from specific membrane-binding sites by un beled  $\alpha$ -adrenoceptor agonists and antagonists. M recently,  $\alpha$ -adrenoceptors also have been demonstratin isolated car placed from specific membrane-binding sites by unla-<br>beled  $\alpha$ -adrenoceptor agonists and antagonists. More all<br>recently,  $\alpha$ -adrenoceptors also have been demonstrated  $B$ <br>in isolated cardiomyocytes, a pure myocardial pr beled  $\alpha$ -adrenoceptor<br>recently,  $\alpha$ -adrenocep<br>in isolated cardiomyo<br>tion free of any vascu<br>and Brunton, 1986).<br>It was demonstrate cently,  $\alpha$ -adrenoceptors also have been demonstrate<br>isolated cardiomyocytes, a pure myocardial prepar-<br>on free of any vascular or neuronal elements (Buxtd<br>d Brunton, 1986).<br>It was demonstrated, using  $\alpha_1$ -subtype-sele

in isolated cardiomyocytes, a pure myocardial preparation free of any vascular or neuronal elements (Buxton and Brunton, 1986).<br>
It was demonstrated, using  $\alpha_1$ -subtype-selective radi-<br>
oligands (e.g., [<sup>3</sup>H]prazosin, [ tion free of any vascular or neuronal elements (Buxt<br>and Brunton, 1986).<br>It was demonstrated, using  $\alpha_1$ -subtype-selective ra<br>oligands (e.g., [<sup>3</sup>H]prazosin, [<sup>125</sup>I]IBE 2254), that cardi<br> $\alpha$ -adrenergic binding sites b and Brunton, 1986).<br>
It was demonstrated, using  $\alpha_1$ -subtype-selective radi-<br>
begands (e.g., [<sup>3</sup>H]prazosin, [<sup>125</sup>I]IBE 2254), that cardiac<br>  $\alpha$ -adrenergic binding sites belong to the  $\alpha_1$ -type (Stein-<br>
berg and Bil It was demonstrated, using  $\alpha_1$ -subtype-selective<br>oligands (e.g., [<sup>3</sup>H]prazosin, [<sup>125</sup>I]IBE 2254), that c<br> $\alpha$ -adrenergic binding sites belong to the  $\alpha_1$ -type (<br>berg and Bilezikian, 1982; Mukherjee et al., 1983).<br>t  $\alpha$ -adrenergic binding sites belong to the  $\alpha_1$ -type (Steinberg and Bilezikian, 1982; Mukherjee et al., 1983). With the aid of the photoaffinity ligand  $[^{125}]$  arylazidoprazosin, Terman and Insel (1986) identified the the aid of the photoaffinity ligand  $[1^{25}]$  ary lazidoprazo-<br>sin, Terman and Insel (1986) identified the  $\alpha_1$ -adreno-<br>ceptor of rat cardiomyocytes as a 77-kDa protein.<br>The density of  $\alpha_1$ -adrenoceptors varies with sp rg and Bilezikian, 1982; Mukherjee et al., 1983). With<br>e aid of the photoaffinity ligand  $[^{125}]$  arylazidoprazo-<br>n, Terman and Insel (1986) identified the  $\alpha_1$ -adreno-<br>ptor of rat cardiomyocytes as a 77-kDa protein.<br>Th

the aid of the photoaffinity ligand  $[{}^{125}]$  arylazidoprazo-<br>sin, Terman and Insel (1986) identified the  $\alpha_1$ -adreno-<br>ceptor of rat cardiomyocytes as a 77-kDa protein.<br>The density of  $\alpha_1$ -adrenoceptors varies with sp ceptor of rat cardiomyocytes as a 77-kDa protein.<br>The density of  $\alpha_1$ -adrenoceptors varies with species.<br>Rat and rabbit myocardia possess a high density of adrenoceptor-binding sites when compared with or species. The d The density of  $\alpha_1$ -adrenoceptors varies with species.<br>
Rat and rabbit myocardia possess a high density of  $\alpha_1$ -<br>
adrenoceptor-binding sites when compared with other<br>
species. The density of binding sites in sarcolemm adrenoceptor-binding sites when compared with other<br>species. The density of binding sites in sarcolemma-<br>enriched membrane fractions of rat, rabbit, dog, and<br>feline hearts is 167, 191, 55, and 15 fmol/mg proteins,<br>respecti adrenoceptor-binding sites when compared with oth species. The density of binding sites in sarcolemm<br>enriched membrane fractions of rat, rabbit, dog, an<br>feline hearts is 167, 191, 55, and 15 fmol/mg protein<br>respectively (M species. The density of binding sites in sarcolemma-<br>enriched membrane fractions of rat, rabbit, dog, and<br>feline hearts is 167, 191, 55, and 15 fmol/mg proteins,<br>respectively (Mukherjee et al., 1983). Buxton and Brun-<br>ton enriched membrane fractions of rat, rabbit, dog, and trifeline hearts is 167, 191, 55, and 15 fmol/mg proteins, IP<br>respectively (Mukherjee et al., 1983). Buxton and Brun-<br>ton (1986), using [<sup>3</sup>H]prazosin as a ligand, esti

ET AL.<br>  $\alpha_1$ -adrenoceptors is comparable to the density of  $\beta_1$ -<br>
adrenoceptors (33/ $\mu$ m<sup>2</sup>) on rat cardiomyocytes (Buxton ET AL.<br>  $\alpha_1$ -adrenoceptors is comparable to the density of  $\beta_1$ -<br>
adrenoceptors (33/ $\mu$ m<sup>2</sup>) on rat cardiomyocytes (Buxton<br>
and Brunton, 1985b). In addition, Endoh et al. (1991) ET AL.<br>  $\alpha_1$ -adrenoceptors is comparable to the density of  $\beta_1$ -<br>
adrenoceptors (33/ $\mu$ m<sup>2</sup>) on rat cardiomyocytes (Buxton<br>
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showed that the ratio of  $\alpha_1$ - to  $\alpha_1$ -adrenoceptors is comparable to the density of  $\beta_1$ -<br>adrenoceptors (33/ $\mu$ m<sup>2</sup>) on rat cardiomyocytes (Buxton<br>and Brunton, 1985b). In addition, Endoh et al. (1991)<br>showed that the ratio of  $\alpha_1$ - to  $\beta$ -recepto  $\alpha_1$ -adrenoceptors is comparable to the density of  $\beta_1$ -<br>adrenoceptors (33/ $\mu$ m<sup>2</sup>) on rat cardiomyocytes (Buxton<br>and Brunton, 1985b). In addition, Endoh et al. (1991)<br>showed that the ratio of  $\alpha_1$ - to  $\beta$ -recepto adrenoceptors (33/ $\mu$ m<sup>2</sup>) on rat cardiomyocytes (Buxton<br>and Brunton, 1985b). In addition, Endoh et al. (1991)<br>showed that the ratio of  $\alpha_1$ - to  $\beta$ -receptors was on average<br>5-fold larger in the rat than in the rabbit and Brunton, 1985b). In addition, Endoh et al. (1<br>showed that the ratio of  $\alpha_1$ - to  $\beta$ -receptors was on ave<br>5-fold larger in the rat than in the rabbit or dog. Alth<br>the number of  $\alpha_1$ -adrenoceptors varies between sp showed that the ratio of  $\alpha_1$ - to  $\beta$ -receptors was on average<br>5-fold larger in the rat than in the rabbit or dog. Although<br>the number of  $\alpha_1$ -adrenoceptors varies between species<br>no significant difference in the den 5-fold larger in the rat than in the rabbit or dog. Although<br>the number of  $\alpha_1$ -adrenoceptors varies between species,<br>no significant difference in the density of  $[^{3}H]$  prazosin-<br>binding sites was found between the le the number of  $\alpha_1$ -adrenoceptors varies between species,<br>no significant difference in the density of  $[^3H]$ prazosin-<br>binding sites was found between the left ventricular<br>subepicardium or subendocardium and the right ven no significant difference in the density of [<sup>3</sup>H]prazosin-<br>binding sites was found between the left ventricular<br>subepicardium or subendocardium and the right ventricle<br>of the rat heart (Muntz et al., 1985). However, in s subepicardium or subendocardium and the right ventricle<br>of the rat heart (Muntz et al., 1985). However, in several<br>species ventricular tissue possesses a higher density of<br> $\alpha_1$ -adrenoceptors than does the atrium (Steinf 1992a). bepourded the rat heart (Muntz et al., 1985). However, in several<br>ecies ventricular tissue possesses a higher density of<br>-adrenoceptors than does the atrium (Steinfath et al.,<br>92a).<br>Developmental changes in the density of

species ventricular tissue possesses a higher density of  $\alpha_1$ -adrenoceptors than does the atrium (Steinfath et al., 1992a).<br>
Developmental changes in the density of myocardial  $\alpha_1$ -adrenoceptors were observed in rabbi  $\alpha_1$ -adrenoceptors than does the atrium (Steinfath et al., 1992a).<br>
Developmental changes in the density of myocardial  $\alpha_1$ -adrenoceptors were observed in rabbit, rat, and dog<br>
hearts. In all three species studied,  $\$ 1992a).<br>
Developmental changes in the density of myocardial  $\alpha_1$ -adrenoceptors were observed in rabbit, rat, and dog<br>
hearts. In all three species studied,  $\alpha_1$ -receptor density<br>
in the newborn was greater than that f  $\alpha_1$ -adrenoceptors were observed in rabbit, rat, and dog hearts. In all three species studied,  $\alpha_1$ -receptor density in the newborn was greater than that found in the adult. For example, in canine hearts,  $\alpha_1$ -adren Specifically, using  $[125]$  IBE2254 as a ligand, del Balzo et hearts. In all three species studied,  $\alpha_1$ -receptor density<br>in the newborn was greater than that found in the adult.<br>For example, in canine hearts,  $\alpha_1$ -adrenoceptors are 10-<br>fold more abundant in the young than in th in the newborn was greater than that found in the adult.<br>For example, in canine hearts,  $\alpha_1$ -adrenoceptors are 10-<br>fold more abundant in the young than in the adult heart.<br>Specifically, using  $[^{125}]$ IBE2254 as a ligand For example, in canine hearts,  $\alpha_1$ -adrenoceptors are 10-<br>fold more abundant in the young than in the adult heart.<br>Specifically, using  $[^{125}]$ JBE2254 as a ligand, del Balzo et<br>al. (1990) found 220 fmol/mg  $\alpha_1$ -adreno fold more abundant in the young than in the adult heart.<br>Specifically, using  $[^{125}]$ IBE2254 as a ligand, del Balzo et al. (1990) found 220 fmol/mg  $\alpha_1$ -adrenoceptors in 1-<br>month-old dogs versus 23 fmol/mg in the adult. Specifically, using  $[1^{25}]$  IBE2254 as a ligand, del Balzo et al. (1990) found 220 fmol/mg  $\alpha_1$ -adrenoceptors in 1-month-old dogs versus 23 fmol/mg in the adult. Using the same ligand, Buchthal et al. (1987) reported t al. (1990) found 220 fmol/mg  $\alpha_1$ -adrenoceptors in 1-<br>month-old dogs versus 23 fmol/mg in the adult. Using<br>the same ligand, Buchthal et al. (1987) reported the<br>presence of high- and low-affinity sites. The density of<br>hi month-old dogs versus 23 fmol/mg in the adult. Using<br>the same ligand, Buchthal et al. (1987) reported the<br>presence of high- and low-affinity sites. The density of<br>high-affinity sites displays no change with age (B<sub>max</sub> 23 the same ligand, Buchthal et al. (1987) reported the presence of high- and low-affinity sites. The density of high-affinity sites displays no change with age ( $B<sub>max</sub>$  25  $\pm$  6 fmol/mg in fetal, 14  $\pm$  10 fmol/mg in n presence of high- and low-affinity sites. The density of<br>high-affinity sites displays no change with age (B<sub>max</sub> 23<br> $\pm$  6 fmol/mg in fetal, 14  $\pm$  10 fmol/mg in neonatal, and<br> $25 \pm 15$  fmol/mg in adult), whereas the den  $\pm$  6 fmol/mg in fetal, 14  $\pm$  10 fmol/mg in neonatal, and 25  $\pm$  15 fmol/mg in adult), whereas the density of low-<br>affinity sites decreases in the adult (B<sub>max</sub> 1460  $\pm$  380<br>fmol/mg in fetal, 1710  $\pm$  440 fmol/mg in 25  $\pm$  15 fmol/mg in adult), whereas the density of low-<br>affinity sites decreases in the adult (B<sub>max</sub> 1460  $\pm$  380<br>fmol/mg in fetal, 1710  $\pm$  440 fmol/mg in neonatal, and<br>510  $\pm$  155 fmol/mg in adult). No age-related fmol/mg in fetal, 1710  $\pm$  440 fmol/mg in neonatal, and 510  $\pm$  155 fmol/mg in adult). No age-related differences in the receptor affinity have been described (Buchthal et al., 1987; Nakanishi et al., 1989; Han et al., 510  $\pm$  155 fmol/mg in adult). No age-related differences<br>in the receptor affinity have been described (Buchthal et<br>al., 1987; Nakanishi et al., 1989; Han et al., 1989; del<br>Balzo et al., 1990). Beyond middle age, the num al., 1987; Nakanishi et al., 1989; Han et al., 1989; del<br>Balzo et al., 1990). Beyond middle age, the number of<br> $\alpha_1$ -adrenoceptors further declines (Kimball et al., 1991).<br>This decline may be due to diminished levels of Balzo et al., 1990). Beyond middle age, the number of  $\alpha_1$ -adrenoceptors further declines (Kimball et al., 1991). This decline may be due to diminished levels of  $\alpha_1$ -adrenoceptor gene transcripts in the aging myocard  $\alpha_1$ -adrenoceptors further declines (Kimball et al., 1991). represent<br>This declined<br>renocept<br>because lev<br>by Norther<br>al., 1991).<br>B. Cardiac adrenoceptor gene transcripts in the a<sub>l</sub><br>because levels of α<sub>1</sub>-adrenoceptor mRN<br>by Northern blot analysis decrease witl<br>al., 1991).<br>*B. Cardiac* α<sub>1</sub>-*Adrenoceptor Subtypes*<br>Evidence has been obtained from se

Evidence has been obtained from several tissues that  $\alpha_1$ -adrenoceptors can be further subdivided into at least two pharmacologically distinct subtypes that appear to at, 1991).<br>
B. Cardiac  $\alpha_1$ -Adrenoceptor Subtypes<br>
Evidence has been obtained from several tissues that<br>  $\alpha_1$ -adrenoceptors can be further subdivided into at least<br>
two pharmacologically distinct subtypes that appear B. Cardiac  $\alpha_1$ -Adrenoceptor Subtypes<br>Evidence has been obtained from several tissues that  $\alpha_1$ -adrenoceptors can be further subdivided into at least<br>two pharmacologically distinct subtypes that appear to<br>be linked to Evidence has been obtained from several tissues that  $\alpha_1$ -adrenoceptors can be further subdivided into at least two pharmacologically distinct subtypes that appear to be linked to different signal transduction pathways These subtypes can be further subdivided into at least<br>two pharmacologically distinct subtypes that appear to<br>be linked to different signal transduction pathways and<br>effector systems (Han et al., 1987; Minneman, 1988).<br>Th two pharmacologically distinct subtypes that appear<br>be linked to different signal transduction pathways a<br>effector systems (Han et al., 1987; Minneman, 198<br>These subtypes, named  $\alpha_{1A}$  and  $\alpha_{1B}$ , can be distinguish<br>o effector systems (Han et al., 1987; Minneman, 1988).<br>These subtypes, named  $\alpha_{1A}$  and  $\alpha_{1B}$ , can be distinguished<br>on the basis of their sensitivity toward selective antago-<br>nists. The  $\alpha_{1A}$ -subtype has a higher af effector systems (Han et al., 1987; Minneman, 1988<br>These subtypes, named  $\alpha_{1A}$  and  $\alpha_{1B}$ , can be distinguish<br>on the basis of their sensitivity toward selective antag<br>nists. The  $\alpha_{1A}$ -subtype has a higher affinity These subtypes, named  $\alpha_{1A}$  and  $\alpha_{1B}$ , can be distinguished<br>on the basis of their sensitivity toward selective antago-<br>nists. The  $\alpha_{1A}$ -subtype has a higher affinity than the  $\alpha_{1B}$ -<br>subtype for the antagonists migts. The  $\alpha_{1A}$ -subtype has a higher affinity than the  $\alpha_1$ <br>subtype for the antagonists 5-methyl-urapidil, Wl<br>4101,‡ and (+)-niguldipine or the novel prazosin deri<br> $\uparrow$  Abbreviations: WB-4101, 2-(2,6-dimethoxypheno

6,7-dimethoxy-2-quinazolinyl-4-(2-bicyclo[2,2,2]octa-2,5 dienylcarbon-4101, 4 and (+)-niguidipline or the novel prazosin deleterations: WB-4101, 2-(2,6-dimethoxyphenoxyethyl)-amethyl-1,4-benzodioxane; PI, phosphatidyl inositol; SZL-49, 4-am<br>6,7-dimethoxy-2-quinazolinyl-4-(2-bicyclo[2,2,2]oct <sup>†</sup> Abbreviations: WB-4101, 2-(2,6-dimethoxyphenoxyethyl)-amino-<br>methyl-1,4-benzodioxane; PI, phosphatidyl inositol; SZL-49, 4-amino-<br>6,7-dimethoxy-2-quinazolinyl-4-(2-bicyclo[2,2,2]octa-2,5 dienylcarbon-<br>yl-2-piperazine; methyl-1,4-benzodioxane; PI, phosphatidyl inositol; SZL-49, 4-amine<br>6,7-dimethoxy-2-quinazolinyl-4-(2-bicyclo[2,2,2]octa-2,5 dienylcarbor<br>yl-2-piperazine; CEC, chlorethylclonidine; AMP, adenosine monopho<br>phate; cAMP, cycli yl-2-piperazine; CEC, chlorethylclonidine; AMP, adenosine monophos-<br>phate; cAMP, cyclic AMP; GTP, guanosine triphosphate;  $IP_3$ , inositol<br>trisphosphate;  $IP_2$ , inositol hephosphate;  $IP_4$ , inositol monophosphate;<br> $IP_4$ , i nase C;  $I_{Ca}$ , inward Ca<sup>2+</sup> current;  $I_{\omega}$ , transient outward K<sup>+</sup> current;  $I_{k}$ , pherazine, CEO, emorelly acomine, Avir, accrossine mortophos-<br>phate; cAMP, cyclic AMP; GTP, guanosine triphosphate; IP<sub>3</sub>, inositol<br>trisphosphate; IP<sub>2</sub>, inositol biphosphate; IP<sub>1</sub>, inositol monophosphate;<br>IP<sub>4</sub>, inositol phace, crivit, cyclic Attri, C11, gualitosine criphosphace, 11 3, mostol<br>trisphosphate;  $IP_2$ , inositol biphosphate;  $IP_1$ , inositol monophosphate;<br> $IP_4$ , inositol tetraphosphate;  $IP_6$ , inositol hexaphosphate;  $PIP_3$ , pho IP<sub>4</sub>, inositol tetraphosphate; IP<sub>6</sub>, inositol hexaphosphate; PIP<sub>3</sub>, phosphoinositide diphosphate; DAG, 1,2-diacylglycerol; PKC, protein kinase C; I<sub>C4</sub>, inward Ca<sup>2+</sup> current; I<sub>k<sub>0</sub></sub>, transient outward K<sup>+</sup> current; I phoinositide diphosphate; DAG, 1,2-dimase C;  $L_{c,s}$ , inward  $Ca^{2+}$  current;  $I_{\omega}$ , tradelayed outward  $K^+$  current;  $I_{k \text{ Ach}}$  mupH<sub>i</sub>, intracellular pH; ANP, atria  $- \log [Ca^{2+}; MLC$ , myosin light chain.

byCEC.

CARDIAC  $\alpha_1$ -ADRI<br>
ive SZL-49. The  $\alpha_{1B}$ -subtype is irreversibly alkylated<br>
CEC.<br>
Based on their respective sensitivity toward selective<br>
A-antagonists, it was concluded that 20% of  $\alpha_1$ -adreative SZL-49. The  $\alpha_{1B}$ -subtype is irreversibly alkyla<br>by CEC.<br>Based on their respective sensitivity toward select<br> $\alpha_{1A}$ -antagonists, it was concluded that 20% of  $\alpha_1$ -ad<br>noceptors belong to the  $\alpha_{1A}$ -subtype i ative SZL-49. The  $\alpha_{1B}$ -subtype is irreversibly alkyla<br>by CEC.<br>Based on their respective sensitivity toward selector-<br> $\alpha_{1A}$ -antagonists, it was concluded that 20% of  $\alpha_1$ -ac<br>noceptors belong to the  $\alpha_{1A}$ -subtyp by CEC. however, the respective sensitivity toward selective reconducted that 20% of  $\alpha_1$ -adre-<br>  $\alpha_{1A}$ -antagonists, it was concluded that 20% of  $\alpha_1$ -adre-<br>
noceptors belong to the  $\alpha_{1A}$ -subtype in the rat myoca Based on their respective sensitivity toward selective  $\alpha_{1A}$ -antagonists, it was concluded that 20% of  $\alpha_1$ -adre-noceptors belong to the  $\alpha_{1A}$ -subtype in the rat myocardium, and the remaining 80% of the binding si  $\alpha_{1A}$ -antagonists, it was concluded that 20% of  $\alpha_1$ -adre-<br>noceptors belong to the  $\alpha_{1A}$ -subtype in the rat myocar-<br>dium, and the remaining 80% of the binding sites could ria<br>correspond to the  $\alpha_{1B}$ -subtype (Gr noceptors belong to the  $\alpha_{1A}$ -subtype in the rat myocar-<br>dium, and the remaining 80% of the binding sites could righ<br>correspond to the  $\alpha_{1B}$ -subtype (Groß and Hanft, 1988; titio<br>Groß et al., 1988a). In the membrane dium, and the remaining 80% of the binding sites could rightcorrespond to the  $\alpha_{1B}$ -subtype (Groß and Hanft, 1988; titic Groß et al., 1988a). In the membrane fraction derived not from rabbit ventricles, pretreatment wi correspond to the  $\alpha_{1B}$ -subtype (Groß and Hanft, 1988; ti<br>Groß et al., 1988a). In the membrane fraction derived in<br>from rabbit ventricles, pretreatment with 10  $\mu$ M CEC si<br>decreased the B<sub>max</sub> of  $\alpha_1$ -adrenoceptors, Gros et al., 1968a). In the membrane fraction derived<br>from rabbit ventricles, pretreatment with 10  $\mu$ M CEC<br>decreased the B<sub>max</sub> of  $\alpha_1$ -adrenoceptors, assessed by [<sup>3</sup>H]<br>prazosin, to 37% of control, suggesting that 63 decreased the B<sub>max</sub> of  $\alpha_1$ -adrenoceptors, assessed by [<sup>3</sup>H] binding affinity, this indicates that cardiac  $\alpha_1$ -adrenocep-<br>prazosin, to 37% of control, suggesting that 63% of  $\alpha_1$ - tors are coupled to a GTP-bindin prazosin, to 37% of control, suggesting that 63% of a<br>adrenoceptors in the rabbit ventricular myocardium b<br>long to the CEC-sensitive  $\alpha_{1B}$ -subtype (Takanashi et a<br>1991). The canine myocardium also contains a subset<br> $\alpha$ adrenoceptors in the rabort ventricular inyocardium be-<br>long to the CEC-sensitive  $\alpha_{1B}$ -subtype (Takanashi et al., I-<br>1991). The canine myocardium also contains a subset of<br> $\alpha_1$ -adrenoceptors that are sensitive to CE 1990). mental change in the density of total  $\alpha_1$ -adrenoceptors<br>not associated with a change in the proportion of  $\alpha_1$ -<br>ceptors that are sensitive to CEC (del Balzo et al.,<br>90).<br>Molecular cloning confirmed the existence of a

is not associated with a change in the proportion of  $\alpha_1$ -<br>receptors that are sensitive to CEC (del Balzo et al., acti-<br>1990). Molecular cloning confirmed the existence of at least ino<br>two subtypes of cardiac  $\alpha_1$ -adr receptors that are sensitive to CEC (del Balzo et al., act 1990).<br>
Molecular cloning confirmed the existence of at least inco<br>
two subtypes of cardiac  $\alpha_1$ -adrenoceptors encoded by two<br>
different genes (Lomasney et al., 1990). Molecular cloning confirmed the existence of at least<br>two subtypes of cardiac  $\alpha_1$ -adrenoceptors encoded by two<br>different genes (Lomasney et al., 1991b; for review, see<br>Lomasney et al., 1991a). The deduced amino Molecular cloning confirmed the existence of a<br>two subtypes of cardiac  $\alpha_1$ -adrenoceptors encoded<br>different genes (Lomasney et al., 1991b; for revid<br>Lomasney et al., 1991a). The deduced amino a<br>quence presumes a recepto two subtypes of cardiac  $\alpha_1$ -adrenoceptors encoded by two<br>different genes (Lomasney et al., 1991b; for review, see<br>Lomasney et al., 1991a). The deduced amino acid se-<br>quence presumes a receptor with a seven-membrane-<br>sp different genes (Lomasney et al., 1991b; for review, s<br>Lomasney et al., 1991a). The deduced amino acid s<br>quence presumes a receptor with a seven-membran<br>spanning domain topography. However, the comple<br>classification of  $\$ spanning domain topography. However, the complete be<br>classification of  $\alpha_1$ -adrenoceptors is still not fully established. Indeed, in heart tissue, Han and Minneman<br>(1991) recently reported the persistence of low-affinit lished. Indeed, in heart tissue, Han and Minneman (1991) recently reported the persistence of low-affinity sites for niguldipine after CEC pretreatment. Thus, the existence of additional receptor subtypes in cardiac muscl (1991) recently reported the persistence of low-affinisites for niguldipine after CEC pretreatment. Thus, t existence of additional receptor subtypes in cardiac mucle is plausible. This receptor does not belong to the  $\alpha$ sites for highlappine after CEC pretreatment. I hus, the<br>existence of additional receptor subtypes in cardiac mus-<br>cle is plausible. This receptor does not belong to the  $\alpha_{1C}$ -<br>subtype that has a high affinity for  $\alpha_{$ cle is plausible. This receptor does not belong to the  $\alpha_{1C}$  situaty<br>subtype that has a high affinity for  $\alpha_{1A}$ -selective antag-<br>onists but is partially inhibited by CEC (Cotecchia et al.,<br>1988; Schwinn et al., 1990 subtype that has a high affinity for  $\alpha_{1A}$ -selective antag-<br>onists but is partially inhibited by CEC (Cotecchia et al.,<br>1988; Schwinn et al., 1990, 1991). A new subtype, named<br> $\alpha_{1D}$ , was recently cloned using soluti onists but is partially inhibited by CEC (Cotecchia et al. 1988; Schwinn et al., 1990, 1991). A new subtype, named  $\alpha_{1D}$ , was recently cloned using solution phase library screening (Perez et al., 1991). It should be po 1988; Schwinn et al., 1990, 1991). A new subtype, name  $\alpha_{\text{1D}}$ , was recently cloned using solution phase librar screening (Perez et al., 1991). It should be pointed ou that the relationship between cloned  $\alpha_1$ -adren  $\alpha_{1D}$ , was recently<br>screening (Perez<br>that the relation<br>and pharmacolog<br>pletely understoo **III. Cardiac and Signally distinct subtypes is not yermacologically distinct subtypes is not yermacologically distinct subtypes is not yermated in Transduction Pathways** 

# logically distinct subtypes is<br>
cood.<br> **Transduction Pathways**<br> *Cardiac α<sub>1</sub>-Adrenoceptors to*<br> *Cardiac α<sub>1</sub>-Adrenoceptors to*

### *A. Cardiac α<sub>1</sub>-Adrenoceptor Signal Transduction Pathways*<br>*A. Coupling of Cardiac α<sub>1</sub>-Adrenoceptors to G-Regulatory Proteins Proteins*

Transduction Pathways<br>
Coupling of Cardiac  $\alpha_1$ -Adrenoceptors to G-Regulatory<br>
oteins<br>
Guanine nucleotide regulatory proteins, G-proteins<br>
ansmit the signal from seven transmembrane domain A. Coupling of Cardiac  $\alpha_1$ -Adrenoceptors to G-Regulatory<br>
Proteins m<br>
Guanine nucleotide regulatory proteins, G-proteins, Ir<br>
transmit the signal from seven transmembrane domain<br>
receptors to intracellular effectors (f A. Couping of Caralac  $\alpha_1$ -Aarenoceptors to G-Regulatory<br>Proteins<br>Guanine nucleotide regulatory proteins, G-proteins,<br>transmit the signal from seven transmembrane domain<br>receptors to intracellular effectors (for review, Proteins<br>
Guanine nucleotide regulatory proteins, G-proteins,<br>
transmit the signal from seven transmembrane domain<br>
receptors to intracellular effectors (for review, see Stryer<br>
and Bourne, 1986; Gilman, 1987; Birnbaumer e Guanine nucleotide regulatory proteins, G-proteins, I<br>transmit the signal from seven transmembrane domain<br>receptors to intracellular effectors (for review, see Stryer I<br>and Bourne, 1986; Gilman, 1987; Birnbaumer et al., 1 transmit the signal from seven transmembrane domain<br>receptors to intracellular effectors (for review, see Stryer<br>and Bourne, 1986; Gilman, 1987; Birnbaumer et al., 1990;<br>Taylor, 1990). G-proteins cycle between an inactive<br> receptors to intracellular effectors (for review, see Stryer I<br>and Bourne, 1986; Gilman, 1987; Birnbaumer et al., 1990;<br>Taylor, 1990). G-proteins cycle between an inactive<br>guanosine diphosphate state and an active GTP stat and Bourne, 1986; Gilman, 1987; Birnbaumer et al., 1990;<br>Taylor, 1990). G-proteins cycle between an inactive<br>guanosine diphosphate state and an active GTP state.<br>The hormone-receptor complex catalyzes the activation<br>of a G Taylor, 1990). G-proteins cycle between an inactive et guanosine diphosphate state and an active GTP state. 197<br>The hormone-receptor complex catalyzes the activation cA.<br>of a G-protein by accelerating the release of guanos guanosine diphosphate state and an active GTP state. 19<br>The hormone-receptor complex catalyzes the activation cof a G-protein by accelerating the release of guanosine we diphosphate and the subsequent entry of GTP. A high The hormone-receptor complex catalyzes the activation of a G-protein by accelerating the release of guanosine well diphosphate and the subsequent entry of GTP. A high and degree of amplification can be achieved because a s of a G-protein b<br>diphosphate and<br>degree of amplifi<br>hormone-recepto<br>many G-proteins

CARDIAC  $\alpha_1$ -ADRENOCEPTORS ative SZL-49. The  $\alpha_{1B}$ -subtype is irreversibly alkylated The property, that GTP diminishes the binding of a<br>by CEC. hormone to its receptor if a G-protein is coupled to the<br>Based on their 149<br>The property, that GTP diminishes the binding of a hormone to its receptor if a G-protein is coupled to the ENOCEPTORS 149<br>The property, that GTP diminishes the binding of a<br>hormone to its receptor if a G-protein is coupled to the<br>receptor, was exploited as a strategy to define whether a<br>G-protein is linked to the cardiac  $\alpha_1$ The property, that GTP diminishes the binding of a<br>hormone to its receptor if a G-protein is coupled to the<br>receptor, was exploited as a strategy to define whether a<br>G-protein is linked to the cardiac  $\alpha_1$ -adrenoceptor. The property, that GTP diminishes the binding of a<br>hormone to its receptor if a G-protein is coupled to the<br>receptor, was exploited as a strategy to define whether a<br>G-protein is linked to the cardiac  $\alpha_1$ -adrenoceptor. hormone to its receptor if a G-protein is coupled to t<br>receptor, was exploited as a strategy to define whethe<br>G-protein is linked to the cardiac  $\alpha_1$ -adrenoceptor. T<br>addition of GTP, or its analogue Gpp(NH)p, causes<br>rig receptor, was exploited as a strategy to define whethe G-protein is linked to the cardiac  $\alpha_1$ -adrenoceptor. T<br>addition of GTP, or its analogue Gpp(NH)p, cause<br>rightward shift and a steepening of the agonist com<br>tition G-protein is linked to the cardiac  $\alpha_1$ -adrenoceptor. The addition of GTP, or its analogue Gpp(NH)p, causes rightward shift and a steepening of the agonist comptition curve, which reflects the competition of  $\alpha_1$ -adre addition of GTP, or its analogue Gpp(NH)p, cause<br>rightward shift and a steepening of the agonist com<br>tition curve, which reflects the competition of  $\alpha_1$ -ad<br>noceptor agonists for labeled  $\alpha_1$ -adrenoceptor-bind<br>sites. rightward shift and a steepening of the agonist co<br>tition curve, which reflects the competition of  $\alpha_1$ -<br>noceptor agonists for labeled  $\alpha_1$ -adrenoceptor-bin<br>sites. Because the addition of GTP reduces the ago<br>binding a tition curve, which reflects the competition of  $\alpha_1$ -adre-<br>noceptor agonists for labeled  $\alpha_1$ -adrenoceptor-binding<br>sites. Because the addition of GTP reduces the agonist-<br>binding affinity, this indicates that cardiac noceptor agonists for labeled  $\alpha_1$ -adrenoceptor-binding<br>sites. Because the addition of GTP reduces the agonist-<br>binding affinity, this indicates that cardiac  $\alpha_1$ -adrenocep-<br>tors are coupled to a GTP-binding protein ( sites. Because the addition of GTP redu<br>binding affinity, this indicates that cardia<br>tors are coupled to a GTP-binding pro<br>al., 1984; Buxton and Brunton, 1986; Gr<br>Han et al., 1989; cf. Stiles et al., 1983).<br>Pertussis toxin Frame and the GTP-binding protein (Colucci<br>
rs are coupled to a GTP-binding protein (Colucci<br>
1984; Buxton and Brunton, 1986; Groß et al., 1988<br>
an et al., 1989; cf. Stiles et al., 1983).<br>
Pertussis toxin interrupts hormo

 $\alpha_1$ -adrenoceptors that are sensitive to CEC. The devel-<br>opmental change in the density of total  $\alpha_1$ -adrenoceptors<br>is toxin treatment has been reported to prevent<br>is not associated with a change in the proportion of quence presumes a receptor with a seven-membrane-<br>spanning domain topography. However, the complete<br>classification of  $\alpha_1$ -adrenoceptors is still not fully estab-<br>lished. Indeed, in heart tissue, Han and Minneman<br>(1991) spanning domain topography. However, the complete<br>classification of  $\alpha_1$ -adrenoceptors is still not fully estab-<br>lished. Indeed, in heart tissue, Han and Minneman<br>(1991) recently reported the persistence of low-affinity tors are coupled to a GTP-binding protein (Colucci et al., 1984; Buxton and Brunton, 1986; Groß et al., 1988b; Han et al., 1989; cf. Stiles et al., 1983). Pertussis toxin interrupts hormonal signaling by ADP-ribosylating al., 1984; Buxton and Brunton, 1986; Groß et al., 1988b;<br>Han et al., 1989; cf. Stiles et al., 1983).<br>Pertussis toxin interrupts hormonal signaling by ADP-<br>ribosylating some G-proteins (e.g., G<sub>i</sub> and G<sub>o</sub> classes).<br>Pertus Han et al., 1989; cf. Stiles et al., 1983).<br>
Pertussis toxin interrupts hormonal signaling by ADP-<br>
ribosylating some G-proteins (e.g., G<sub>i</sub> and G<sub>o</sub> classes).<br>
Pertussis toxin treatment has been reported to prevent<br>
seve Pertussis toxin interrupts hormonal signaling by ADP-<br>ribosylating some G-proteins (e.g., G<sub>i</sub> and G<sub>o</sub> classes).<br>Pertussis toxin treatment has been reported to prevent<br>several  $\alpha_1$ -adrenoceptor-mediated effects includi ribosylating some G-proteins (e.g.,  $G_i$  and  $G_o$  classes).<br>Pertussis toxin treatment has been reported to prevent<br>several  $\alpha_1$ -adrenoceptor-mediated effects including the<br>activation of the Na<sup>+</sup>/K<sup>+</sup> pump (Steinberg et Pertussis toxin treatment has been reported to prevent<br>several  $\alpha_1$ -adrenoceptor-mediated effects including the<br>activation of the Na<sup>+</sup>/K<sup>+</sup> pump (Steinberg et al., 1985;<br>Shah et al., 1988; Rosen et al., 1989) or the po several  $\alpha_1$ -adrenoceptor-mediated effects including th<br>activation of the Na<sup>+</sup>/K<sup>+</sup> pump (Steinberg et al., 1985<br>Shah et al., 1988; Rosen et al., 1989) or the positiv<br>inotropic effect (Böhm et al., 1987). However, pert activation of the Na<sup>+</sup>/K<sup>+</sup> pump (Steinberg et al., 1985;<br>Shah et al., 1988; Rosen et al., 1989) or the positive<br>inotropic effect (Böhm et al., 1987). However, pertussis<br>toxin does not prevent all  $\alpha_1$ -adrenoceptor-med Shah et al., 1988; Rosen et al., 1989) or the positive inotropic effect (Böhm et al., 1987). However, pertussitival to the 74-adrenoceptor-mediated effects. Indeed, a pertussis toxin-insensitive G-protein which could hypo frotiophe effect (Bohin et al., 1991). However, pertussis<br>toxin does not prevent all  $\alpha_1$ -adrenoceptor-mediated ef-<br>fects. Indeed, a pertussis toxin-insensitive G-protein<br>which could hypothetically be the 74-kDa protein which could hypothetically be the 74-kDa protein idenwhich could hypothetically be the 74-kDa protein identified as  $G_h$  (Im and Graham, 1990; Im et al., 1990) has been implicated in linking the cardiac  $\alpha_1$ -adrenoceptor to phospholipase C and to the stimulation of phosph tified as  $G_h$  (Im and Graham, 1990; Im et al., 1990) has<br>been implicated in linking the cardiac  $\alpha_1$ -adrenoceptor<br>to phospholipase C and to the stimulation of phosphati-<br>dyl inositol turnover, at least in rat cardiac t been implicated in linking the cardiac  $\alpha_1$ -adrenoce to phospholipase C and to the stimulation of phosph dyl inositol turnover, at least in rat cardiac times (Schmitz et al., 1987c; Steinberg et al., 1989).  $G_h$  app to to phospholipase C and to the stimulation of phospholipase C and to the stimulation of phospholip discreption (Schmitz et al., 1987c; Steinberg et al., 1989).  $G_h$  appto be different, by its molecular mass and chron graph dyl inositol turnover, at least in rat cardiac tissue (Schmitz et al., 1987c; Steinberg et al., 1989).  $G_h$  appears to be different, by its molecular mass and chromatographic behavior, from the other pertussis toxin-insen (Schmitz et al., 1987c; Steinberg et al., 1989).  $G_h$  appears<br>to be different, by its molecular mass and chromato-<br>graphic behavior, from the other pertussis toxin-insen-<br>sitive G-proteins, including the  $G_q$  family, usua to be different, by its molecular mass and chromato-<br>graphic behavior, from the other pertussis toxin-insensitive G-proteins, including the  $G_q$  family, usually de-<br>scribed as regulating the isozyme  $\beta_1$  of phospholipas sitive G-proteins, including the  $G_q$  family, usually described as regulating the isozyme  $\beta_1$  of phospholipase C (Berstein et al., 1992; Blank et al., 1991; Martin et al., 1991; Im and Graham, 1990; Im et al., 1990). T sitive G-proteins, including the G<sub>q</sub> family, usually described as regulating the isozyme  $\beta_1$  of phospholipase C (Berstein et al., 1992; Blank et al., 1991; Martin et al., 1991; Im and Graham, 1990; Im et al., 1990). T Scribed as regularing the isozyme  $p_1$  or phosphonpase C<br>(Berstein et al., 1992; Blank et al., 1991; Martin et al., 1991; Im and Graham, 1990; Im et al., 1990). Thus,<br>several G-proteins, both pertussis toxin sensitive an *B. Second G-proteins, bother*<br>*B. Second Messengers*<br>*B. Second Messengers*<br>It is now well establis

Second Messengers<br>
It is now well established that various molecules could<br>
The is now well established that various molecules could<br>
The assecond messengers to convey the signal from the<br>
The second messengers to convey intracellular effectors (table 1).<br>B. Second Messengers<br>It is now well established that various molecules could<br>serve as second messengers to convey the signal from the<br>activated receptor-G-protein complex to different int B. Second Messengers<br>It is now well established that various molecules could<br>serve as second messengers to convey the signal from the<br>activated receptor-G-protein complex to different intra-<br>cellular targets. These include It is now well established that various molecules could<br>serve as second messengers to convey the signal from the<br>activated receptor-G-protein complex to different intra-<br>cellular targets. These include cAMP, cylic guanosin activated receptor-G-protein complex to different intracellular targets. These include cAMP, cylic guanosine monophosphate, and IP<sub>3</sub> (Sutherland, 1972; Berridge and Irvine, 1989). tivated receptor-G-protein complex to different intra-<br>Ilular targets. These include cAMP, cylic guanosine<br>onophosphate, and IP<sub>3</sub> (Sutherland, 1972; Berridge and<br>vine, 1989).<br>In heart muscle,  $\alpha_1$ -adrenoceptor agonists

cellular targets. These include cAMP, cylic guanosi<br>monophosphate, and IP<sub>3</sub> (Sutherland, 1972; Berridge a<br>Irvine, 1989).<br>In heart muscle,  $\alpha_1$ -adrenoceptor agonists were ported not to affect either basal cAMP or cyclic monophosphate, and IP<sub>3</sub> (Sutherland, 1972; Berridge and Irvine, 1989).<br>In heart muscle,  $\alpha_1$ -adrenoceptor agonists were reported not to affect either basal cAMP or cyclic guanosine monophosphate levels (Osnes and Øye, Irvine, 1989).<br>
In heart muscle,  $\alpha_1$ -adrenoceptor agonists were re-<br>
ported not to affect either basal cAMP or cyclic guano-<br>
sine monophosphate levels (Osnes and Øye, 1975; Brodde<br>
et al., 1978; review: Osnes et al., In heart muscle,  $\alpha_1$ -adrenoceptor agonists were re-<br>ported not to affect either basal cAMP or cyclic guano-<br>sine monophosphate levels (Osnes and Øye, 1975; Brodde<br>et al., 1978; review: Osnes et al., 1985; cf. Keely et ported not to affect either basal cAMP or cyclic guano-<br>sine monophosphate levels (Osnes and Øye, 1975; Brodde<br>et al., 1978; review: Osnes et al., 1985; cf. Keely et al.,<br>1977).  $\alpha_1$ -Adrenoceptor agonists caused a decre sine monophosphate levels (Osnes and Øye, 1975; Brodder al., 1978; review: Osnes et al., 1985; cf. Keely et al. 1977).  $\alpha_1$ -Adrenoceptor agonists caused a decrease in cAMP levels but only under conditions in which cAME et al., 1978; review: Osnes et al., 1985; cf. Keely et al., 1977).  $\alpha_1$ -Adrenoceptor agonists caused a decrease in cAMP levels but only under conditions in which cAMP was elevated by the prior application of a  $\beta$ -adre 1977).  $\alpha_1$ -Adrenoceptor agonists caused a decrease in cAMP levels but only under conditions in which cAMP was elevated by the prior application of a  $\beta$ -adrenoceptor agonist (Watanabe et al., 1977; Buxton and Brunton, cAMP levels but only under conditions in which cAMP<br>was elevated by the prior application of a  $\beta$ -adrenoceptor<br>agonist (Watanabe et al., 1977; Buxton and Brunton,<br>1985a). This effect was attributed to  $\alpha_1$ -adrenergic was elevated by the prior application of a  $\beta$ -adrenocepto:<br>agonist (Watanabe et al., 1977; Buxton and Brunton<br>1985a). This effect was attributed to  $\alpha_1$ -adrenergic stim<br>ulation of the cAMP-phosphodiesterase activity,

TABLE 1 **PERZIC ET AL.**<br> **Pertussis toxin-sensitive and -insensitive**  $\alpha_1$ **-adrenergic effects reported in cardiac tissue**<br> **Pertussis toxin insensitive**<br> **Pertussis toxin insensitive** 

| Pertussis toxin sensitive                             | Pertussis toxin insensitive                           | References                |
|---|---|---------------------------|
| Negative chronotropy                                  |   | Steinberg et al. (1985)   |
| Na/K pump activation                                  |   | Shah et al. (1988)        |
|   | Positive chronotopy                                   | Han et al. (1989)         |
| Modulation of intracellular Ca and cell<br>shortening |   | Sen et al. (1990)         |
|   | <b>PLC</b>  | Steinberg et al. (1989)   |
|   | PI turnover   | Schmitz et al. (1987c)    |
|   | $I_{\text{to}}$ , $I_{\text{k1}}$ , $I_{\text{kACH}}$ | Braun et al. (1990, 1992) |
|   |   | Fedida et al. (1991)      |
|   |   | Lee et al. (1991)         |
|   | Positive inotropic effect                             | Böhm et al. (1987)        |
| Positive inotropic effect                             |   | <b>Kim et al.</b> (1987)  |
|   | Induction of the Egr1 gene                            | Iwaki et al. (1990)       |

Positive inotropic effect<br>
inhibitors. In rat ventricular cardiac myocytes, it was epiceently demonstrated that CEC completely inhibits the 2,5<br>  $\alpha_1$ -adrenergic effect on cAMP, suggesting that the occu-Induction<br>
inhibitors. In rat ventricular cardiac myocytes, it we<br>
recently demonstrated that CEC completely inhibits the<br>  $\alpha_1$ -adrenergic effect on cAMP, suggesting that the occu-<br>
pation of  $\alpha_{1B}$ -receptors leads to inhibitors. In rat ventricular cardiac myocytes, it was eph<br>recently demonstrated that CEC completely inhibits the 2,3<br> $\alpha_1$ -adrenergic effect on cAMP, suggesting that the occu-<br>pation of  $\alpha_{1B}$ -receptors leads to the inhibitors. In rat ventricular cardiac m<br>recently demonstrated that CEC complet<br> $\alpha_1$ -adrenergic effect on cAMP, suggesting<br>pation of  $\alpha_{1B}$ -receptors leads to the activ<br>breakdown (Hilal-Dandan et al., 1991).<br>The first  $\alpha_1$ -adrenergic effect on cAMP, suggesting that the occupation of  $\alpha_{1B}$ -receptors leads to the activation of cAMP breakdown (Hilal-Dandan et al., 1991).<br>The first evidence that the adrenergic system regulates phospho  $\alpha_1$ -adrenergic effect on cAMP, suggesting that the occu-<br>pation of  $\alpha_{1B}$ -receptors leads to the activation of cAMP IP<sub>2</sub>). T<br>breakdown (Hilal-Dandan et al., 1991). acid wi<br>The first evidence that the adrenergic syst

pation of  $\alpha_{1B}$ -receptors leads to the activation of cAMP<br>breakdown (Hilal-Dandan et al., 1991).<br>The first evidence that the adrenergic system regulates<br>phosphoinositide metabolism (PI) in the heart came from<br>the work The first evidence that the adrenergic system regular<br>phosphoinositide metabolism (PI) in the heart came fithe work of Gaut and Huggins (1966). After radiolabe<br>Na<sup>+</sup> orthophosphate was administered in vivo, epine<br>rine incr The first evidence that the adrenergic system regulates the phosphoinositide metabolism (PI) in the heart came from fit the work of Gaut and Huggins (1966). After radiolabeled Na<sup>+</sup> orthophosphate was administered in vivo, phosphoinositide metabolism (PI) in the heart came from<br>the work of Gaut and Huggins (1966). After radiolabeled<br>Na<sup>+</sup> orthophosphate was administered in vivo, epineph-<br>rine increased the radioactivity of the PI fraction of the work of Gaut and Huggins (1900). First radiofabele Na<sup>+</sup> orthophosphate was administered in vivo, epinephrine increased the radioactivity of the PI fraction of cardiac phospholipids. In 1985, Brown et al. showed that t rine increased the radioactivity of the PI fraction of cardiac phospholipids. In 1985, Brown et al. showed that the addition of norepinephrine to  $[^3H]$ inositol-labeled trat ventricular cardiomyocytes caused a rapid (sign cardiac phospholipids. In 1985, Brown et al. showed that tography and demonstrated that norepinephrine, in cul-<br>the addition of norepinephrine to [<sup>3</sup>H]inositol-labeled tured rat ventricular myocytes, produced a rapid, tr the addition of norepinephrine to [<sup>3</sup>H]inositol-labeled<br>rat ventricular cardiomyocytes caused a rapid (signifi-<br>cant at 5 min) and prolonged (at least 40 min) increase<br>in [<sup>3</sup>H]inositol phosphate formation. The stimulato rat ventricular cardiomyocytes caused a rapid (significant at 5 min) and prolonged (at least 40 min) increase sust<br>in [<sup>3</sup>H]inositol phosphate formation. The stimulatory the<br>effect of norepinephrine was maximal (5-fold th cant at 5 min) and prolonged (at least 40 min) increase<br>in [<sup>3</sup>H]inositol phosphate formation. The stimulatory<br>effect of norepinephrine was maximal (5-fold the control<br>level of [<sup>3</sup>H]inositol phosphate) at 30  $\mu$ M, with effect of norepinephrine was maximal (5-fold the control<br>level of [<sup>3</sup>H]inositol phosphate) at 30  $\mu$ M, with an EC<sub>50</sub><br>of 1  $\mu$ M. The  $\alpha_1$ -adrenoceptor antagonist, prazosin, an-<br>tagonized this effect.<br>Subsequently, it

Subsequently, it was confirmed that  $\alpha_1$ -adrenergic agmever of  $\lfloor$  H jinositor phosphate) at 30  $\mu$ m, with an EC<sub>50</sub> good  $\lfloor$   $\mu$ m. The  $\alpha_1$ -adrenceptor antagonist, prazosin, antagonized this effect.<br>
Subsequently, it was confirmed that  $\alpha_1$ -adrenergic ag-<br>
onists tagonized this effect.<br>
Subsequently, it was confirmed that  $\alpha_1$ -adrenergic ag-<br>
onists stimulate PI breakdown in different cardiac prep-<br>
arations. These include embryonic chick heart cells<br>
i (Brown and Jones, 1986), Subsequently, it was confirmed that  $\alpha_1$ -adrenergic ag-<br>onists stimulate PI breakdown in different cardiac prep-<br>arations. These include embryonic chick heart cells is<br>(Brown and Jones, 1986), rat perfused heart (Woodco onists stimulate PI breakdown in different cardiac preparations. These include embryonic chick heart cells is<br>(Brown and Jones, 1986), rat perfused heart (Woodcock Het al., 1987), rat ventricles (Poggioli et al., 1986), cu arations. These include embryonic chick heart cells<br>(Brown and Jones, 1986), rat perfused heart (Woodcock<br>et al., 1987), rat ventricles (Poggioli et al., 1986), cultured<br>rat myocardial cells (Steinberg et al., 1987), rat p (Brown and Jones, 1986), rat perfused heart (Woodcock et al., 1987), rat ventricles (Poggioli et al., 1986), cultured rat myocardial cells (Steinberg et al., 1987), rat papillary muscles (Otani et al., 1988), rat atria (S et al., 1987), rat ventricles (Poggioli et al., 1986), cultured<br>rat myocardial cells (Steinberg et al., 1987), rat papillary<br>muscles (Otani et al., 1988), rat atria (Scholz et al., 1988;<br>Kohl et al., 1990), and canine car rat myocardial cells (Steinberg et al., 1987), rat papillary<br>muscles (Otani et al., 1988), rat atria (Scholz et al., 1988;<br>Kohl et al., 1990), and canine cardiomyocytes (Heathers<br>et al., 1989). The  $\alpha_1$ -adrenoceptor-med muscles (Otani et al., 1988), rat atria (Scholz et al., 1988;<br>Kohl et al., 1990), and canine cardiomyocytes (Heathers<br>et al., 1989). The  $\alpha_1$ -adrenoceptor-mediated PI turnover<br>is not affected by the composition of the m Kohl et al., 1990), and canine cardiomyocytes (Heathers put al., 1989). The  $\alpha_1$ -adrenoceptor-mediated PI turnover M<br>is not affected by the composition of the membrane's (1<br>phospholipids in polyunsaturated fatty acids ( et al., 1989). The  $\alpha_1$ -adrenoceptor-mediated P1 turnover<br>is not affected by the composition of the membrane's<br>phospholipids in polyunsaturated fatty acids (Meij et al.,<br>1990). Endoh et al. (1991) reported a correlation is not affected by the composition of the membrane's<br>phospholipids in polyunsaturated fatty acids (Meij et al.,<br>1990). Endoh et al. (1991) reported a correlation between<br>the acceleration of PI turnover and the density of phospholipids in polyunsaturated fatty acids (Meij et al., perf<br>1990). Endoh et al. (1991) reported a correlation between 674<br>the acceleration of PI turnover and the density of sar-30 s<br>colemmal  $\alpha_1$ -adreneceptors. This 1990). Endoh et al. (1991) report<br>the acceleration of PI turnover<br>colemmal  $\alpha_1$ -adrenoceptors. Thi<br>iations in the magnitude of the<br>PI breakdown between species.<br>Poggioli et al. (1986) showe colemmal  $\alpha_1$ -adrenoceptors. This could explain the value of the  $\alpha_1$ -adrenergic effect (PI breakdown between species.<br>Poggioli et al. (1986) showed that  $\alpha_1$ -adrenocept stimulation of rat muscles resulted in a sign

iations in the magnitude of the  $\alpha_1$ -adrenergic effect on atria<br>
PI breakdown between species. time<br>
Poggioli et al. (1986) showed that  $\alpha_1$ -adrenoceptor inosi<br>
stimulation of rat muscles resulted in a significant bre PI breakdown between species.<br>
Poggioli et al. (1986) showed that  $\alpha_1$ -adrenoceptor<br>
stimulation of rat muscles resulted in a significant break-<br>
down of PIP<sub>2</sub> that was concomitant with a maximum<br>
increase in IP<sub>3</sub> for Poggioli et al. (1986) showed that  $\alpha_1$ -adrenoceptor<br>stimulation of rat muscles resulted in a significant break-<br>down of PIP<sub>2</sub> that was concomitant with a maximum<br>increase in IP<sub>3</sub> formation within 30 s. Otani et al. ( stimulation of rat muscles resulted in a significant breadown of  $\text{PIP}_2$  that was concomitant with a maximulation increase in  $\text{IP}_3$  formation within 30 s. Otani et al. (19) further extended these results. The additio

 $\frac{2}{3}$  Egr1 gene livaki et al. (1987)<br>
2,3-Diphosphoglyceric acid is a competitive inhibitor of<br>
2,3-Diphosphoglyceric acid is a competitive inhibitor of<br>
2,3-Diphosphatase (the enzyme that hydrolyzes IP<sub>3</sub> into the Egrl gene<br>
1930)<br>
1930 phosphates.<br>
1930 phosphoglyceric acid is a competitive inhibitor of<br>
1933 phosphatase (the enzyme that hydrolyzes  $IP_3$  into<br>
1933. The combined addition of 2,3-diphosphoglyceric<br>
1939. ephrine-induced formation of  $[^{3}H]$ inositol phosphate<br>2,3-Diphosphoglyceric acid is a competitive inhibitor of<br>IP<sub>3</sub> phosphatase (the enzyme that hydrolyzes IP<sub>3</sub> int<br>IP<sub>2</sub>). The combined addition of 2,3-diphosphoglycer ephrine-induced formation of [<sup>3</sup>H]inositol phosphates.<br>
2,3-Diphosphoglyceric acid is a competitive inhibitor of<br>
IP<sub>3</sub> phosphatase (the enzyme that hydrolyzes IP<sub>3</sub> into<br>
IP<sub>2</sub>). The combined addition of 2,3-diphosphogl IP<sub>3</sub> phosphatase (the enzyme that hydrolyzes IP<sub>3</sub> into IP<sub>2</sub>). The combined addition of 2,3-diphosphoglyceric further. acid with phenylephrine doubled the IP<sub>3</sub> formation. In these experiments, the IP<sub>3</sub> fraction was not separated further.<br>To resolve what individual inositol phosphate isomers are formed following  $\alpha_1$ -adrenoceptor occup these experiments, the  $IP_3$  fraction was not separated

these experiments, the IP<sub>3</sub> fraction was not separa<br>further.<br>To resolve what individual inositol phosphate isom<br>are formed following  $\alpha_1$ -adrenoceptor occupation, Ste<br>berg et al. (1989) used high-performance liquid chr further.<br>To resolve what individual inositol phosphate isomers<br>are formed following  $\alpha_1$ -adrenoceptor occupation, Stein-<br>berg et al. (1989) used high-performance liquid chroma-<br>tography and demonstrated that norepinephr To resolve what individual inositol phosphate isomer<br>are formed following  $\alpha_1$ -adrenoceptor occupation, Stein<br>berg et al. (1989) used high-performance liquid chroma<br>tography and demonstrated that norepinephrine, in cul<br> sustained increase in 1,3,4-IP<sub>3</sub>, IP<sub>2</sub>, and IP<sub>1</sub>. 4-IP<sub>1</sub> was the predominant  $IP_1$  isomer formed during stimulation tured rat ventricular myocytes, produced a rapid, transient increase in  $1,4,5$ -IP<sub>3</sub> which was followed by a slower, sustained increase in  $1,3,4$ -IP<sub>3</sub>, IP<sub>2</sub>, and IP<sub>1</sub>. 4-IP<sub>1</sub> was the predominant IP<sub>1</sub> isomer formed sient increase in 1,4,5-IP<sub>3</sub> which was followed by a slow<br>sustained increase in 1,3,4-IP<sub>3</sub>, IP<sub>2</sub>, and IP<sub>1</sub>. 4-IP<sub>1</sub> v<br>the predominant IP<sub>1</sub> isomer formed during stimulati<br>with norepinephrine. IP<sub>2</sub> and IP<sub>3</sub> accumulat sustained increase in 1,3,4-IP<sub>3</sub>, IP<sub>2</sub>, and IP<sub>1</sub>. 4-IP<br>the predominant IP<sub>1</sub> isomer formed during stimul<br>with norepinephrine. IP<sub>2</sub> and IP<sub>3</sub> accumulation<br>greater than IP<sub>1</sub> accumulation in response to  $\alpha_1$ -<br>noceptor with norepinephrine. IP<sub>2</sub> and IP<sub>3</sub> accumulation v<br>greater than IP<sub>1</sub> accumulation in response to  $\alpha_1$ -ad<br>noceptor stimulation. This suggests that phosphoine<br>tides, rather than PI, are the prime targets of nore<br>nephrin with norepinephrine. IP<sub>2</sub> and IP<sub>3</sub> accumulation was<br>greater than IP<sub>1</sub> accumulation in response to  $\alpha_1$ -adre-<br>noceptor stimulation. This suggests that phosphoinosi-<br>tides, rather than PI, are the prime targets of nore eater than IP<sub>1</sub> accumulation in response to  $\alpha_1$ -adre-<br>ceptor stimulation. This suggests that phosphoinosi-<br>les, rather than PI, are the prime targets of norepi-<br>phrine-stimulated phospholipase activity in the heart.<br>T

noceptor stimulation. This suggests that phosphoino<br>tides, rather than PI, are the prime targets of nore<br>nephrine-stimulated phospholipase activity in the hea<br>To quantify inositol phosphate fractions in cani<br>isolated cardi tides, rather than PI, are the prime targets of norepi-<br>nephrine-stimulated phospholipase activity in the heart.<br>To quantify inositol phosphate fractions in canine<br>isolated cardiomyocytes stimulated with norepinephrine,<br>He mephrine-stimulated phospholipase activity in the heart.<br>To quantify inositol phosphate fractions in canine<br>isolated cardiomyocytes stimulated with norepinephrine,<br>Heathers et al. (1988) used gas chromatography coupled<br>wi isolated cardiomyocytes stimulated with norepinephrine,<br>Heathers et al. (1988) used gas chromatography coupled<br>with high-performance liquid chromatography and<br>showed that  $\alpha_1$ -adrenoceptor agonists increase, within<br>30 s Solated cardiomyocytes stimulated with horepinephrine,<br>Heathers et al. (1988) used gas chromatography coupled<br>with high-performance liquid chromatography and<br>showed that  $\alpha_1$ -adrenoceptor agonists increase, within<br>30 s, with high-performance liquid chromatography and<br>showed that  $\alpha_1$ -adrenoceptor agonists increase, within<br>30 s, 1,4,5-IP<sub>3</sub> from a baseline level of 10 to up to 40<br>pmol/mg protein and IP<sub>4</sub> from 3 to 15 pmol/mg protein.<br>M showed that  $\alpha_1$ -adrenoceptor agonists increase, within 30 s, 1,4,5-IP<sub>3</sub> from a baseline level of 10 to up to 40 pmol/mg protein and IP<sub>4</sub> from 3 to 15 pmol/mg protein.<br>More recently, using a radioimmunoassay, Mouton e 30 s, 1,4,5-IP<sub>3</sub> from a baseline level of 10 to up to 40 pmol/mg protein and IP<sub>4</sub> from 3 to 15 pmol/mg protein.<br>More recently, using a radioimmunoassay, Mouton et al. (1991) reported that  $\alpha_1$ -adrenergic stimulation o binot) ing protein and 114 from 5 to 15 pmol/ing protein.<br>More recently, using a radioimmunoassay, Mouton et al.<br>(1991) reported that  $\alpha_1$ -adrenergic stimulation of isolated<br>perfused heart increases 1,4,5-IP<sub>3</sub> from a b (1991) reported that  $\alpha_1$ -adrenergic stimulation of isolated<br>perfused heart increases 1,4,5-IP<sub>3</sub> from a basal value of<br>674  $\pm$  75 to 2387  $\pm$  385 pmol/g dry heart weight within<br>30 s.<br>Kohl et al. (1990), using electri

perfused heart increases  $1,4,5$ -IP<sub>3</sub> from a basal value of  $674 \pm 75$  to  $2387 \pm 385$  pmol/g dry heart weight within 30 s.<br>Kohl et al. (1990), using electrically driven rat left atria labeled with [<sup>3</sup>H]inositol, studie 30 s.<br>  $10^{14} \pm 10^{16}$  to 2507  $\pm$  500 phot/g ary neart weight with  $130$  s.<br>  $130$  s.<br>
Kohl et al. (1990), using electrically driven rat left<br>
atria labeled with  $[{}^{3}H]$  inositol, studied in more detail the<br>
time co Kohl et al. ( 1990), using electrically driven rat left<br>atria labeled with [<sup>3</sup>H]inositol, studied in more detail the<br>time course of the effects of phenylephrine on individual<br>inositol phosphate isomers.  $1,4,5$ -IP<sub>3</sub> was atria labeled with [<sup>3</sup>H]inositol, studied in more detail the<br>time course of the effects of phenylephrine on individual<br>inositol phosphate isomers.  $1,4,5$ -IP<sub>3</sub> was the first com-<br>pound to increase maximally within 30 s time course of the effects of phenylephrine on individual<br>inositol phosphate isomers.  $1,4,5$ -IP<sub>3</sub> was the first com-<br>pound to increase maximally within 30 s and to remain<br>elevated for at least 5 min; this increase was f inositol phosphate isomers. 1,4,5-IP<sub>3</sub> was the first com-<br>pound to increase maximally within 30 s and to remain<br>elevated for at least 5 min; this increase was followed by<br>an increase in inositol tetrakisphosphate, 1,3,4, pound to increase maximally within 30 s and to remain<br>elevated for at least 5 min; this increase was followed by<br>an increase in inositol tetrakisphosphate,  $1,3,4,5$ -IP<sub>4</sub>, and<br> $1,4$ -IP<sub>2</sub> beginning within 2 min. The incr

CARDIAC  $\alpha_1$ -ADRENOCEPTORS 151

within 15 mm. Thus, in addition to 1,4,5-1P3, a1-adre-CARDIAC  $\alpha_1$ -AD<br>within 15 min. Thus, in addition to 1,4,5-IP<sub>3</sub>,  $\alpha_1$ -adre-<br>noceptor stimulation elevates 1,3,4,5-IP<sub>4</sub> in rat atria.<br>Guse et al. (1989) also showed that 1,4,5-IP<sub>3</sub> reached a CARDIAC  $\alpha_1$ -ADREN<br>within 15 min. Thus, in addition to 1,4,5-IP<sub>3</sub>,  $\alpha_1$ -adre-<br>noceptor stimulation elevates 1,3,4,5-IP<sub>4</sub> in rat atria. cel<br>Guse et al. (1989) also showed that 1,4,5-IP<sub>3</sub> reached a per<br>peak within 30 minutes, and 1,3,4-IP<sub>3</sub> and 1,3,4,5-IP<sub>4</sub> in rat atria.<br>
Guse et al. (1989) also showed that  $1,4,5$ -IP<sub>3</sub> reached a p<br>
peak within 30 s; this isomer remained high for several c<br>
minutes, and  $1,3,4$ -IP<sub>3</sub> and  $1,3,4,5$ slowed then rapidly decreased toward their basal peak within 30 s; this isomer remained high for several minutes, and 1,3,4-IP<sub>3</sub> and 1,3,4,5-IP<sub>4</sub> increased more slowly and then rapidly decreased toward their basal level peak within 30 s; this isomer remained high for several minutes, and 1,3,4-IP<sub>3</sub> and 1,3,4,5-IP<sub>4</sub> increased more slowly and then rapidly decreased toward their basal level within 5 min. Recently, Woodcock et al. (1992) r minutes, and 1,3,4-IP<sub>3</sub> and 1,3,4,5-IP<sub>4</sub> increased more slowly and then rapidly decreased toward their basal<br>level within 5 min. Recently, Woodcock et al. (1992)<br>reported that  $\alpha_1$ -adrenergic stimulation induces an in slowly and then raphuy decreased toward then be<br>level within 5 min. Recently, Woodcock et al. (19<br>reported that  $\alpha_1$ -adrenergic stimulation induces an<br>crease in IP<sub>4</sub> in cultured neonatal cells but not in int<br>neonatal h rever whilm 5 mm. Recently, Woodcock et al. (1552)<br>reported that  $\alpha_1$ -adrenergic stimulation induces an in-<br>crease in IP<sub>4</sub> in cultured neonatal cells but not in intact<br>respective in the intact heart despite the presenc crease in  $H_4$  in cultured neonatal cens out not in intact<br>neonatal hearts. The authors concluded that the metab-<br>olism of  $IP_3$  occurred mainly by dephosphorylation in<br>the intact heart despite the presence of an  $IP_3$  k neonatal hearts. The authors concluded that the met<br>olism of IP<sub>3</sub> occurred mainly by dephosphorylation<br>the intact heart despite the presence of an IP<sub>3</sub> kin<br>activity in this cardiac preparation (Renard and Poggi<br>1987); in onsin of I<sub>3</sub> occurred mainly by dephosphorylation in<br>the intact heart despite the presence of an IP<sub>3</sub> kinase<br>activity in this cardiac preparation (Renard and Poggioli,<br>1987); in isolated cultured neonatal cells, both dep activity in this cardiac preparation (Renard and Poggioli, particle 1987); in isolated cultured neonatal cells, both dephos-<br>phorylation and phosphorylation pathways operate. It These authors advise caution in interpreting 1987); in isolated cultured neonatal cells, both dephos-<br>phorylation and phosphorylation pathways operate.<br>These authors advise caution in interpreting data con-<br>cerning the phosphoinositide turnover obtained in cul-<br>tured phorylation and phosphorylation pathways operate<br>These authors advise caution in interpreting data concerning the phosphoinositide turnover obtained in cultured neonatal cells, because these cells could have lost<br>in part, riese authors advise caution in interpreting data concerning the phosphoinositide turnover obtained in cutured neonatal cells, because these cells could have los in part, their cellular differentiation. The physiologic rol terming the phosphomositic turnover obtained in cur-<br>tured neonatal cells, because these cells could have lost,<br>in part, their cellular differentiation. The physiological<br>role of 1,3,4,5-IP<sub>4</sub> in the heart remains to be d

in part, their central differentiation. The physiological<br>role of 1,3,4,5-IP<sub>4</sub> in the heart remains to be determined.<br>Using the high-performance liquid chromatography<br>metal dye detection technique, Scholz et al. (1992b)<br> The only 1,3,4,5-1P<sub>4</sub> in the neart remains to be determined. Using the high-performance liquid chromatography Takenetal dye detection technique, Scholz et al. (1992b) al. (recently showed that  $\alpha_1$ -adrenergic stimulati metal dye detection technique, Scholz et al. (19)<br>recently showed that  $\alpha_1$ -adrenergic stimulation enhas<br>not only 1,4,5-IP<sub>3</sub> and 1,3,4,5-IP<sub>4</sub> but also the cell<br>content of 1,3,4,6-IP<sub>4</sub> (by 2-fold) and IP<sub>6</sub> (by 1.5-fo recently showed that  $\alpha_1$ -adrenergic stimulation enhances<br>not only 1,4,5-IP<sub>3</sub> and 1,3,4,5-IP<sub>4</sub> but also the cellular<br>content of 1,3,4,6-IP<sub>4</sub> (by 2-fold) and IP<sub>6</sub> (by 1.5-fold) in<br>isolated perfused hearts. These effe not only 1,4,5-IP<sub>3</sub> and 1,3,4,5-IP<sub>4</sub> but also the cellular location of 1,3,4,6-IP<sub>4</sub> (by 2-fold) and IP<sub>6</sub> (by 1.5-fold) in fisolated perfused hearts. These effects were concentration dependent, reaching a maximum at  $1$ content of 1,3,4,6-IP<sub>4</sub> (by 2-fold) and IP<sub>6</sub> (by 1.5-fold) in fisolated perfused hearts. These effects were concentra-<br>tion dependent, reaching a maximum at 100  $\mu$ M phenyl-<br>ephrine for IP<sub>3</sub> and IP<sub>4</sub> and at 10 nM for and 1P<sub>6</sub> were significantly augmented at 5 min.<br>
We would like to draw attention to the fact that, in the would like to draw attention to the fact that, in the most studies related to the  $\alpha_1$ -adrenoceptor-mediated for at 1 min, 1,3,4,5-IP<sub>4</sub> increased at 2 min, and 1,3,4,6-IP<sub>4</sub> and IP<sub>6</sub> were significantly augmented at 5 min.<br>We would like to draw attention to the fact that, in

at 1 mm, 1,0,4,0-114 increased at 2 mm, and 1,0,4,0-114<br>and IP<sub>6</sub> were significantly augmented at 5 min.<br>We would like to draw attention to the fact that, in<br>most studies related to the  $\alpha_1$ -adrenoceptor-mediated<br>increa We would like to draw attention to the fact that, in<br>
most studies related to the  $\alpha_1$ -adrenoceptor-mediated<br>
increase in labeled inositol phosphatases. Even if this exper-<br>
imental approach is very useful in such exper increase in labeled inositol phosphate, LiCl  $(10 \text{ mM})$  was used to inhibit inositol phosphatases. Even if this experimental approach is very useful in such experiments, it should be kept in mind that its use may not accu increase in labeled inositol phosphate, LiCl (10<br>used to inhibit inositol phosphatases. Even if the<br>imental approach is very useful in such experi<br>should be kept in mind that its use may not a<br>reflect the turnover of PI as ed to inhibit inositol phosphatases. Even if this exper-<br>ental approach is very useful in such experiments, it<br>ould be kept in mind that its use may not accurately<br>flect the turnover of PI as it occurs in vivo.<br>Some patho

mental approach is very useful in such experiments, it<br>should be kept in mind that its use may not accurately<br>reflect the turnover of PI as it occurs in vivo.<br>Some pathological conditions enhance the effect of  $\alpha_1$ -<br>adr reflect the turnover of PI as it occurs in vivo. In:<br>Some pathological conditions enhance the effect of  $\alpha_1$ -<br>adrenoceptor agonists on PI metabolism. For example, of<br>Xiang and McNeil (1991) observed a higher formation a Some pathological conditions enhance the effect of  $\alpha_1$ <br>adrenoceptor agonists on PI metabolism. For example<br>Xiang and McNeil (1991) observed a higher formation<br>of IP<sub>3</sub> in response to  $\alpha_1$ -adrenoceptors in diabetic th adrenoceptor agonists on PI metabolism. For example,<br>Xiang and McNeil (1991) observed a higher formation<br>of IP<sub>3</sub> in response to  $\alpha_1$ -adrenoceptors in diabetic than<br>in control rats. A greater increase, by  $\alpha_1$ -adrenoc Xiang and McNeil (1991) observed a higher for IP<sub>3</sub> in response to  $\alpha_1$ -adrenoceptors in diab<br>in control rats. A greater increase, by  $\alpha_1$ -adre<br>stimulation, of 1,4,5-IP<sub>3</sub> was reported in ventric<br>beculae isolated from of IP<sub>3</sub> in response to  $\alpha_1$ -adrenoceptors in diabetic than<br>in control rats. A greater increase, by  $\alpha_1$ -adrenoceptor<br>stimulation, of 1,4,5-IP<sub>3</sub> was reported in ventricular tra-<br>beculae isolated from malignant hypert in control rats. A greater increase, by  $\alpha_1$ -adrenoceptor<br>stimulation, of 1,4,5-IP<sub>3</sub> was reported in ventricular tra-<br>beculae isolated from malignant hyperthermia-suscepti-<br>ble swine when compared with healthy ones (Sc stimulation, of 1,4,5-IP<sub>3</sub> was reported in ventricular tra-<br>beculae isolated from malignant hyperthermia-suscepti-<br>ble swine when compared with healthy ones (Scholz et tion<br>al., 1991). Hypoxia also affects the  $\alpha_1$ -adr beculae isolated from malignant hyperthermia-suscepti-<br>ble swine when compared with healthy ones (Scholz et tion<br>al., 1991). Hypoxia also affects the  $\alpha_1$ -adrenergic effect been<br>on PI turnover. Canine myocytes exposed f ble swife when compared with healthy ones (Schotz et tal., 1991). Hypoxia also affects the  $\alpha_1$ -adrenergic effect bon PI turnover. Canine myocytes exposed for 10 min to chypoxia exhibit an increase in the production of on PI turnover. Canine myocytes exposed for 10 min to chypoxia exhibit an increase in the production of  $IP_3$  in or response to submaximal concentrations of norepineph-<br>rine; the EC<sub>50</sub> for norepinephrine stimulation in h hypoxia exhibit an increase in the production of IP<sub>3</sub> is<br>response to submaximal concentrations of norepineph<br>rine; the EC<sub>50</sub> for norepinephrine stimulation in hypoxi<br>cells was found to be 6-fold lower than in normoxic c response to submaximal concentrations of norepineph-<br>rine; the EC<sub>50</sub> for norepinephrine stimulation in hypoxic<br>cells was found to be 6-fold lower than in normoxic cells<br>(Heathers et al., 1989). In neonatal rat ventricula cells was found to be 6-fold lower than in normoxic cells a<br>
(Heathers et al., 1989). In neonatal rat ventricular myo-<br>
cytes, Kagiya et al. (1991b) observed an increase in  $\alpha_1$ -<br>
adrenoceptor-induced inositol phosphate (Figure 1) and the based of the based of the discreption of the addrenoceptor-induced inosited phosphate formation during the first hour of hypoxia. This effect was abolished by a prolonged hypoxia, whereas the basal leve

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sitol phosphates increased. In contrast, using the same<br>
cellular model, Steinberg and Alter (1993) observed a<br>
persistent enhancement of  $\alpha_1$ -adrenoceptor-mediated in-15<br>sitol phosphates increased. In contrast, using the same<br>cellular model, Steinberg and Alter (1993) observed<br>persistent enhancement of  $\alpha_1$ -adrenoceptor-mediated in<br>crease in inositol phosphate by hypoxia up to 6 h. T sitol phosphates increased. In contrast, using the same<br>cellular model, Steinberg and Alter (1993) observed a<br>persistent enhancement of  $\alpha_1$ -adrenoceptor-mediated in-<br>crease in inositol phosphate by hypoxia up to 6 h. T sitol phosphates increased. In contrast, using the solution reduced crease in inositol phosphate by hypoxia up to 6 h. Teffect was attributed to the stimulation of the  $\alpha_{1A}$ -rector subtype. cellular mod<br>persistent en<br>crease in inc<br>effect was at<br>tor subtype.<br>Regarding rsistent enhancement of  $\alpha_1$ -adrenoceptor-mediated in-<br>ease in inositol phosphate by hypoxia up to 6 h. This<br>fect was attributed to the stimulation of the  $\alpha_{1A}$ -recep-<br>r subtype.<br>Regarding the other limb of the PI pa

crease in inositol phosphate by hypoxia up to 6 h. This<br>effect was attributed to the stimulation of the  $\alpha_{1A}$ -recep-<br>tor subtype.<br>Regarding the other limb of the PI pathway, Okumura<br>et al. (1988) directly measured the effect was attributed to the stimulation of the  $\alpha_{1A}$ -receptor subtype.<br>
Regarding the other limb of the PI pathway, Okumura<br>
et al. (1988) directly measured the formation of DAG in<br>
response to the application of  $\alpha_$ tor subtype.<br>Regarding the other limb of the PI pathway, Okumura<br>et al. (1988) directly measured the formation of DAG in<br>response to the application of  $\alpha_1$ -adrenoceptor agonists.<br> $\alpha_1$ -Adrenoceptor stimulation produce Regarding the other limb of the PI pathway, Okumu<br>et al. (1988) directly measured the formation of DAG<br>response to the application of  $\alpha_1$ -adrenoceptor agonist<br> $\alpha_1$ -Adrenoceptor stimulation produced an increase<br>DAG ac response to the application of  $\alpha_1$ -adrenoceptor agonists.<br> $\alpha_1$ -Adrenoceptor stimulation produced an increase in DAG accumulation in the myocardium. DAG was measured in vivo in rat hearts using thin-layer chromatograp response to the application of  $\alpha_1$ -adrenoceptor agonists.<br> $\alpha_1$ -Adrenoceptor stimulation produced an increase in<br>DAG accumulation in the myocardium. DAG was meas-<br>ured in vivo in rat hearts using thin-layer chromatogr  $\alpha_1$ -Adrenoceptor stimulation produced an increase in DAG accumulation in the myocardium. DAG was measured in vivo in rat hearts using thin-layer chromatography and a flame ionization technique. Bordoni et al. (1991) al DRU accumulation in the injocarium. DRU was measured in vivo in rat hearts using thin-layer chromatography and a flame ionization technique. Bordoni et al. (1991) also demonstrated a DAG accumulation induced by  $\alpha_1$ -adr diomyocytes. iy and a flame ionization technique. Bordoni et al.<br>991) also demonstrated a DAG accumulation induced<br> $\alpha_1$ -adrenoceptor agonists in cultured neonatal car-<br>omyocytes.<br> $\alpha_1$ -Adrenergic stimulation increases PKC activity

(1991) also demonstrated a DAG accumulation induced<br>by  $\alpha_1$ -adrenoceptor agonists in cultured neonatal car-<br>diomyocytes.<br> $\alpha_1$ -Adrenergic stimulation increases PKC activity and<br>induces the translocation of this kinase by  $\alpha_1$ -adrenoceptor agonists in cultured neonatal c<br>diomyocytes.<br> $\alpha_1$ -Adrenergic stimulation increases PKC activity  $\epsilon$ <br>induces the translocation of this kinase from the cyto<br>to the sarcolemma (Henrich and Simpson, diomyocytes.<br>  $\alpha_1$ -Adrenergic stimulation increases PKC activity and<br>
induces the translocation of this kinase from the cytosol<br>
to the sarcolemma (Henrich and Simpson, 1988; Mochly-<br>
Rosen et al., 1990; Kaku et al., 19  $\alpha_1$ -Adrenergic stimulation increases PKC activity and<br>induces the translocation of this kinase from the cytosol<br>to the sarcolemma (Henrich and Simpson, 1988; Mochly-<br>Rosen et al., 1990; Kaku et al., 1991; Otani et al., induces the translocation of this kinase from the cytosol<br>to the sarcolemma (Henrich and Simpson, 1988; Mochly-<br>Rosen et al., 1990; Kaku et al., 1991; Otani et al., 1992;<br>Talosi and Kranias, 1992). In addition, Mochly-Rose to the sarcolemma (Henrich and Simpson, 1988; Mochl<br>Rosen et al., 1990; Kaku et al., 1991; Otani et al., 199<br>Talosi and Kranias, 1992). In addition, Mochly-Rosen<br>al. (1990), using an immunofluorescence technique, r<br>ported Rosen et al., 1990; Kaku et al., 1991; Otani et al., 1992<br>Talosi and Kranias, 1992). In addition, Mochly-Rosen e<br>al. (1990), using an immunofluorescence technique, re<br>ported that specific isozymes of the kinase were trans Falosi and Kramas, 1992). In addition, Mociny-Rosen et al. (1990), using an immunofluorescence technique, reported that specific isozymes of the kinase were translocated to specific sites inside the cell (membrane, myofil at. (1990), using an immunoindorescence decimique, re-<br>ported that specific isozymes of the kinase were trans-<br>located to specific sites inside the cell (membrane, myo-<br>filaments, and nucleus).  $\alpha_1$ -Adrenergic agonists located to specific sites inside the cell (membrane, myo-<br>filaments, and nucleus).  $\alpha_1$ -Adrenergic agonists induced<br>the translocation of the Ca<sup>2+</sup>-insensitive PKC isoform  $\epsilon$ <br>to the sarcolemma in both neonatal and adu aments, and nucleus).  $\alpha_1$ -Adrenergic agonists induced<br>e translocation of the Ca<sup>2+</sup>-insensitive PKC isoform  $\epsilon$ <br>the sarcolemma in both neonatal and adult cardio-<br>yocytes (Bogoyevitch et al., 1993; Pucéat et al., 1993b ementation increases PKC activity and<br>diomyocytes.<br> $\alpha_1$ -Adrenergic stimulation increases PKC activity and<br>induces the translocation of this kinase from the cytosol<br>to the sarcolemma (Henrich and Simpson, 1988; Mochly-<br>R

to the sarcolemma in both neonatal and adult cardio-<br>myocytes (Bogoyevitch et al., 1993; Pucéat et al., 1993b).<br>The hydrolysis of phosphatidylcholine is currently<br>emerging as a novel transduction pathway activated by<br>hormo for reviews, see Billah and Anthes, 1990; Exton, 1990).<br>The hydrolysis of phosphatidylcholine is currently<br>emerging as a novel transduction pathway activated by<br>hormones that accelerate PI turnover (Slivka et al., 1988;<br>fo emerging as a novel transduction pathway activate<br>hormones that accelerate PI turnover (Slivka et al., 1<br>for reviews, see Billah and Anthes, 1990; Exton, 19<br>Phosphatidylcholine breakdown is catalyzed by phos<br>lipase  $A_2$ , r reviews, see Billah and Anthes, 1990; Exton, 1988;<br>
r reviews, see Billah and Anthes, 1990; Exton, 1990).<br>
hosphatidylcholine breakdown is catalyzed by phospho-<br>
ase A<sub>2</sub>, phospholipase C, and phospholipase D.<br>
In numer

for reviews, see Billah and Anthes, 1990; Exton, 1990).<br>Phosphatidylcholine breakdown is catalyzed by phospholipase  $A_2$ , phospholipase C, and phospholipase D.<br>In numerous tissues,  $\alpha_1$ -adrenergic stimulation has<br>been Phosphatidylcholine breakdown is catalyzed by phospho-<br>lipase  $A_2$ , phospholipase C, and phospholipase D.<br>In numerous tissues,  $\alpha_1$ -adrenergic stimulation has<br>been reported to activate phospholipases  $A_2$  (Slivka and<br> lipase  $A_2$ , phospholipase C, and phospholipase D.<br>In numerous tissues,  $\alpha_1$ -adrenergic stimulation has<br>been reported to activate phospholipases  $A_2$  (Slivka and<br>Insel, 1987; Weiss and Insel, 1991; for reviews, see Ax In numerous tissues,  $\alpha_1$ -adrenergic stimulation has<br>been reported to activate phospholipases  $A_2$  (Slivka and<br>Insel, 1987; Weiss and Insel, 1991; for reviews, see Ax-<br>elrod et al., 1988 and Insel et al., 1991). The hy Insel, 1987; Weiss and Insel, 1991; for reviews, see Axelrod et al., 1988 and Insel et al., 1991). The hydrolysis of phosphatidylcholine by phospholipase  $A_2$  releases arelrod et al., 1988 and Insel et al., 1991). The hydrolysis elrod et al., 1988 and Insel et al., 1991). The hydrolysis<br>of phosphatidylcholine by phospholipase  $A_2$  releases ar-<br>achidonic acid. Arachidonic acid can also be generated<br>by the degradation of DAG following phospholipas of phosphatidylcholine by phospholipase  $A_2$  releases arachidonic acid. Arachidonic acid can also be generated<br>by the degradation of DAG following phospholipase C-<br>induced  $PIP_2$  hydrolysis. Arachidonic acid can activate by the degradation of DAG following phospholipase C-<br>induced  $PIP_2$  hydrolysis. Arachidonic acid can activate<br> $PKC$  by a mechanism different from DAG (for review,<br>see Bell and Burns, 1991); more specifically, this activa-<br> induced  $\text{PIP}_2$  hydrolysis. Arachidonic acid can activate PKC by a mechanism different from DAG (for review, see Bell and Burns, 1991); more specifically, this activation does not require phospholipids. Therefore, it ha induced  $\text{PIP}_2$  hydrolysis. Arachidonic acid can activate  $\text{PKC}$  by a mechanism different from DAG (for review, see Bell and Burns, 1991); more specifically, this activation does not require phospholipids. Therefore, PKC by a mechanism different from DAG (for review,<br>see Bell and Burns, 1991); more specifically, this activa-<br>tion does not require phospholipids. Therefore, it has<br>been speculated that arachidonic acid, as well as other<br>c see Bell and Burns, 1991); more specifically, this activation does not require phospholipids. Therefore, it has been speculated that arachidonic acid, as well as other *cis*-unsaturated fatty acids generated by the hydroly tion does not require phospholipids. Therefore, it has<br>been speculated that arachidonic acid, as well as other<br>cis-unsaturated fatty acids generated by the hydrolysis<br>of phospholipids, could under physiological conditions<br> been speculated that arachidonic acid, as well as other cis-unsaturated fatty acids generated by the hydrolysis of phospholipids, could under physiological conditions directly activate cytosoluble PKC without inducing the cis-unsaturated fatty acids generated by the hydrolysis<br>of phospholipids, could under physiological conditions<br>directly activate cytosoluble PKC without inducing the<br>kinase translocation (Khan et al., 1992). Arachidonic<br>ac of phospholipids, could under physiological conditions<br>directly activate cytosoluble PKC without inducing the<br>kinase translocation (Khan et al., 1992). Arachidonic<br>acid is also further metabolized inside the cell through<br>t directly activate cytosoluble PKC without inducing the kinase translocation (Khan et al., 1992). Arachidonic acid is also further metabolized inside the cell through three pathways: (*a*) the cyclooxygenase pathway leading kinase translocation (Khan et al., 1992). Arachidonic<br>acid is also further metabolized inside the cell through<br>three pathways: (a) the cyclooxygenase pathway leading<br>to the formation of prostaglandins, (b) the epoxygenase<br> acid is also further metabolized inside the cell throut<br>three pathways: (*a*) the cyclooxygenase pathway leadii<br>to the formation of prostaglandins, (*b*) the epoxygena<br>pathway leading to the generation of epoxides, and (<br> to the formation of prostaglandins,  $(b)$  the epoxygenase pathway leading to the generation of epoxides, and  $(c)$  the lipoxygenase pathway which generates the leuko-<br>trienes. It has been reported that arachidonic acid or i

metabolites could be involved in the  $\alpha_1$ -adrenoceptor-<br>mediated effect seen in cardiac muscle (Molderings and<br>Schümann, 1987; Kurachi et al., 1989, 1992).<br>Phospholipase C-mediated hydrolysis of phosphatidyl-<br>choline le mediated effect seen in cardiac muscle (Molderings and Schümann, 1987; Kurachi et al., 1989, 1992).<br>Phospholipase C-mediated hydrolysis of phosphatidylcholine leads to a direct formation of DAG, whereas phospholipase D act Schümann, 1987; Kurachi et al., 1989, 1992). tiat<br>
Phospholipase C-mediated hydrolysis of phosphatidy!<br>
choline leads to a direct formation of DAG, whereas tor<br>
phospholipase D activation generates phosphatidic acid, tial Phospholipase C-mediated hydrolysis of phosphatidyl-<br>choline leads to a direct formation of DAG, whereas<br>phospholipase D activation generates phosphatidic acid,<br>which can be metabolized to DAG. Phosphatidic acid<br>alone coul choline leads to a direct formation of DAG, whereas<br>phospholipase D activation generates phosphatidic acid,<br>which can be metabolized to DAG. Phosphatidic acid<br>alone could also serve as a genuine second messenger<br>because ph which can be metabolized to DAG. Phosphatidic acid<br>alone could also serve as a genuine second messenger<br>because phosphatidate-dependent phosphorylations<br>have been reported in several tissues including the heart<br>(Bocckino e because phosphatidate-dependent phosphorylation<br>have been reported in several tissues including the he<br>(Bocckino et al., 1991). Data are now available to supp<br>the idea that phospholipase D can be coupled to recept<br>(for re have been reported in several tissues including the (Bocckino et al., 1991). Data are now available to sup the idea that phospholipase D can be coupled to rece (for review, see Thompson et al., 1991). Such a hypesis could (Bocckino et al., 1991). Data are now available to suppote the idea that phospholipase D can be coupled to receptor (for review, see Thompson et al., 1991). Such a hypothesis could potentially be applied to cardiac  $\alpha_1$ the idea that phospholipase D can be coupled to receptors<br>(for review, see Thompson et al., 1991). Such a hypoth-<br>esis could potentially be applied to cardiac  $\alpha_1$ -adrenocep-<br>tors. Moreover, PKC has been shown to activa (for review, see Thompson et al., 1991). Such a hypothesis could potentially be applied to cardiac  $\alpha_1$ -adrenoceptors. Moreover, PKC has been shown to activate phospholipase D in numerous tissues (Martinson et al., 1990 esis could potentially be applied to cardiac  $\alpha_1$ -adrenoceptors. Moreover, PKC has been shown to activate phospholipase D in numerous tissues (Martinson et al., 1990; Conricode et al., 1992). These pathways could be of tors. Moreover, PKC has been shown to activate pholipase D in numerous tissues (Martinson et al., 19<br>Conricode et al., 1992). These pathways could be of graphysiological importance because sarcolemma conta<br>much more phosph pholipase D in numerous tissues (Martinson et al., 1990; afferencies of conricode et al., 1992). These pathways could be of great and physiological importance because sarcolemma contains of much more phosphatidylcholine th Conricode et al., 1992). These pathways could be of great<br>physiological importance because sarcolemma contains<br>much more phosphatidylcholine than phosphoinositides.<br>Moreover, DAG generated through these pathways could<br>be r From DAG generated through these pathways<br>ponsible for a sustained activation of PKC.<br>**IV. Cellular Effects Resulting from the Stimulation of Cardiac**  $\alpha_1$ **-Adrenocepto**<br>*fects on the Cardiac Action Potential and Ion* 

### **IV. Cellular Effects Resulting from the**<br>Stimulation of Cardiac  $\alpha_1$ -Adrenoceptors

### **A. Effects on the Cardiac Activition of Price.**<br>**A. Effects on the Cardiac**  $\alpha_1$ **-Adrenoceptors**<br>**A. Effects on the Cardiac Action Potential and Ionic**<br>**Currents** *Currents*

Stimulation of Cardiac  $\alpha_1$ -Adrenoceptors<br>*Effects on the Cardiac Action Potential and Ionic*<br>*urrents*<br>Using conventional microelectrode techniques, Pap-<br>no (1971) demonstrated that the action potential (a A. Effects on the Cardiac Action Potential and Ionic<br>Currents<br>Using conventional microelectrode techniques, Pap-<br>pano (1971) demonstrated that the action potential (at<br>90% repolarization) of guinea pig atria is prolonged b A. Effects on the Caralac Action Potential and Tonic<br>Currents<br>Using conventional microelectrode techniques, Pap-<br>pano (1971) demonstrated that the action potential (at<br>90% repolarization) of guinea pig atria is prolonged Using conventional microelectrode techniques, Pappano (1971) demonstrated that the action potential (at 90% repolarization) of guinea pig atria is prolonged by catecholamines in a propranolol-insensitive manner. Following Using conventional microelectrode techniques, Pap-<br>pano (1971) demonstrated that the action potential (at<br>90% repolarization) of guinea pig atria is prolonged by<br>catecholamines in a propranolol-insensitive manner. Fol-<br>lo pano (1971) demonstrated that the action potential (at 90% repolarization) of guinea pig atria is prolonged by catecholamines in a propranolol-insensitive manner. Following this report,  $\alpha_1$ -adrenergic stimulation has b 90% repolarization) of guinea pig atria is prolonged by catecholamines in a propranolol-insensitive manner. Following this report,  $\alpha_1$ -adrenergic stimulation has been repeatedly shown to increase the duration of cardia cate<br>cholamines in a propranolol-insensitive manner. Fol-<br>lowing this report,  $\alpha_1$ -adrenergic stimulation has been<br>repeatedly shown to increase the duration of cardiac<br>action potentials in different multicellular myocar lowing this report,  $\alpha_1$ -adrenergic stimulation has been<br>repeatedly shown to increase the duration of cardiac<br>action potentials in different multicellular myocardial<br>preparations from various species, including sheep an repeatedly shown to increase the duration of cardiac<br>action potentials in different multicellular myocardial<br>preparations from various species, including sheep and<br>dog Purkinje fibers (Giotti et al., 1973; Rosen et al.,<br>19 preparations from various species, including sheep and<br>dog Purkinje fibers (Giotti et al., 1973; Rosen et al., pott<br>1977), rabbit atria (Miura and Inui, 1984), rabbit papil-<br>1987), rabbit atria (Handa et al., 1982), and b 1977), rabbit atria (Miura and Inui, 1984), rabbit papil-<br>lary muscles (Handa et al., 1982), and bovine ventricular<br>trabeculae (Brückner and Scholz, 1984). In contrast to<br>these preparations, the guinea pig ventricle was f 1977), rabbit atria (Miura and Inui, 1984), rabbit papillary muscles (Handa et al., 1982), and bovine ventricular trabeculae (Brückner and Scholz, 1984). In contrast to these preparations, the guinea pig ventricle was foun lary muscles (Handa et al., 1982), and bovine ventricular<br>trabeculae (Brückner and Scholz, 1984). In contrast to<br>these preparations, the guinea pig ventricle was found<br>either to be unresponsive (Ledda et al., 1980; Hesche trabeculae (Brückner and Scholz, 1984). In contrast to <sup>p</sup><br>these preparations, the guinea pig ventricle was found S<br>either to be unresponsive (Ledda et al., 1980; Hescheler n<br>et al., 1988) or to respond by a decrease in t these preparations, the guinea pig ventricle was found<br>
either to be unresponsive (Ledda et al., 1980; Hescheler<br>
et al., 1988) or to respond by a decrease in the action<br>
in potential duration to  $\alpha_1$ -adrenoceptor agoni et al., 1988) or to respond by a decrease in the action<br>potential duration to  $\alpha_1$ -adrenoceptor agonists (Dirksen<br>and Sheu, 1990). Even in very responsive species, such<br>as the rat, the prolongation of the action potenti potential duration to  $\alpha_1$ -adrenoceptor ago<br>and Sheu, 1990). Even in very responsive as the rat, the prolongation of the action p<br>adrenoceptor agonists is more pronounce<br>in ventricular muscle (Ertl et al., 1991).<br>In sin In single, isolated ventricular myocytes, such the rat, the prolongation of the action potential by  $\alpha_1$ .<br>
The rate ventricular muscle (Ertl et al., 1991). In single, isolated ventricular myocytes, i.e., a pure curricul

as the rat, the prolongation of the action potential by  $\alpha_1$ -<br>adrenoceptor agonists is more pronounced in atrial than<br>in ventricular muscle (Ertl et al., 1991). in<br>In single, isolated ventricular myocytes, i.e., a pure<br> adrenoceptor agonists is more pronounced in atrial th<br>in ventricular muscle (Ertl et al., 1991).<br>In single, isolated ventricular myocytes, i.e., a potentiac preparation, catecholamines or synthetic adrenoceptor mimetics us in ventricular muscle (Ertl et al., 1991).<br>
In single, isolated ventricular myocytes, i.e., a pure<br>
cardiac preparation, catecholamines or synthetic  $\alpha_1$ -<br>
adrenoceptor mimetics usually prolong the action poten-<br>
tial d In single, isolated ventricular myocytes, i.e., a pure<br>cardiac preparation, catecholamines or synthetic  $\alpha_1$ -<br>adrenoceptor mimetics usually prolong the action poten-<br>tial duration (Apkon and Nerbonne, 1988; Fedida et al cardiac preparation, catecholamines or synthetic  $\alpha_1$ -<br>adrenoceptor mimetics usually prolong the action poten-<br>tial duration (Apkon and Nerbonne, 1988; Fedida et al., Bo<br>1989; Ravens et al., 1989; Vogel and Terzic, 1989 adrenoceptor mimetics usually prolong the action potential duration (Apkon and Nerbonne, 1988; Fedida et al., Bout 1989; Ravens et al., 1989; Vogel and Terzic, 1989). Vogel nel and Terzic (1989) observed a rapid increase i tial duration (Apkon and Nerbonne, 1988; Fedida et al., 1989; Ravens et al., 1989; Vogel and Terzic, 1989). Vogel and Terzic (1989) observed a rapid increase in the action potential duration in rat cells exposed to epinep 1989; Ravens et al., 1989; Vogel and Terzic, 1989). Vogel nand Terzic (1989) observed a rapid increase in the action were potential duration in rat cells exposed to epinephrine in ferticle presence of propranolol and stim and Terzic (1989) observed a rapid increase in the action potential duration in rat cells exposed to epinephrine in the presence of propranolol and stimulated at  $0.15$  Hz at  $37^{\circ}$ C. This effect was concentration depen

ET AL.<br>90% repolarization to increase by 56%. Prazosin (100<br>nM) inhibited, whereas lithium chloride (10 mM) poten-ET AL.<br>90% repolarization to increase by 56%. Prazosin (1<br>nM) inhibited, whereas lithium chloride (10 mM) pote<br>tiated, epinephrine's action. ET AL.<br>90% repolarization to increas<br>nM) inhibited, whereas lithiu<br>tiated, epinephrine's action.<br>Little is known about the is % repolarization to increase by 56%. Prazosin<br>
A) inhibited, whereas lithium chloride (10 mM) p<br>
tted, epinephrine's action.<br>
Little is known about the identity of the  $\alpha_1$ -adrenor<br>
r subtype involved in the modulation

90% repolarization to increase by 56%. Prazosin (1 nM) inhibited, whereas lithium chloride (10 mM) pote tiated, epinephrine's action.<br>Little is known about the identity of the  $\alpha_1$ -adrenoce tor subtype involved in the m nM) inhibited, whereas lithium chloride (10 mM) potentiated, epinephrine's action.<br>Little is known about the identity of the  $\alpha_1$ -adrenoceptor subtype involved in the modulation of action potential duration in cardiac c tiated, epinephrine's action.<br>Little is known about the identity of the  $\alpha_1$ -adrenocep<br>tor subtype involved in the modulation of action poten<br>tial duration in cardiac cells. Lee et al. (1991) showed<br>that in canine Purki Little is known about the identity of the  $\alpha_1$ -adrenoceptor subtype involved in the modulation of action potential duration in cardiac cells. Lee et al. (1991) showed that in canine Purkinje fibers the WB-4101-sensitive tial duration in cardiac cells. Lee et al. (1991) showed<br>that in canine Purkinje fibers the WB-4101-sensitive<br> $\alpha_{1A}$ -receptor subtype mediates the prolongation of repo-<br>larization via a pertussis toxin-insensitive pathw

In contrast to  $\beta$ -adrenoceptor agonists, which mostly that in canine Purkinje fibers the WB-4101-sensitive  $\alpha_{1A}$ -receptor subtype mediates the prolongation of repolarization via a pertussis toxin-insensitive pathway.<br>In contrast to  $\beta$ -adrenoceptor agonists, which mostly  $\alpha_{1A}$ -receptor subtype mediates the prolongation of repolarization via a pertussis toxin-insensitive pathway.<br>In contrast to  $\beta$ -adrenoceptor agonists, which mostly prolong the plateau phase and do not change or even larization via a pertussis toxin-insensitive pathway.<br>In contrast to  $\beta$ -adrenoceptor agonists, which mostly<br>prolong the plateau phase and do not change or even<br>shorten the final phase of repolarization (Nathan and<br>Beele In contrast to  $\beta$ -adrenoceptor agonists, which mostly<br>prolong the plateau phase and do not change or even<br>shorten the final phase of repolarization (Nathan and<br>Beeler, 1975),  $\alpha_1$ -adrenoceptor agonists increase the ac prolong the plateau phase and do not change or even<br>shorten the final phase of repolarization (Nathan and<br>Beeler, 1975),  $\alpha_1$ -adrenoceptor agonists increase the ac-<br>tion potential to a similar extent at both 20 and 90%<br> shorten the final phase of repolarization (Nathan and Beeler, 1975),  $\alpha_1$ -adrenoceptor agonists increase the action potential to a similar extent at both 20 and 90% repolarization in bovine ventricular trabeculae withou Beeler, 1975),  $\alpha_1$ -adrenoceptor agonists increase the action potential to a similar extent at both 20 and 90% repolarization in bovine ventricular trabeculae without affecting the amplitude of the action potential (Brü tion potential to a similar extent at both 20 and 90% repolarization in bovine ventricular trabeculae without affecting the amplitude of the action potential (Brückner and Scholz, 1984). The ratio of increases in the durat repolarization in bovine ventricular trabeculae without<br>affecting the amplitude of the action potential (Brückner<br>and Scholz, 1984). The ratio of increases in the duration<br>of action potential at 50% to increases in the dur affecting the amplitude of the action potential (Brückner and Scholz, 1984). The ratio of increases in the duration of action potential at 50% to increases in the duration of action potential at 90% was measured to be 0.8 and Scholz, 1984). The ratio of increases in the duration<br>of action potential at 50% to increases in the duration of<br>action potential at 90% was measured to be 0.86 in single<br>rat cells, indicating even a slightly smaller of action potential at 50% to increases in the duration of action potential at 90% was measured to be 0.86 in single rat cells, indicating even a slightly smaller effect of epinephrine (1 to 3  $\mu$ M) on the earlier phases action potential at 90% was measured to be 0.86 in single rat cells, indicating even a slightly smaller effect of epinephrine (1 to 3  $\mu$ M) on the earlier phases of the action potential repolarization (Vogel and Terzic, rat cells, indicating even a slightly smaller effect<br>epinephrine (1 to 3  $\mu$ M) on the earlier phases of s<br>action potential repolarization (Vogel and Terzic, 198<br>In rabbit atria, Ni<sup>+</sup>, which is known to suppress C<br>curren epinephrine (1 to 3  $\mu$ M) on the earlier phases of the action potential repolarization (Vogel and Terzic, 1989).<br>In rabbit atria, Ni<sup>+</sup>, which is known to suppress Ca<sup>2+</sup> current, does not affect the prolonging effect of action potential repolarization (Vogel and Terzic, 1989).<br>In rabbit atria, Ni<sup>+</sup>, which is known to suppress  $Ca^{2+}$ <br>current, does not affect the prolonging effect of phenyl-<br>ephrine at 90% repolarization. The Na<sup>+</sup> chann In rabbit atria, Ni<sup>+</sup>, which is known to suppress  $Ca^{2+}$ <br>current, does not affect the prolonging effect of phenyl-<br>ephrine at 90% repolarization. The Na<sup>+</sup> channel blocker,<br>tetrodotoxin, also does not affect the prolong current, does not affect t<br>ephrine at 90% repolariza<br>tetrodotoxin, also does n<br>of phenylephrine on the (Miura and Inui, 1984).<br>Phenylephrine also pro hrine at 90% repolarization. The Na<sup>+</sup> channel blo<br>trodotoxin, also does not affect the prolonging e<br>phenylephrine on the duration of the action pote<br>fiura and Inui, 1984).<br>Phenylephrine also prolongs or restores Ca<sup>2+</sup>-d

derivologian, also does not antect the prolonging enect<br>of phenylephrine on the duration of the action potential<br>(Miura and Inui, 1984).<br>Phenylephrine also prolongs or restores  $Ca^{2+}$ -depend-<br>ent (slow) action potentials (Miura and Inui, 1984).<br>
Phenylephrine also prolongs or restores Ca<sup>2+</sup>-depend<br>
ent (slow) action potentials in partially depolarized prep<br>
arations (Miura et al., 1978; Handa et al., 1982; Brückne<br>
and Scholz, 1984). It ent (slow) action potentials in partially depolarized preparations (Miura et al., 1978; Handa et al., 1982; Brückner and Scholz, 1984). It was proposed that  $\alpha_1$ -adrenoceptor agonists increase this current to a small ex agonists increase this current to a small extent, assuming potential reflects the  $Ca^{2+}$  inward current. d Scholz, 1984). It was proposed that  $\alpha_1$ -adrenoceptor<br>
onists increase this current to a small extent, assuming<br>
at the maximum rate of increase of the slow action<br>
tential reflects the Ca<sup>2+</sup> inward current.<br>
When th

potential duration to  $\alpha_1$ -adrenoceptor agonists (Dirksen<br>and Sheu, 1990). Even in very responsive species, such difficult in multicellular preparations to separate the<br>as the rat, the prolongation of the action potenti agonists increase this current to a small extent, assuming<br>that the maximum rate of increase of the slow action<br>potential reflects the  $Ca^{2+}$  inward current.<br>When the slow  $I_{Ca}$  is directly measured, increases in<br> $I_{Ca}$ that the maximum rate of increase of the slow action<br>potential reflects the Ca<sup>2+</sup> inward current.<br>When the slow  $I_{Ca}$  is directly measured, increases in<br> $I_{Ca}$  are rarely observed even if the action potential is<br>prolong potential reflects the Ca<sup>2+</sup> inward current.<br>When the slow  $I_{Ca}$  is directly measured, increases in  $I_{Ca}$  are rarely observed even if the action potential iprolonged by  $\alpha_1$ -adrenoceptor stimulation. Brückner an Scho  $I_{Ca}$  are rarely observed even if the action potential is prolonged by  $\alpha_1$ -adrenoceptor stimulation. Brückner and prolonged by  $\alpha_1$ -adrenoceptor stimulation. Brückner and Scholz (1984), using the sucrose-gap voltage clamp technique on bovine ventricular trabeculae, found an increase in peak  $I_{C_a}$  induced by phenylephrine as well difficult in multicellular trabeculae, found an increase<br>in peak  $I_{C_a}$  induced by phenylephrine as well as a slowing<br>down in the inactivation of this current. Because it is<br>difficult in multicellular preparations to sep down in the inactivation of this current. Because it is difficult in multicellular preparations to separate the  $Ca<sup>2+</sup>$  current from overlapping outward  $K<sup>+</sup>$  currents, it may also be difficult to determine whether a net increase<br>in inward current resulted from an increase in inward<br>current or from a decrease in outward currents. Apkon<br>and Nerbonne (1988), Hartmann et al. (1988), Hescheler<br>e may also be difficult to determine whether a net increase<br>in inward current resulted from an increase in inward<br>current or from a decrease in outward currents. Apkon<br>and Nerbonne (1988), Hartmann et al. (1988), Hescheler<br>e in inward current resulted from an increase in inward<br>current or from a decrease in outward currents. Apkor<br>and Nerbonne (1988), Hartmann et al. (1988), Heschele<br>et al. (1988), Ravens et al. (1989), Ertl et al. (1991)<br>Bout current or from a decrease in outward currents. Apkon<br>and Nerbonne (1988), Hartmann et al. (1988), Hescheler<br>et al. (1988), Ravens et al. (1989), Ertl et al. (1991),<br>Boutjdir et al. (1992), Fedida and Bouchard (1992), Jahand Nerbonne (1988), Hartmann et al. (1988), Hescheler<br>et al. (1988), Ravens et al. (1989), Ertl et al. (1991),<br>Boutjdir et al. (1992), Fedida and Bouchard (1992), Jah-<br>nel et al. (1992b), and Terzic et al. (1992a), using et al. (1988), Ravens et al. (1989), Ertl et al. (1991),<br>Boutjdir et al. (1992), Fedida and Bouchard (1992), Jah-<br>nel et al. (1992b), and Terzic et al. (1992a), using the<br>whole-cell patch clamp method in rabbit, guinea pi Boutjdir et al. (1992), Fedida and Bouchard (1992), Jahnel et al. (1992b), and Terzic et al. (1992a), using the whole-cell patch clamp method in rabbit, guinea pig, feline, or rat ventricular or atrial cells, found no inc nel et al. (1992b), and Terzic et al. (1992a), using the<br>whole-cell patch clamp method in rabbit, guinea pig,<br>feline, or rat ventricular or atrial cells, found no increase<br>in  $I_{C_a}$  following  $\alpha_1$ -adrenoceptor stimulat whole-cell patch clamp method in rabbit, guinea pig,<br>feline, or rat ventricular or atrial cells, found no increase<br>in  $I_{Ca}$  following  $\alpha_1$ -adrenoceptor stimulation. These ex-<br>periments were conducted under conditions i

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CARDIAC  $\alpha_1$ -AD<br>ventricular cells, Alvarez et al. (1987) observed an in-<br>crease in  $I_{Ca}$  following phenylephrine stimulation. This **CARDIAC**  $\alpha_1$ -ADR<br>
ventricular cells, Alvarez et al. (1987) observed an in-<br>
crease in  $I_{Ca}$  following phenylephrine stimulation. This<br>
effect was more pronounced on the T-type  $Ca^{2+}$  current<br>
in frog atrial cells in ventricular cells, Alvarez et al. (1987) observed an in-<br>crease in  $I_{Ca}$  following phenylephrine stimulation. This  $(I_{ki})$ <br>effect was more pronounced on the T-type Ca<sup>2+</sup> current tox<br>in frog atrial cells in which a 117% i effect was more pronounced on the T-type  $Ca^{2+}$  current<br>in frog atrial cells in which a 117% increase was reported<br>compared to 48% for the L-type current (Alvarez and<br>Vassort, 1992). Similarly, an increase in T-type  $Ca^{2$ In 110g atrial cells in which a 117% increase was reported<br>compared to 48% for the L-type current (Alvarez and<br>Vassort, 1992). Similarly, an increase in T-type Ca<sup>2+</sup><br>current is observed in canine ventricular and Purkinje Vassort, 1992). Similarly, an increase in T-type Ca<sup>2+</sup><br>current is observed in canine ventricular and Purkinje<br>cells (Tseng and Boyden, 1989). The mechanism of ac-<br>tion of the  $\alpha_1$ -adrenoceptor agonist on T-type Ca<sup>2+</sup> current is observed in canine ventricular and Purking<br>cells (Tseng and Boyden, 1989). The mechanism of action of the  $\alpha_1$ -adrenoceptor agonist on T-type Ca<sup>2+</sup> current is unknown. Recent observations of canine Purking<br>c cells (Tseng and Boyden, 1989). The mechanism of action of the  $\alpha_1$ -adrenoceptor agonist on T-type Ca<sup>2+</sup> current is unknown. Recent observations of canine Purkinje cells suggest that the T-type Ca<sup>2+</sup> current can be tr concentration (Tseng and Byden, 1991) as has been<br>concentration (Tseng and Byden, 1991) as has been by<br>described in smooth muscle of the rat portal vein (Pacaud in<br>et al., 1987). More recently, phenylephrine was shown to cells suggest that the T-type  $Ca^{2+}$  current can be tran-<br>siently increased by increasing the intracellular  $Ca^{2+}$  cellu<br>concentration (Tseng and Byden, 1991) as has been by I<br>described in smooth muscle of the rat porta siently increased by increasing the intracellular C<br>concentration (Tseng and Byden, 1991) as has be<br>described in smooth muscle of the rat portal vein (Pace<br>et al., 1987). More recently, phenylephrine was shown<br>increase th described in smooth muscle of the rat portal vein (Pacaud et al., 1987). More recently, phenylephrine was shown to increase the L-type  $Ca^{2+}$  current in neonatal rat ventricular cells, an effect that occurred within 20 m et al., 1987). More recently, phenylephrine was shown to<br>increase the L-type Ca<sup>2+</sup> current in neonatal rat ventric-<br>ular cells, an effect that occurred within 20 min (Liu et<br>al., 1992).<br>In rat ventricular myocytes,  $\alpha_1$ al., 1987). More recently, phenylephrine was shown to<br>crease the L-type Ca<sup>2+</sup> current in neonatal rat ventric-<br>ar cells, an effect that occurred within 20 min (Liu et<br>, 1992).<br>In rat ventricular myocytes,  $\alpha_1$ -adrenoce

increase the L-type  $Ca^{2+}$  current in neonatal rat ventric-<br>ular cells, an effect that occurred within 20 min (Liu et<br>al., 1992).<br>In rat ventricular myocytes,  $\alpha_1$ -adrenoceptor agonists<br>decrease the L-type  $I_{Ca}$  when ular cells, an effect that occurred within 20 min (Liu et b<br>al., 1992).<br>In rat ventricular myocytes,  $\alpha_1$ -adrenoceptor agonists a<br>decrease the L-type  $I_{Ca}$  when this  $Ca^{2+}$  current is en-<br>hanced by  $\beta$ -adrenoceptor s al., 1992).<br>In rat ventricular myocytes,  $\alpha_1$ -adrenoceptor agonists<br>decrease the L-type  $I_{Ca}$  when this  $Ca^{2+}$  current is en-<br>hanced by  $\beta$ -adrenoceptor stimulation or by forskolin<br>(Boutjdir et al., 1992). However, In fat ventricular myocytes,  $\alpha_1$ -autenoceptor agonists act<br>decrease the L-type  $I_{Ca}$  when this  $Ca^{2+}$  current is encyt<br>hanced by  $\beta$ -adrenoceptor stimulation or by forskolin gui<br>(Boutjdir et al., 1992). However,  $\alpha$ decrease the L-type  $I_{CA}$  when this Ca current is enhanced by  $\beta$ -adrenoceptor stimulation or by forskolin (Boutjdir et al., 1992). However,  $\alpha_1$ -adrenoceptor agonists do not inhibit  $I_{CA}$  if this current is increase Hanced by p-adienceptor simulation of by fors<br>(Boutjdir et al., 1992). However,  $\alpha_1$ -adrenceptor<br>nists do not inhibit  $I_{Ca}$  if this current is increase<br>intracellular perfusion of cAMP, even though thes<br>onists may stimu nists do not inhibit  $I_{Ca}$  if this current is increased by may be due to the absence of  $I_{to}$  channels (presumed to intracellular perfusion of cAMP, even though these ag-<br>be responsible for the prolonging effect observe nists do not inhibit  $I_{C_a}$  if this current is increased by r<br>intracellular perfusion of cAMP, even though these ag-<br>onists may stimulate the cAMP-phosphodiesterase r<br>(Buxton and Brunton, 1985a). Boutjdir et al. (1992)<br>p intracellular perfusion of cAMP, even though these ag-<br>onists may stimulate the cAMP-phosphodiesterase r<br>(Buxton and Brunton, 1985a). Boutjdir et al. (1992)<br>proposed that the  $\alpha_1$ -adrenoceptor-mediated inhibition<br>of  $\beta$ onists may stimulate the cAMP-ph<br>(Buxton and Brunton, 1985a). Boutjd<br>proposed that the  $\alpha_1$ -adrenoceptor-med<br>of  $\beta$ -adrenoceptor-activated  $I_{Ca}$  is due t<br>G-protein coupled to adenylate cyclase.<br> $\alpha_1$ -Adrenergic agoni Suxton and Brunton, 1985a). Boutjdir et al. (1992)<br>oposed that the  $\alpha_1$ -adrenoceptor-mediated inhibition<br> $\beta$ -adrenoceptor-activated  $I_{Ca}$  is due to an inhibitory<br>protein coupled to adenylate cyclase.<br> $\alpha_1$ -Adrenergic

proposed that the  $\alpha_1$ -adrenoceptor-mediated inhibition<br>of  $\beta$ -adrenoceptor-activated  $I_{Ca}$  is due to an inhibitory<br>G-protein coupled to adenylate cyclase.<br> $\alpha_1$ -Adrenergic agonists decrease K<sup>+</sup> outward current:<br>in of  $\beta$ -adrenoceptor-activated I<sub>Ca</sub> is due to an inhibitory<br>
G-protein coupled to adenylate cyclase. I<br>  $\alpha_1$ -Adrenergic agonists decrease K<sup>+</sup> outward currents<br>
in cardiomyocytes isolated from rat (Apkon and Ner-<br>
bonn G-protein coupled to adenylate cyclase.<br>  $\alpha_1$ -Adrenergic agonists decrease K<sup>+</sup> outward currents<br>
in cardiomyocytes isolated from rat (Apkon and Ner-<br>
bonne, 1988; Ravens et al., 1989; Tohse et al., 1990; Ertl<br>
et al.,  $\alpha_1$ -Autenergic agomsus decrease K outward currents differentially in cardiomyocytes isolated from rat (Apkon and Ner-86) bonne, 1988; Ravens et al., 1989; Tohse et al., 1990; Ertl indet al., 1991; Fedida and Bouchard, bonne, 1988; Ravens et al., 1989; Tohse et al., 1990; Ei<br>et al., 1991; Fedida and Bouchard, 1992) and rabb<br>hearts (Fedida et al., 1989, 1990). Specifically, it has be<br>reported that  $\alpha_1$ -adrenergic stimulation decreases et al., 1991; Fedida and Bouchard, 1992) and rabbit<br>hearts (Fedida et al., 1989, 1990). Specifically, it has been<br>reported that  $\alpha_1$ -adrenergic stimulation decreases both<br>the peak and the late current component of the ( hearts (Fedida et al., 1989, 1990). Specifically, it has been reported that  $\alpha_1$ -adrenergic stimulation decreases bothe peak and the late current component of the (time dependent)  $I_{to}$  (Wang et al., 1991). Fedida et a reported that  $\alpha_1$ -adrenergic stimulation decreases both  $I_k$ ,<br>the peak and the late current component of the (time-<br>dependent)  $I_{\omega}$  (Wang et al., 1991). Fedida et al. (1989) in<br>suggested that the decrease in  $I_{\omega}$ dependent) I<sub>to</sub> (Wang et al., 1991). Fedida et al. (1989) in guinea pig ventricular cells suggested that the  $\alpha_1$ -<br>suggested that the decrease in I<sub>to</sub> could provide an expla-<br>nation for the  $\alpha_1$ -adrenoceptor-induced suggested that the decrease in  $I_{to}$  could provide an expla-<br>adrenoceptor agonist norepinephrine, in the presence of<br>nation for the  $\alpha_1$ -adrenoceptor-induced increase in the  $\beta$ -blocker propranolol, activated a chlori suggested that the decrease in  $I_{\infty}$  could provide an explemation for the  $\alpha_1$ -adrenoceptor-induced increase in t<br>action potential duration. Inositol phosphates, PKC, an<br>a pertussis toxin sensitive G-protein appeared nation for the  $\alpha_1$ -adrenoceptor-induced increase in the action potential duration. Inositol phosphates, PKC, and a pertussis toxin sensitive G-protein appeared not to be involved in transducing the  $\alpha_1$ -adrenoceptora pertussis toxin sensitive G-protein appeared not to be childrenotical intensity of protein appeared not to be childrenoceptor in transducing the  $\alpha_1$ -adrenoceptor-mediated Inhibition of  $I_{\omega}$  (Braun et al., 1990); T a pertussis want sensitive G-protein appeared not to be<br>involved in transducing the  $\alpha_1$ -adrenoceptor-mediated<br>inhibition of  $I_{to}$  (Braun et al., 1990; Tohse et al., 1990).<br>Stimulation of both  $\alpha_1$ -adrenoceptor subty inhibition of  $I_{to}$  (Braun et al., 1990; Tohse et al., 1990).<br>Stimulation of both  $\alpha_1$ -adrenoceptor subtypes,  $\alpha_{1A}$  and  $\alpha_{1B}$ , contributes to the phenylephrine-induced reduction<br>in  $I_{to}$  of isolated rat myocytes inhibition of  $I_{\infty}$  (Braun et al., 1990; Tohse et al., 1990). erable Stimulation of both  $\alpha_1$ -adrenoceptor subtypes,  $\alpha_{1A}$  and reg  $\alpha_{1B}$ , contributes to the phenylephrine-induced reduction serin  $I_{\infty}$  of iso Stimulation of both  $\alpha_1$ -adrenoceptor subtypes,  $\alpha_{1A}$  and  $\alpha_{1B}$ , contributes to the phenylephrine-induced reduction in  $I_{to}$  of isolated rat myocytes (Wang et al., 1991). Specifically, stimulation of both adrenoc  $\alpha_{1B}$ , contributes to the phenylephrine-induced reduction<br>in  $I_{to}$  of isolated rat myocytes (Wang et al., 1991). Spe-<br>cifically, stimulation of both adrenoceptor subtypes is<br>required for the reduction of the peak curr in  $I_{\text{to}}$  of isolated rat myocytes (Wang et al., 1991). Specifically, stimulation of both adrenoceptor subtypes is required for the reduction of the peak current component of  $I_{\text{to}}$ , whereas stimulation of either th cifically, stimulation of both advergined for the reduction of the pof  $I_{\text{to}}$ , whereas stimulation of eith subtype is sufficient for the reduction<br>component (Wang et al., 1991). Following 4-aminopyridine tree quired for the reduction of the peak current component  $I_{to}$ , whereas stimulation of either the  $\alpha_{1A}$ - or the  $\alpha_{1B}$ -<br>btype is sufficient for the reduction of the late current deponent (Wang et al., 1991).<br>Following

subtype is sufficient for the reduction of the late current domponent (Wang et al., 1991).<br>
Following 4-aminopyridine treatment to block  $I_{\text{to}}$ ,  $\alpha_1$ -<br>
radrenoceptor agonists decrease the magnitude of two<br>
inward rec component (Wang et al., 1991).<br>
Following 4-aminopyridine treatment to block ladrenoceptor agonists decrease the magnitude cinward rectifying  $K^+$  currents: (*a*) the inwardly rect background current,  $I_{k1}$ , and (*b*) Following 4-aminopyridine treatment to block  $I_{\text{to}}$ ,  $\alpha_1$ -<br>adrenoceptor agonists decrease the magnitude of two<br>inward rectifying  $K^+$  currents: (*a*) the inwardly rectifying tie<br>background current,  $I_{\text{k1}}$ , and (

effect was more pronounced on the T-type Ca<sup>2+</sup> current toxin and does not involve the activation of PKC (Fedida in frog atrial cells in which a 117% increase was reported et al., 1991; Braun et al., 1992).  $\alpha_1$ -Adrener ENOCEPTORS 153<br>  $\alpha_1$ -adrenergic effect on inward rectifying K<sup>+</sup> channels<br>  $(I_{k1}$  and  $I_{kAch}$ ) was reported to be insensitive to pertussis ENOCEPTORS 153<br>  $\alpha_1$ -adrenergic effect on inward rectifying K<sup>+</sup> channels<br>  $(I_{k1}$  and  $I_{kAch}$ ) was reported to be insensitive to pertussis<br>
toxin and does not involve the activation of PKC (Fedida ENOCEPTORS 153<br>  $\alpha_1$ -adrenergic effect on inward rectifying K<sup>+</sup> channels<br>  $(I_{k1}$  and  $I_{k \text{ Ach}}$ ) was reported to be insensitive to pertussis<br>
toxin and does not involve the activation of PKC (Fedida<br>
et al., 1991; Bra  $\alpha_1$ -adrenergic effect on inward rectifying K<sup>+</sup> channels ( $I_{k1}$  and  $I_{kAch}$ ) was reported to be insensitive to pertussis toxin and does not involve the activation of PKC (Fedida et al., 1991; Braun et al., 1992).  $\$  $a_1$ -adrenergic effect on inward rectifying it chank<br>( $I_{k1}$  and  $I_{kAch}$ ) was reported to be insensitive to pertu<br>toxin and does not involve the activation of PKC (Fee<br>et al., 1991; Braun et al., 1992).  $\alpha_1$ -Adrenerg ( $I_{k1}$  and  $I_{kAch}$ ) was reported to be insensitive to pertussis toxin and does not involve the activation of PKC (Fedida et al., 1991; Braun et al., 1992).  $\alpha_1$ -Adrenergic agonists also reduce the steady state curren with and does not invoive the activation of  $\overline{F}$  red et al., 1991; Braun et al., 1992).  $\alpha_1$ -Adrenergic agon also reduce the steady state current and  $I_k$  in rat cardivocytes (Ravens et al., 1989; Tohse et al., 1990 et al., 1991; Braun et al., 1992).  $\alpha_1$ -Adrener<br>also reduce the steady state current and  $I_k$  in<br>yocytes (Ravens et al., 1989; Tohse et al., 1<br>et al., 1991) and decrease the background lance in Purkinje fibers (Shah et So reduce the steady state current and  $I_k$  in rat cardiom-<br>cytes (Ravens et al., 1989; Tohse et al., 1990; Jahnel<br>al., 1991) and decrease the background  $K^+$  conduct-<br>ce in Purkinje fibers (Shah et al., 1988).<br>In guinea

yocytes (Ravens et al., 1989; Tohse et al., 1990; Jahnel<br>et al., 1991) and decrease the background  $K^+$  conduct-<br>ance in Purkinje fibers (Shah et al., 1988).<br>In guinea pig, contrary to rat, ventricular myocytes,<br>phenylep et al., 1991) and decrease the background  $K^+$  conduc<br>ance in Purkinje fibers (Shah et al., 1988).<br>In guinea pig, contrary to rat, ventricular myocyte<br>phenylephrine (10 to 30  $\mu$ M) increased the  $I_k$  (Tohse  $\alpha$ <br>al., 19 In guinea pig, contrary to rat, ventricular myocytes,<br>phenylephrine (10 to 30  $\mu$ M) increased the I<sub>k</sub> (Tohse et<br>al., 1987b, 1992). This effect was observed when intra-<br>cellular Ca<sup>2+</sup> was clamped to pCa 8. It was reprod in guinea pig, contrary to rat, ventricular inyotytes<br>phenylephrine (10 to 30  $\mu$ M) increased the I<sub>k</sub> (Tohse e<br>al., 1987b, 1992). This effect was observed when intra<br>cellular Ca<sup>2+</sup> was clamped to pCa 8. It was reproduc phenylephilite (10 to 50  $\mu$ m) increased the  $r_k$  (1 onse et al., 1987b, 1992). This effect was observed when intracellular Ca<sup>2+</sup> was clamped to pCa 8. It was reproduced by PKC activators, occluded by pretreatment with cellular Ca<sup>2+</sup> was clamped to pCa 8. It was reproduced<br>by PKC activators, occluded by pretreatment with max-<br>imally effective concentrations of PKC activators, and<br>blocked by PKC inhibitors (Tohse et al., 1987b, 1992).<br>H by PKC activators, occluded by pretreatment with maximally effective concentrations of PKC activators, and blocked by PKC inhibitors (Tohse et al., 1987b, 1992). Hence, this  $\alpha_1$ -adrenoceptor-mediated increase in  $I_k$  m blocked by PKC inhibitors (Tohse et al., 1987b, 1992)<br>Hence, this  $\alpha_1$ -adrenoceptor-mediated increase in I<sub>k</sub> ma<br>be related to an activation of PKC. The increase in I<br>could explain why  $\alpha_1$ -adrenoceptor agonists decre Hence, this  $\alpha_1$ -adrenoceptor-mediated increase in  $I_k$  may<br>be related to an activation of PKC. The increase in  $I_k$ <br>could explain why  $\alpha_1$ -adrenoceptor agonists decrease the<br>action potential duration in guinea pig ve guinea pig ventricle and other species with respect to the could explain why  $\alpha_1$ -adrenoceptor agonists decrease the action potential duration in guinea pig ventricular myocytes (Dirksen and Sheu, 1990). The difference could explain why  $\alpha_1$ -adrenoceptor agomsts decrease the<br>action potential duration in guinea pig ventricular myo-<br>cytes (Dirksen and Sheu, 1990). The difference between<br>guinea pig ventricle and other species with respec action potential duration in guinea pig ventricular myocytes (Dirksen and Sheu, 1990). The difference between<br>guinea pig ventricle and other species with respect to the<br> $\alpha_1$ -adrenergic effects on the duration of action cytes (Dirksen and Sheu, 1990). The difference between<br>guinea pig ventricle and other species with respect to the<br> $\alpha_1$ -adrenergic effects on the duration of action potentials<br>may be due to the absence of  $I_{to}$  channels  $\alpha_1$ -adrenergic effects on the duration of action potentials<br>may be due to the absence of  $I_{to}$  channels (presumed to<br>be responsible for the prolonging effect observed in the<br>rat, rabbit, and other species) from guinea cells (Tohse et al., 1992).<br>
In guinea pig atria, Kurachi et al. (1989) demonstrated<br>
that  $\alpha_1$ -adrenoceptor stimulation activates the I<sub>k Ach</sub>.

rat, rabbit, and other species) from guinea pig ventricular cells (Tohse et al., 1992).<br>
In guinea pig atria, Kurachi et al. (1989) demonstrated<br>
that  $\alpha_1$ -adrenoceptor stimulation activates the  $I_k$   $\alpha_0$ .<br>
Phenylephr In guinea pig atria, Kurachi et al. (1989) demonstrated In guinea pig atria, Kuratin et al. (1969) demonstrated<br>that  $\alpha_1$ -adrenoceptor stimulation activates the  $I_k$   $_{\text{Ach}}$ .<br>Phenylephrine-induced activation was prevented by nor-<br>dihydroguaiaretic acid, a lipoxygenase inhi Phenylephrine-induced activation was prevented by nor-<br>dihydroguaiaretic acid, a lipoxygenase inhibitor, and AA-<br>861, a 5-lipoxygenase inhibitor, but was not affected by<br>indomethacin, a cycloxygenase inhibitor. It was con dihydroguaiaretic acid, a lipoxygenase inhibitor, and AA-<br>861, a 5-lipoxygenase inhibitor, but was not affected by<br>indomethacin, a cycloxygenase inhibitor. It was con-<br>cluded that 5-lipoxygenase metabolites of arachidonic 861, a 5-lipoxygenase inhibitor, but was indomethacin, a cycloxygenase inhibitor<br>cluded that 5-lipoxygenase metabolites<br>acid may be involved in the  $\alpha_1$ -adrenergi<br> $I_{k \text{ Ach}}$  (reviewed by Kurachi et al., 1992).<br>In additi domethacin, a cycloxygenase inhibitor. It was con-<br>ided that 5-lipoxygenase metabolites of arachidonic<br>id may be involved in the  $\alpha_1$ -adrenergic activation of<br> $\alpha_{ch}$  (reviewed by Kurachi et al., 1992).<br>In addition to K

in guinear pieza di I<sub>k Ach</sub> (reviewed by Kurachi et al., 1992).<br>
In addition to K<sup>+</sup> currents, a recent study performed<br>
in guinea pig ventricular cells suggest It Ach (reviewed by Kuracin et al., 1992).<br>In addition to  $K^+$  currents, a recent study perform<br>in guinea pig ventricular cells suggested that the<br>adrenoceptor agonist norepinephrine, in the presence<br>the  $\beta$ -blocker pro in guinea pig ventricular cells suggested that the  $\alpha_1$ adrenoceptor agonist norepinephrine, in the presence of renoceptor agonist norepinephrine, in the presence of<br>e  $\beta$ -blocker propranolol, activated a chloride conduct-<br>ce (Walsh, 1991; Ackerman and Clapham, 1993). This<br>loride conductance was PKC dependent.<br>In summary,  $\alpha_1$ -a

ance (Walsh, 1991; Ackerman and Clapham, 1993). This<br>chloride conductance was PKC dependent.<br>In summary,  $\alpha_1$ -adrenoceptor agonists modulate sev-<br>eral conductances in heart muscle. In some cases, this<br>regulation does no In summary,  $\alpha_1$ -adrenoceptor agonists modulate several conductances in heart muscle. In some cases, this regulation does not depend on PKC or a pertussis toxinsensitive G-protein; in others, it does, suggesting a multi In summary,  $\alpha_1$ -aurence poor agons is modulate several conductances in heart muscle. In some cases, this regulation does not depend on PKC or a pertussis toxinsensitive G-protein; in others, it does, suggesting a multi gulation does not depend on PKC or a pertussis toxin-<br>nsitive G-protein; in others, it does, suggesting a mul-<br>plicity of subcellular coupling processes (for review, see<br>idoh, 1991).<br>The effects of the  $\alpha_1$ -adrenoceptor

of  $I_{\infty}$ , whereas stimulation of either the  $\alpha_{1A}$ - or the  $\alpha_{1B}$ -resting membrane potential varies with the tissue. In-<br>subtype is sufficient for the reduction of the late current deed, it has been reported that sensitive G-protein; in others, it does, suggesting a multiplicity of subcellular coupling processes (for review, see Endoh, 1991).<br>The effects of the  $\alpha_1$ -adrenoceptor stimulation on the resting membrane potential vari tiplicity of subcellular coupling processes (for review, s<br>Endoh, 1991).<br>The effects of the  $\alpha_1$ -adrenoceptor stimulation on t<br>resting membrane potential varies with the tissue. I<br>deed, it has been reported that  $\alpha_1$ -Endoh, 1991).<br>
The effects of the  $\alpha_1$ -adrenoceptor stimulation on the<br>
resting membrane potential varies with the tissue. In-<br>
deed, it has been reported that  $\alpha_1$ -adrenoceptor stimu-<br>
lation depolarizes, hyperpolari The effects of the  $\alpha_1$ -adrenoceptor stimulation on the<br>resting membrane potential varies with the tissue. In-<br>deed, it has been reported that  $\alpha_1$ -adrenoceptor stimu-<br>lation depolarizes, hyperpolarizes, or does not c deed, it has been reported that  $\alpha_1$ -adrenoceptor stimulation depolarizes, hyperpolarizes, or does not change the resting membrane potential. Miura and Inui (1984) showed that  $\alpha_1$ -adrenoceptor stimulation produces a deed, it has been reported that  $\alpha_1$ -adrenoceptor stimulation depolarizes, hyperpolarizes, or does not change the resting membrane potential. Miura and Inui (1984) showed that  $\alpha_1$ -adrenoceptor stimulation produces a lation depolarizes, hyperpolarizes, or does not change the<br>resting membrane potential. Miura and Inui (1984)<br>showed that  $\alpha_1$ -adrenoceptor stimulation produces a par-<br>tial depolarization of the resting membrane potentia resting membrane potential. Miura and Inui (1984)<br>showed that  $\alpha_1$ -adrenoceptor stimulation produces a par-<br>tial depolarization of the resting membrane potential in<br>the rabbit atrium. More recently, Jahnel et al. (1991)

 $154$  TERZIC ET AL. 154<br>depolarization in rat heart atria. This depolarization was<br>attributed to the decrease in K<sup>+</sup> currents in the presence un 154 TERZIC Exercise 154<br>depolarization in rat heart atria. This depolarization was<br>attributed to the decrease in K<sup>+</sup> currents in the presence<br>of a depolarizing Na<sup>+</sup> inward current. However, in mul-TERZIC E<br>depolarization in rat heart atria. This depolarization was<br>attributed to the decrease in  $K^+$  currents in the presence<br>of a depolarizing  $Na^+$  inward current. However, in mul-<br>ticellular ventricular preparations depolarization in rat heart atria. This depolarization wa<br>attributed to the decrease in  $K^+$  currents in the presenc<br>of a depolarizing Na<sup>+</sup> inward current. However, in mul<br>ticellular ventricular preparations or in Purki depolarization in rat heart atria. This depolarization was veattributed to the decrease in  $K^+$  currents in the presence urof a depolarizing Na<sup>+</sup> inward current. However, in mul-<br>ticellular ventricular preparations or i attributed to the decrease in  $K^+$  currents in the presence<br>of a depolarizing  $Na^+$  inward current. However, in mul-<br>ticellular ventricular preparations or in Purkinje myo-<br>cytes,  $\alpha_1$ -adrenoceptor stimulation hyperpol of a depolarizing Na<sup>+</sup> inward current. However, in multicellular ventricular preparations or in Purkinje myocytes,  $\alpha_1$ -adrenoceptor stimulation hyperpolarizes the membrane (Tohse et al., 1987b; Shah et al., 1988). Whe ticellular ventricular preparations or in Purkinje myocytes,  $\alpha_1$ -adrenoceptor stimulation hyperpolarizes the omembrane (Tohse et al., 1987b; Shah et al., 1988). 1 Whereas Tohse et al. (1987b) reported that the Na<sup>+</sup>/K<sup></sup> cytes,  $\alpha_1$ -adrenoceptor stimulation hyperpolarizes the omembrane (Tohse et al., 1987b; Shah et al., 1988).<br>Whereas Tohse et al. (1987b) reported that the Na<sup>+</sup>/K<sup>+</sup><br>pump was not involved in this  $\alpha_1$ -adrenoceptor med Whereas Tohse et al., 1967b, Shan et al., 1966).<br>Whereas Tohse et al. (1987b) reported that the Na<sup>+</sup>/K<sup>+</sup> r<br>pump was not involved in this  $\alpha_1$ -adrenoceptor mediated<br>effect, Shah et al. (1988) and Ertl et al. (1991) att pump was not involved in this  $\alpha_1$ -adrenoceptor mediated<br>effect, Shah et al. (1988) and Ertl et al. (1991) attributed<br>this hyperpolarizing action to the stimulation of the Na<sup>+</sup>/<br>K<sup>+</sup> pump because, in their experimental effect, Shah et al. (1988) and Ertl et al. (1991) attributhis hyperpolarizing action to the stimulation of the N<br>K<sup>+</sup> pump because, in their experimental conditions<br>was abolished by digitalis glycosides. A ouabain-sensiti this hyperpolarizing action to the stimulation of the Na<sup>+</sup>/  $\mu$ K<sup>+</sup> pump because, in their experimental conditions, it in was abolished by digitalis glycosides. A ouabain-sensitive the hyperpolarization induced by  $\alpha_1$ K<sup>+</sup> pump because, in their experimental conditions, it intr<br>was abolished by digitalis glycosides. A ouabain-sensitive tor-<br>hyperpolarization induced by  $\alpha_1$ -adrenoceptor stimula-<br>was<br>tion has also been reported in rat was abolished by digitalis glycosides. A ouabain-sensitive to<br>hyperpolarization induced by  $\alpha_1$ -adrenoceptor stimula-<br>tion has also been reported in rat atrial muscle (Terzic H<sup>+</sup><br>et al., 1991). In isolated rat ventricu hyperpolarization induced by  $\alpha_1$ -adrenoceptor stimulation has also been reported in rat atrial muscle (Terzicet al., 1991). In isolated rat ventricular myocytes, no significant effect on resting membrane potential has notion has also been reported in rat attraitmistic (Terzic 11<br>et al., 1991). In isolated rat ventricular myocytes, no<br>observed following the addition of  $\alpha_1$ -adrenoceptor ago-<br>nists (Ertl et al., 1991). Ertl et al. (199 observed following the addition of  $\alpha_1$ -adrenoceptor agonists (Ertl et al., 1991). Ertl et al. (1991) suggested that cells in isolation respond differently to a Na<sup>+</sup>/K<sup>+</sup> pump stimulation than do cells in their natural nists (Ertl et al., 1991). Ertl et al. (1991) suggested that cells in isolation respond differently to a Na<sup>+</sup>/K<sup>+</sup> pump stimulation than do cells in their natural environment.<br>*B. Effects on Intracellular H<sup>+</sup>*, *Na<sup>+</sup>*,

# **Ionic Transport Mechanisms**<br>*B. Effects on Intracellular Honic Transport Mechanism*

B. Effects on Intracellular  $H^+$ ,  $Na^+$ , and  $Ca^{2+}$  and on conic Transport Mechanisms at  $\alpha_1$ -Adrenoceptor agonists produce an intracellular al-<br>kalinization. This finding has been described in atria no (Terzic et al. (B). Effects on Intracement H , Iva, and Ca and on<br>Ionic Transport Mechanisms<br> $\alpha_1$ -Adrenoceptor agonists produce an intracellular al-<br>kalinization. This finding has been described in atria<br>(Terzic et al., 1991), perfuse  $\alpha_1$ -Adrenoceptor agonists produce an intracellular al-<br>kalinization. This finding has been described in atria no<br>(Terzic et al., 1991), perfused hearts (Fuller et al., 1991), this<br>single isolated ventricular cardiomyoc kalinization. This finding has been described in atria (Terzic et al., 1991), perfused hearts (Fuller et al., 1991), single isolated ventricular cardiomyocytes (Astarie et al., 1991; Gambassi et al., 1992; Terzic et al., 1 (Terzic et al., 1991), perfused hearts (Fuller et al., 1991),<br>single isolated ventricular cardiomyocytes (Astarie et al.,<br>1991; Gambassi et al., 1992; Terzic et al., 1992a; Pucéat<br>et al., 1993a), cardiac cells in suspensio single isolated ventricular cardiomyocytes (Astarie et al., 1991; Gambassi et al., 1992; Terzic et al., 1992a; Pucéat<br>et al., 1993a), cardiac cells in suspension (Iwakura et al., 1990; Wallert and Fröhlich, 1992), and Purk 1991; Gambassi et al., 1992; Terzic et al., 1992a; Pucéat<br>et al., 1993a), cardiac cells in suspension (Iwakura et al.,<br>1990; Wallert and Fröhlich, 1992), and Purkinje fibers<br>(Breen and Pressler, 1988; Pressler et al., 1989 1990; Wallert and Fröhlich, 1992), and Purkinje fibers (Breen and Pressler, 1988; Pressler et al., 1989; see, however, Guo et al., 1992). To measure pH<sub>i</sub>, ion-selective microelectrodes (Terzic et al., 1991) and pH<sub>i</sub>-sen (Breen and Pressler, 1988; Pressler et al., 1989; see, l<br>however, Guo et al., 1992). To measure pH<sub>i</sub>, ion-selective<br>microelectrodes (Terzic et al., 1991) and pH<sub>i</sub>-sensitive<br>fluorescent indicators (Iwakura et al., 1990; however, Guo et al., 1992). To measure pH<sub>i</sub>, ion-<br>microelectrodes (Terzic et al., 1991) and pH<sub>i</sub>-<br>fluorescent indicators (Iwakura et al., 1990; Ga<br>al., 1992; Terzic et al., 1992a; Wallert and Fröhli<br>have been used. In ad microelectrodes (Terzic et al., 1991) and pH<sub>i</sub>-sensitive PH<br>fluorescent indicators (Iwakura et al., 1990; Gambassi et al., 1992; Terzic et al., 1992a; Wallert and Fröhlich, 1992) pe<br>have been used. In addition,  $[^{14}C]5$ fluorescent indicators (Iwakura et al., 1990; Gambassi et ad., 1992; Terzic et al., 1992a; Wallert and Fröhlich, 1992) phave been used. In addition,  $[^{14}C]5,5'$ -dimethyloxazoli-adine-2,4-dione, a compound that partition al., 1992; Terzic et al., 1992a; Wallert and Fröhlich, 1992)<br>have been used. In addition,  $[^{14}C]5,5'$ -dimethyloxazoli-<br>dine-2,4-dione, a compound that partitions between the<br>intracellular and extracellular spaces as a fu dine-2,4-dione, a compound that partitions between the<br>intracellular and extracellular spaces as a function of<br>intracellular and extracellular pH, was used to assess<br> $pH_i$  (Fuller et al., 1991).<br>Both synthetic sympathomim ne-2,4-dione, a compound that partitions between the tracellular and extracellular spaces as a function of tracellular and extracellular pH, was used to assess  $H_i$  (Fuller et al., 1991).<br>Both synthetic sympathomimetics a intracellular and extracellular spaces as a function<br>intracellular and extracellular pH, was used to asse<br>pH<sub>i</sub> (Fuller et al., 1991).<br>Both synthetic sympathomimetics and endogeno<br>catecholamines (in the presence of  $\beta$ -a

ers) induce an alkalinization that typically amounts to<br>
cate cholamines (in the presence of β-adrenoceptor block-<br>
ers) induce an alkalinization that typically amounts to<br>
0.1 pH units at 30  $\mu$ M epinephrine or 100  $\mu$ Both synthetic sympathomimetics and endogenous<br>catecholamines (in the presence of  $\beta$ -adrenoceptor block-<br>ers) induce an alkalinization that typically amounts to<br>0.1 pH units at 30  $\mu$ M epinephrine or 100  $\mu$ M phenylep catecholamines (in the presence of  $\beta$ -adrenoceptor block-<br>ers) induce an alkalinization that typically amounts to<br>0.1 pH units at 30  $\mu$ M epinephrine or 100  $\mu$ M phenyleph-<br>rine either in bicarbonate-poor or -rich bat ers) induce an alkalinization that typically amounts to 0.1 pH units at 30  $\mu$ M epinephrine or 100  $\mu$ M phenylephrine either in bicarbonate-poor or -rich bathing solutions (Astarie et al., 1991; Fuller et al., 1991; Ter 0.1 pH units at 30  $\mu$ M epinephrine or 100  $\mu$ M phenylephrine either in bicarbonate-poor or -rich bathing solution (Astarie et al., 1991; Fuller et al., 1991; Terzic et al. 1992a). The selective  $\alpha_1$ -adrenoceptor bloc rine either in bicarbonate-poor or -rich bathing solutions<br>(Astarie et al., 1991; Fuller et al., 1991; Terzic et al.<br>1992a). The selective  $\alpha_1$ -adrenoceptor blocker, prazosin<br>but not the  $\alpha_2$ -adrenoceptor blocker, yoh (Astarie et al., 1991; Fuller et al., 1991; Terzic et al. 1992a). The selective  $\alpha_1$ -adrenoceptor blocker, prazosir but not the  $\alpha_2$ -adrenoceptor blocker, yohimbine, abolished this alkalinization, indicating that the 1992a). The selective  $\alpha_1$ -adrenoceptor blocker, but not the  $\alpha_2$ -adrenoceptor blocker, yohimbished this alkalinization, indicating that the sar  $\alpha_1$ -adrenoceptor is responsible for the effect on zic et al., 1992a; it not the  $\alpha_2$ -adrenoceptor blocker, yohimbine, abol-<br>
ed this alkalinization, indicating that the sarcolemmal Na<sup>+</sup><br>
-adrenoceptor is responsible for the effect on pH<sub>i</sub> (Ter-<br>
et al., 1992a; Wallert and Fröhlich, 199

ished this alkalinization, indicating that the sarcolemmal  $\alpha_1$ -adrenoceptor is responsible for the effect on pH<sub>i</sub> (Ter-<br>zic et al., 1992a; Wallert and Fröhlich, 1992).<br>The origin of the alkalinization has been ascribe  $\alpha_1$ -autenoceptor is responsible for the effect on pri<sub>1</sub> (ref-<br>zic et al., 1992a; Wallert and Fröhlich, 1992).<br>The origin of the alkalinization has been ascribed to<br>the stimulation of Na<sup>+</sup>/H<sup>+</sup> exchange, a major alkal 21c et al., 1992a; wanter and Fromch, 1992).<br>The origin of the alkalinization has been ascribed to<br>the stimulation of Na<sup>+</sup>/H<sup>+</sup> exchange, a major alkalinizing<br>transporter. Three findings support that conclusion: (a)<br>selec

FT AL.<br>vent the <sub>α1</sub>-adrenoceptor-mediated alkalinization (Iwa<br>ura et al., 1990; Terzic et al., 1991; Gambassi et al., 19 ET AL.<br>vent the  $\alpha_1$ -adrenoceptor-mediated alkalinization (Iwak-<br>ura et al., 1990; Terzic et al., 1991; Gambassi et al., 1992;<br>Terzic et al., 1992a), *(b)* replacement of extracellular Na<sup>+</sup><br>with *N*-methylglucamine blo vent the  $\alpha_1$ -adrenoceptor-mediated alkalinization (Iwakura et al., 1990; Terzic et al., 1992; Gambassi et al., 1992; Terzic et al., 1992a), (b) replacement of extracellular Na<sup>+</sup> with N-methylglucamine blocks the  $\alpha_1$ vent the  $\alpha_1$ -adrenoceptor-mediated alkalinization (Iwak-<br>ura et al., 1990; Terzic et al., 1991; Gambassi et al., 1992;<br>Terzic et al., 1992a), (b) replacement of extracellular Na<sup>+</sup><br>with N-methylglucamine blocks the  $\alpha$ ura et al., 1990; Terzic et al., 1991; Gambassi et al., 1992;<br>Terzic et al., 1992a), (*b*) replacement of extracellular Na<sup>+</sup><br>with *N*-methylglucamine blocks the  $\alpha_1$ -adrenoceptor ag-<br>onist-induced alkalinization (Walle Terzic et al., 1992a), (b) replacement of extracellular Na<sup>+</sup><br>with N-methylglucamine blocks the  $\alpha_1$ -adrenoceptor ag-<br>onist-induced alkalinization (Wallert and Fröhlich,<br>1992), and (c)  $\alpha_1$ -adrenoceptor agonists enhan with *I*v-methylgideamine blocks the  $\alpha_1$ -adrenoceptor ag-<br>onist-induced alkalinization (Wallert and Fröhlich,<br>1992), and (c)  $\alpha_1$ -adrenoceptor agonists enhance pH<sub>i</sub><br>recovery from acidosis under conditions in which t 1992), and (c)  $\alpha_1$ -adrenoceptor agonists enhance pH<sub>i</sub><br>recovery from acidosis under conditions in which this<br>recovery primarily depends on Na<sup>+</sup>/H<sup>+</sup> exchange (Terzic<br>et al., 1992a; Pucéat et al., 1993a). Furthermore, recovery from acidosis under conditions in which<br>recovery primarily depends on  $Na^+/H^+$  exchange (T<br>et al., 1992a; Pucéat et al., 1993a). Furthermore, i<br>pears that  $\alpha_1$ -adrenoceptor agonists do not affec<br>intracellular b recovery primarily depends on Na<sup>+</sup>/H<sup>+</sup> exchange (Terzic et al., 1992a; Pucéat et al., 1993a). Furthermore, it appears that  $\alpha_1$ -adrenoceptor agonists do not affect the intracellular buffering capacity. A lack of  $\alpha_1$ et al., 1992a, I detail et al., 1999a). Furthermore, it appears that  $\alpha_1$ -adrenoceptor agonists do not affect the intracellular buffering capacity. A lack of  $\alpha_1$ -adrenoceptor-mediated effects on the apparent bufferin pears that  $a_1$ -adrenoteptor agonsts do not arrect the<br>intracellular buffering capacity. A lack of  $\alpha_1$ -adrenocep-<br>tor-mediated effects on the apparent buffering capacity<br>was established in both the presence and absenc 1993a). tor-mediated effects on the apparent buffering capacity<br>was established in both the presence and absence of Na<sup>+</sup>/<br>H<sup>+</sup> antiport inhibitors (Terzic et al., 1992a; Pucéat et al.,<br>1993a).<br>The results concerning pH<sub>i</sub> review

stimulation than do cells in their natural environment.<br>
B. Effects on Intracellular H<sup>+</sup>, Na<sup>+</sup>, and Ca<sup>2+</sup> and on<br>
Ionic Transport Mechanisms<br>  $\alpha_1$ -Adrenoceptor agonists produce an intracellular al-<br>
kalinization. Thi was established in both the presence and absence of N<br> $H^+$  antiport inhibitors (Terzic et al., 1992a; Pucéat et<br>1993a).<br>The results concerning pH<sub>i</sub> reviewed above were<br>tained under physiological extracellular pH.  $\alpha_1$ H<sup>+</sup> antiport inhibitors (Terzic et al., 1992a; Pucéat et al.<br>1993a).<br>The results concerning pH<sub>i</sub> reviewed above were of<br>tained under physiological extracellular pH.  $\alpha_1$ -Adrenceptor agonists also produce an alkaliniza 1993a).<br>The results concerning pH<sub>i</sub> reviewed above were obtained under physiological extracellular pH.  $\alpha_1$ -Adrenoceptor agonists also produce an alkalinization and accelerate the recovery of pH<sub>i</sub> following an imposed The results concerning pH<sub>i</sub> reviewed above were obtained under physiological extracellular pH.  $\alpha_1$ -Adrenoceptor agonists also produce an alkalinization and accelerate the recovery of pH<sub>i</sub> following an imposed acid ch tained under physiological extracellular pH.  $\alpha_1$ -Adreno-<br>ceptor agonists also produce an alkalinization and accel-<br>erate the recovery of pH<sub>i</sub> following an imposed acid<br>challenge via the stimulation of Na<sup>+</sup>/H<sup>+</sup> excha erate the recovery of pH<sub>i</sub> following an imposed acid challenge via the stimulation of  $\text{Na}^+/H^+$  exchange under extracellular acidosis (Pucéat et al., 1993a). These effects could potentially be significant under condit erate the recovery of pH<sub>i</sub> following an imposed acid<br>challenge via the stimulation of Na<sup>+</sup>/H<sup>+</sup> exchange under<br>extracellular acidosis (Pucéat et al., 1993a). These effects<br>could potentially be significant under conditio challenge via the stimulation of Na<sup>+</sup>/H<sup>+</sup> exchange unextracellular acidosis (Pucéat et al., 1993a). These effecould potentially be significant under conditions associed with extracellular acidosis, such as ischemia hypo extracellular acidosis (Pucéat et al., 1993a). These effects<br>could potentially be significant under conditions associ-<br>ated with extracellular acidosis, such as ischemia or<br>hypoxia. By stimulating the Na<sup>+</sup>/H<sup>+</sup> antiport, could potentially be significant under conditions associated with extracellular acidosis, such as ischemia or hypoxia. By stimulating the Na<sup>+</sup>/H<sup>+</sup> antiport,  $\alpha_1$ -adrenceptor agonist could modulate cardiac mechanisms t steps responsible for cardiac contraction and cell growth.<br>The model growth are sensitive to changes in pH<sub>i</sub>. This includes various<br>steps responsible for cardiac contraction and cell growth.<br>The molecular pathway by whic poxia. By stimulating the Na<sup>+</sup>/H<sup>+</sup> antiport,  $\alpha_1$ -adre-<br>ceptor agonist could modulate cardiac mechanisms<br>at are sensitive to changes in pH<sub>i</sub>. This includes various<br>ps responsible for cardiac contraction and cell grow

1990; Wallert and Fröhlich, 1992), and Purkinje fibers As in many noncardiac tissues (Frelin et al., 1988), it has (Breen and Pressler, 1988; Pressler et al., 1989; see, been suggested that PKC is responsible for the acti that are sensitive to changes in pH<sub>i</sub>. This includes various<br>steps responsible for cardiac contraction and cell growth.<br>The molecular pathway by which  $\alpha_1$ -adrenoceptor ag-<br>onists stimulate the Na<sup>+</sup>/H<sup>+</sup> antiport is s steps responsible for cardiac contraction and cell growth.<br>The molecular pathway by which  $\alpha_1$ -adrenoceptor agonists stimulate the Na<sup>+</sup>/H<sup>+</sup> antiport is still not known. steps responsible for cardiac contraction and cell growth.<br>The molecular pathway by which  $\alpha_1$ -adrenoceptor agonists stimulate the Na<sup>+</sup>/H<sup>+</sup> antiport is still not known.<br>As in many noncardiac tissues (Frelin et al., 19 The molecular pathway by which  $\alpha_1$ -adrenoceptor agonists stimulate the Na<sup>+</sup>/H<sup>+</sup> antiport is still not known.<br>As in many noncardiac tissues (Frelin et al., 1988), it has been suggested that PKC is responsible for the onists stimulate the Na<sup>+</sup>/H<sup>+</sup> antiport is still not known.<br>As in many noncardiac tissues (Frelin et al., 1988), it has<br>been suggested that PKC is responsible for the activation<br>of the exchanger because phorbol esters mi been suggested that PKC is responsible for the activation been suggested that  $F_{\text{NC}}$  is responsible for the activation<br>of the exchanger because phorbol esters mimic, whereas<br>PKC inhibitors (e.g., H7, staurosporine) block, the  $\alpha_1$ -<br>adrenoceptor agonist-mediated alkalinizati of the exchanger because phorbol esters mimic, whereas PKC inhibitors (e.g., H7, staurosporine) block, the  $\alpha_1$ -adrenoceptor agonist-mediated alkalinization in a suspension of ventricular cells or in Purkinje fibers (Sh PKC inhibitors (e.g., H7, staurosporine) block, the<br>adrenoceptor agonist-mediated alkalinization in a s<br>pension of ventricular cells or in Purkinje fibers (Shar<br>and Sheu, 1987; Breen and Pressler, 1988; Iwakura et<br>1990; Wa pension of ventricular cells or in Purkinje fibers (Sharma<br>and Sheu, 1987; Breen and Pressler, 1988; Iwakura et al.,<br>1990; Wallert and Fröhlich, 1992). Likewise, in cardiom-<br>yocytes preincubated with the phorbol ester, pho and Sheu, 1987; Breen and Pressler, 1988; Iwakura et al., 1990; Wallert and Fröhlich, 1992). Likewise, in cardiom-<br>yocytes preincubated with the phorbol ester, phorbol-12-<br>myristate-13-acetate, or with staurosporine to do nists did not produce an alkalinization (Gambassi et al., 1992). A role for  $Ca^{2+}$ -calmodulin-dependent kinase has yocytes preincubated with the phorotol ester, phoroto-12-<br>myristate-13-acetate, or with staurosporine to down-reg-<br>ulate or inhibit PKC, respectively,  $\alpha_1$ -adrenoceptor ago-<br>nists did not produce an alkalinization (Gamb myristate-13-acetate, or with statubally and the waven-reg-<br>ulate or inhibit PKC, respectively,  $\alpha_1$ -adrenoceptor ago-<br>nists did not produce an alkalinization (Gambassi et al.,<br>1992). A role for Ca<sup>2+</sup>-calmodulin-depend nists did not produce an alkalinization (Gambassi et al., 1992). A role for Ca<sup>2+</sup>-calmodulin-dependent kinase has also been proposed because W7, an inhibitor of Ca<sup>2+</sup>-calmodulin-dependent kinase, also inhibits the  $\alpha_1$ 1992). A fole for Ca --Calmodulff-dependent kinase has<br>also been proposed because W7, an inhibitor of Ca<sup>2+</sup>-<br>calmodulin-dependent kinase, also inhibits the  $\alpha_1$ -me-<br>diated alkalinization (Iwakura et al., 1990; Wallert calmodulin-dependent kinase, also inhibits the  $\alpha_1$ -me-<br>diated alkalinization (Iwakura et al., 1990; Wallert and<br>Fröhlich, 1992). However, Pucéat et al., (1993a) could<br>not confirm these results in rat single ventricular diated alkalinization (Iwakura et al., 1990; Wallert and<br>Fröhlich, 1992). However, Pucéat et al., (1993a) could<br>not confirm these results in rat single ventricular myo-<br>cytes. Indeed, in this latter study, the stimulation Fröhlich, 1992). However, Pucéat et al., (1993a) could<br>not confirm these results in rat single ventricular myo-<br>cytes. Indeed, in this latter study, the stimulation of<br>Na<sup>+</sup>/H<sup>+</sup> exchange by  $\alpha_1$ -adrenoceptor agonists w not confirm these results in rat single ventricular myocytes. Indeed, in this latter study, the stimulation of  $\text{Na}^+/\text{H}^+$  exchange by  $\alpha_1$ -adrenoceptor agonists was not affected by the presence of an intracellular cytes. Indeed, in this latter study, the stimulation of  $\text{Na}^+/\text{H}^+$  exchange by  $\alpha_1$ -adrenoceptor agonists was not affected by the presence of an intracellular  $\text{Ca}^{2+}$  chelator, suggesting that changes in intra  $Na^+/H^+$  exchange by  $\alpha_1$ -adrenoceptor agonists was not affected by the presence of an intracellular  $Ca^{2+}$  chelator, suggesting that changes in intracellular  $Ca^{2+}$  are not required for these effects. Neither stauros affected by the presence of an intracellular  $Ca^{2+}$  chelato<br>suggesting that changes in intracellular  $Ca^{2+}$  are n<br>required for these effects. Neither staurosporine no<br>GF109203X, two inhibitors of PKC, was able to prever suggesting that changes in intracellular  $Ca^{2+}$  are n<br>required for these effects. Neither staurosporine n<br>GF109203X, two inhibitors of PKC, was able to preve<br>the phenylephrine-induced alkalinization. Furthermon<br>the  $\alpha_1$ required for these effects. Neither staurosporine nor GF109203X, two inhibitors of PKC, was able to prevent the phenylephrine-induced alkalinization. Furthermore, the  $\alpha_1$ -adrenoceptor-triggered acceleration of pH<sub>i</sub> re

CARDIAC  $\alpha_1$ -ADRE<br>rosporine. Although the signal transduction pathway to<br>linking the  $\alpha_1$ -adrenoceptor to the activation of the Na<sup>+</sup>/ e CARDIAC  $\alpha_1$ -AD<br>rosporine. Although the signal transduction pathway<br>linking the  $\alpha_1$ -adrenoceptor to the activation of the Na<sup>+</sup>/<br>H<sup>+</sup> exchange still remains a question of controversy, **CARDIAC**  $\alpha_1$ -<br> **WE rosporine.** Although the signal transduction pathware linking the  $\alpha_1$ -adrenoceptor to the activation of the Na<sup>+</sup><br>  $H^+$  exchange still remains a question of controversy,<br>
evidence was obtained s rosporine. Although the signal transduction pathwa<br>linking the  $\alpha_1$ -adrenoceptor to the activation of the Na<sup>+</sup><br>H<sup>+</sup> exchange still remains a question of controversy<br>evidence was obtained suggesting that  $\alpha_1$ -adrenoce rosporine. Although the signal transduction pathwa<br>linking the  $\alpha_1$ -adrenoceptor to the activation of the Na<sup>4</sup><br>H<sup>+</sup> exchange still remains a question of controvers<br>evidence was obtained suggesting that  $\alpha_1$ -adrenocep in the Na<sup>+</sup> exchange still remains a question of controversy, sulevidence was obtained suggesting that  $\alpha_1$ -adrenoceptor 1993 agonists produce an increase both in the apparent affinity of the Na<sup>+</sup>/H<sup>+</sup> antiport for pr evidence was obtained suggesting that  $\alpha_1$ -adrenoceptor 1<br>agonists produce an increase both in the apparent affin-<br>ity of the Na<sup>+</sup>/H<sup>+</sup> antiport for protons and in its maximal o<br>ionic exchange activity (Pucéat et al., 1992). In a of the Na<sup>+</sup>/H<sup>+</sup> antiport for protons and in its maximal<br>
ince exchange activity (Pucéat et al., 1993a; also see<br>
ggadic-Gossmann et al., 1992b; Wallert and Fröhlich,<br>
92).<br>
In addition to the Na<sup>+</sup>/H<sup>+</sup> antiport, c

Sessional exchange activity (1 decat et al., 1999a, also see<br>Lagadic-Gossmann et al., 1992b; Wallert and Fröhlich<br>1992).<br>In addition to the Na<sup>+</sup>/H<sup>+</sup> antiport, cardiac cells pos<br>sess a bicarbonate-dependent alkalinizing t Lagadic-Gossmann et al., 1992b; Wallert and Fröhli<br>1992).<br>In addition to the Na<sup>+</sup>/H<sup>+</sup> antiport, cardiac cells p<br>sess a bicarbonate-dependent alkalinizing transpor<br>(Liu et al., 1990; Dart and Vaughan-Jones, 1992; Lagad<br>G 1992).<br>In addition to the Na<sup>+</sup>/H<sup>+</sup> antiport, cardiac cells possess a bicarbonate-dependent alkalinizing transporter<br>(Liu et al., 1990; Dart and Vaughan-Jones, 1992; Lagadic-<br>Gossmann et al., 1992a). Selective  $\alpha_1$ -adr in addition to the Na /H antiport, cardiac tens pos-<br>sess a bicarbonate-dependent alkalinizing transporter s<br>(Liu et al., 1990; Dart and Vaughan-Jones, 1992; Lagadic-<br>Gossmann et al., 1992a). Selective  $\alpha_1$ -adrenoceptor (Liu et al., 1990; Dart and Vaughan-Jones, 1992; Lagadic-<br>Gossmann et al., 1992a). Selective  $\alpha_1$ -adrenoceptor ago-<br>mists, such as phenylephrine, do enhance the recovery of ex-<br>pH<sub>i</sub> from acidosis under conditions in wh Gossmann et al., 1992a). Selective  $\alpha_1$ -adrenoceptor agonists, such as phenylephrine, do enhance the recovery of pH<sub>i</sub> from acidosis under conditions in which the Na<sup>+</sup>/H<sup>+</sup> antiport is blocked (Terzic et al., 1992b). T nists, such as phenylephrine, do enhance the recovery of pH<sub>i</sub> from acidosis under conditions in which the Na<sup>+</sup>/H<sup>+</sup> antiport is blocked (Terzic et al., 1992b). This effect is absent in bicarbonate-free solutions and, th pH<sub>i</sub> from acidosis under conditions in which the Na<sup>+</sup>, antiport is blocked (Terzic et al., 1992b). This effect<br>absent in bicarbonate-free solutions and, thus, suggethat  $\alpha_1$ -adrenoceptor could activate not only Na<sup>+</sup>, antiport is blocked (Terzic et al., 1992b). This effect is mob<br>absent in bicarbonate-free solutions and, thus, suggests W<br>that  $\alpha_1$ -adrenoceptor could activate not only Na<sup>+</sup>/H<sup>+</sup> cont<br>exchange but also a bicarbonate-de absent in bicarbonate-free solutions and, thus, suggests<br>that  $\alpha_1$ -adrenoceptor could activate not only  $\text{Na}^+/H^+$ <br>exchange but also a bicarbonate-dependent, amiloride-<br>insensitive, alkalinizing transport mechanism at that  $\alpha_1$ -adrenoceptor could activate not only Na<sup>+</sup>/H<sup>+</sup> constrainance but also a bicarbonate-dependent, amiloride-<br>insensitive, alkalinizing transport mechanism at least in  $\alpha_1$ -<br>rat ventricular cardiomyocytes (Terz exchange but also a bicarbonate-dependent, amiloride-<br>insensitive, alkalinizing transport mechanism at least in  $\alpha_1$ - $\alpha$ <br>rat ventricular cardiomyocytes (Terzic et al., 1992b). croi<br>However, in guinea pig cardiac cells, insensitive, alkalinizing transport mechanism at least in  $\alpha_1$ -<br>rat ventricular cardiomyocytes (Terzic et al., 1992b). cro<br>However, in guinea pig cardiac cells, epinephrine, which gro<br>stimulates both  $\alpha$ - and  $\beta$ -adre rat ventricular cardiomyocytes (Terzic et al., 1992b).<br>However, in guinea pig cardiac cells, epinephrine, which<br>stimulates both  $\alpha$ - and  $\beta$ -adrenoceptors, inhibits pH<sub>i</sub><br>recovery from acidosis in the presence of amilor stimulates both  $\alpha$ - and  $\beta$ -adrenoceptors, inhibits pH<sub>i</sub><br>recovery from acidosis in the presence of amiloride and<br>bicarbonate (Lagadic-Gossmann et al., 1992b). The rea-<br>son underlying the difference between these two s is unknown but could be due to opposing effects of  $\alpha$ -<br>is unknown but could be due to opposing effects of  $\alpha$ -<br>is unknown but could be due to opposing effects of  $\alpha$ -<br>in and  $\beta$ -adrenergic stimulation on cardiac pH<sub>i</sub> carbonate (Lagadic-Gossmann et al., 1992b). The<br>n underlying the difference between these two stu<br>unknown but could be due to opposing effects of<br> $\beta$ -adrenergic stimulation on cardiac pH<sub>i</sub> regulati<br>In addition to produc

is unknown but could be due to opposing effects of<br>and  $\beta$ -adrenergic stimulation on cardiac pH<sub>i</sub> regulation.<br>In addition to producing an intracellular alkalini<br>tion, the activation of the Na<sup>+</sup>/H<sup>+</sup> antiport by  $\alpha_1$ is unknown but could be due to opposing effects of<br>and  $\beta$ -adrenergic stimulation on cardiac pH<sub>i</sub> regulatio<br>In addition to producing an intracellular alkalini<br>tion, the activation of the Na<sup>+</sup>/H<sup>+</sup> antiport by  $\alpha_1$ -ad and  $\beta$ -adrenergic stimulation on cardiac pH<sub>i</sub> regulation. cha<br>In addition to producing an intracellular alkaliniza-<br>tion, the activation of the Na<sup>+</sup>/H<sup>+</sup> antiport by  $\alpha_1$ -adre-<br>noceptor agonists could be expected to In addition to producing an intracellular alkaliniza-<br>tion, the activation of the Na<sup>+</sup>/H<sup>+</sup> antiport by  $\alpha_1$ -adre-<br>noceptor agonists could be expected to increase intracel- (Ga<br>lular Na<sup>+</sup>. However,  $\alpha_1$ -adrenoceptor tion, the activation of the Na<sup>+</sup>/H<sup>+</sup> antiport by  $\alpha_1$ -adre-<br>noceptor agonists could be expected to increase intracel-<br>lular Na<sup>+</sup>. However,  $\alpha_1$ -adrenoceptor stimulation also<br>increases Na<sup>+</sup>/K<sup>+</sup> pump activity leadi noceptor agonists could be expected to increase intracel-<br>
lular Na<sup>+</sup>. However,  $\alpha_1$ -adrenoceptor stimulation also<br>
increases Na<sup>+</sup>/K<sup>+</sup> pump activity leading to a decrease in<br>
intracellular Na<sup>+</sup> (Zaza et al., 1990; W increases Na<sup>+</sup>/K<sup>+</sup> pump activity leading to a decrease in intracellular Na<sup>+</sup> (Zaza et al., 1990; Wilde and Kleber, 1991) and an increase in K<sup>+</sup> uptake (Ellingsen et al., 1987). Indeed, Terzic et al. (1991) observed an intracellular Na<sup>+</sup> (Zaza et al., 1990; Wilde and Kleber, Fa<br>1991) and an increase in K<sup>+</sup> uptake (Ellingsen et al., (19<br>1987). Indeed, Terzic et al. (1991) observed an increase to<br>in intracellular Na<sup>+</sup> only when the  $\alpha$ 1991) and an increase in  $K^+$  uptake (Ellingsen et al., 1987). Indeed, Terzic et al. (1991) observed an increase in intracellular  $Na^+$  only when the  $\alpha_1$ -adrenoceptors agonist was applied in the presence of ouabain, w 1987). Indeed, Terzic et al. (1991) observed an increase to 2 in intracellular Na<sup>+</sup> only when the  $\alpha_1$ -adrenoceptors phenosponist was applied in the presence of ouabain, which concomitabilities Na<sup>+</sup>/K<sup>+</sup> pumping. It c in intracellular Na<sup>+</sup> only when the  $\alpha_1$ -adrenoceptors plagonist was applied in the presence of ouabain, which continuities Na<sup>+</sup>/K<sup>+</sup> pumping. It could be hypothesized that the concomitant stimulation of Na<sup>+</sup>/K<sup>+</sup> pu inhibits  $Na^+/K^+$  pumping. It could be hypothesized that the concomitant stimulation of  $Na^+/K^+$  pumping, and in O<br>turn  $Na^+$  efflux, counterbalanced the increased influx of an<br> $Na^+$  produced by  $Na^+/H^+$  antiport activati minots iva /ix pumping. it collects be hypothesized that<br>the concomitant stimulation of  $Na^+/K^+$  pumping, and in<br>turn  $Na^+$  efflux, counterbalanced the increased influx of<br> $Na^+$  produced by  $Na^+/H^+$  antiport activation. U turn Na<sup>+</sup> efflux, counterbalanced the increased influx  $Na^+$  produced by  $Na^+/H^+$  antiport activation. Usin radiolabeled  ${}^{22}Na$ , Jahnel et al. (1991) reported an increase in unidirectional Na<sup>+</sup> influx in resting atria Na<sup>+</sup> produced by Na<sup>+</sup>/H<sup>+</sup> antiport activation. Using iold radiolabeled <sup>22</sup>Na, Jahnel et al. (1991) reported an increase in unidirectional Na<sup>+</sup> influx in resting atria stimulated with phenylephrine. This effect was at radiolabeled <sup>22</sup>Na, Jahnel et al. (1991) reported an in-<br>crease in unidirectional Na<sup>+</sup> influx in resting atria stim-<br>ulated with phenylephrine. This effect was attributed to<br>a depolarization-triggered activation of the crease in unidirectional Na<sup>+</sup> influx in resting atria stim-<br>ulated with phenylephrine. This effect was attributed to<br>a depolarization-triggered activation of the tetrodotoxin-<br>sensitive Na<sup>+</sup> window current because the a ulated with phenylephrine. This effect was attributed to<br>a depolarization-triggered activation of the tetrodotoxin-<br>sensitive Na<sup>+</sup> window current because the agonist in-<br>duces a depolarization of atrial cells. It can be a depolarization-triggered activation of the tetrodotoxinsensitive Na<sup>+</sup> window current because the agonist induces a depolarization of atrial cells. It can be argued uthat  $\alpha_1$ -adrenergic stimulation enhances both Na<sup>+</sup> sensitive Na<sup>+</sup> wind<br>duces a depolarizat<br>that  $\alpha_1$ -adrenergic s<br>and efflux mechani<br>the other direction.<br>The effects of  $\alpha_1$ ces a depolarization of atrial cells. It can be arget  $\alpha_1$ -adrenergic stimulation enhances both Na<sup>+</sup> in d efflux mechanisms with a slight net effect in on e other direction.<br>The effects of  $\alpha_1$ -adrenoceptor agonists that  $\alpha_1$ -adrenergic stimulation enhances both Na<sup>+</sup> influx<br>and efflux mechanisms with a slight net effect in one or<br>the other direction.<br>The effects of  $\alpha_1$ -adrenoceptor agonists on intracellu-<br>lar Ca<sup>2+</sup> have not be

and efflux mechanisms with a slight net effect in one or<br>the other direction.<br>The effects of  $\alpha_1$ -adrenoceptor agonists on intracellu-<br>lar Ca<sup>2+</sup> have not been elucidated unequivocally as yet.<br>Regarding diastolic Ca<sup>2+</sup> the other direction. of precise of a contracellu-<br>
The effects of  $\alpha_1$ -adrenoceptor agonists on intracellu-<br>
lar Ca<sup>2+</sup> have not been elucidated unequivocally as yet. and<br>
Regarding diastolic Ca<sup>2+</sup>, studies using Ca<sup>2+</sup> The effects of  $\alpha_1$ -adrenoceptor agonists on intracellu-<br>lar Ca<sup>2+</sup> have not been elucidated unequivocally as yet.<br>Regarding diastolic Ca<sup>2+</sup>, studies using Ca<sup>2+</sup>-sensitive a<br>fluorescent indicators (Indo-1, Fura-2) and

ENOCEPTORS<br>to coverslips, showed that  $\alpha_1$ -adrenoceptor agonists moderately increased diastolic intracellular Ca<sup>2+</sup>. These re ENOCEPTORS 155<br>to coverslips, showed that  $\alpha_1$ -adrenoceptor agonists moderately increased diastolic intracellular  $Ca^{2+}$ . These re-<br>sults were obtained in quiescent rat cells (Iwakura et al., ENOCEPTORS 155<br>to coverslips, showed that  $\alpha_1$ -adrenoceptor agonists mod-<br>erately increased diastolic intracellular Ca<sup>2+</sup>. These re-<br>sults were obtained in quiescent rat cells (Iwakura et al.,<br>1990; Eckel et al., 1991) erately increased diastolic intracellular Ca<sup>2+</sup>. These results were obtained in quiescent rat cells (Jwakura et al., 1990); Eckel et al., 1991) or electrically stimulated rat atrial cells (Jahnel et al., 1992b) and hamst erately increased diastolic intracellular  $Ca^{2+}$ . These results were obtained in quiescent rat cells (Iwakura et al., 1990; Eckel et al., 1991) or electrically stimulated rat atrial cells (Jahnel et al., 1992b) and hamst the modulation of diastolic  $Ca^{2+}$  in hamster cardiac myo-1990; Eckel et al., 1991) or electrically stimulated ra<br>atrial cells (Jahnel et al., 1992b) and hamster cardiomy<br>ocytes (Sen et al., 1990). A pertussis toxin-sensitive G<br>protein has been implicated to link  $\alpha_1$ -adrenoce atrial cells (Jahnel et al., 1992b) and hamster cardiomy-<br>ocytes (Sen et al., 1990). A pertussis toxin-sensitive G-<br>protein has been implicated to link  $\alpha_1$ -adrenoceptors to<br>the modulation of diastolic Ca<sup>2+</sup> in hamster ocytes (Sen et al., 1990). A pertussis toxin-sensitive G-<br>protein has been implicated to link  $\alpha_1$ -adrenoceptors to<br>the modulation of diastolic  $Ca^{2+}$  in hamster cardiac myo-<br>cytes (Sen et al., 1990). Jahnel et al. (19 protein has been implicated to link  $\alpha_1$ -adrenoceptors to<br>the modulation of diastolic Ca<sup>2+</sup> in hamster cardiac myo-<br>cytes (Sen et al., 1990). Jahnel et al. (1991) observed a<br>significant increase in <sup>45</sup>Ca<sup>2+</sup> uptake in the modulation of diastolic  $Ca^{2+}$  in hamster cardiac myocytes (Sen et al., 1990). Jahnel et al. (1991) observed a significant increase in <sup>45</sup>Ca<sup>2+</sup> uptake in beating atria stimulated with phenylephrine. Whereas Iwakura significant increase in  $^{45}Ca^{2+}$  uptake in beating atria<br>stimulated with phenylephrine. Whereas Iwakura et al.<br>(1990) and Jahnel et al. (1991, 1992b) postulated that<br>the increase in intracellular  $Ca^{2+}$  was due to  $Na^$ significant increase in <sup>49</sup>Ca<sup>2+</sup> uptake in beating atria<br>stimulated with phenylephrine. Whereas Iwakura et al.<br>(1990) and Jahnel et al. (1991, 1992b) postulated that<br>the increase in intracellular Ca<sup>2+</sup> was due to Na<sup>+</sup> stimulated with phenylephrine. Whereas Iwakura et al. (1990) and Jahnel et al. (1991, 1992b) postulated that the increase in intracellular Ca<sup>2+</sup> was due to Na<sup>+</sup>/Ca<sup>2+</sup> exchange following an increase in intracellular Na<sup></sup> Eckel et al. (1991) proposed that  $\alpha_1$ -adrenergic agonists<br>mobilized an intracellular Ca<sup>2+</sup> pool.<br>With regard to systolic Ca<sup>2+</sup> associated with twitch<br>contractions, Endoh and Blinks (1988) showed a small e increase in intracellular Ca<sup>2+</sup> was due to Na<sup>+</sup>/Ca<sup>2+</sup><br>change following an increase in intracellular Na<sup>+</sup>,<br>kel et al. (1991) proposed that  $\alpha_1$ -adrenergic agonists<br>obilized an intracellular Ca<sup>2+</sup> pool.<br>With regard exchange following an increase in intracellular Na<sup>+</sup>,<br>Eckel et al. (1991) proposed that  $\alpha_1$ -adrenergic agonists<br>mobilized an intracellular Ca<sup>2+</sup> pool.<br>With regard to systolic Ca<sup>2+</sup> associated with twitch<br>contraction

Eckel et al. (1991) proposed that  $\alpha_1$ -adrenergic agonists<br>mobilized an intracellular Ca<sup>2+</sup> pool.<br>With regard to systolic Ca<sup>2+</sup> associated with twitch<br>contractions, Endoh and Blinks (1988) showed a small<br>increase in C mobilized an intracellular Ca<sup>2+</sup> pool.<br>With regard to systolic Ca<sup>2+</sup> associated with twitch<br>contractions, Endoh and Blinks (1988) showed a small<br>increase in Ca<sup>2+</sup> transients following the application of<br> $\alpha_1$ -adrenoce With regard to systolic Ca<sup>2+</sup> associated with twitt contractions, Endoh and Blinks (1988) showed a smaincrease in Ca<sup>2+</sup> transients following the application  $\alpha_1$ -adrenoceptor agonists to rabbit papillary muscles m cro increase in Ca<sup>2+</sup> transients following the application of  $\alpha_1$ -adrenoceptor agonists to rabbit papillary muscles micronijected with aequorin. O'Rourke (1990) and Capogrossi et al. (1991) demonstrated that the ability o  $\alpha_1$ -autencceptor agomsts to rabbit papmary muscles incronnicated with aequorin. O'Rourke (1990) and Capogrossi et al. (1991) demonstrated that the ability of  $\alpha_1$ -adrenoceptor agonists to affect systolic Ca<sup>2+</sup> depen grossi et al. (1991) demonstrated that the ability of  $\alpha_1$ -<br>adrenoceptor agonists to affect systolic Ca<sup>2+</sup> depends on<br>the external Ca<sup>2+</sup> concentration (O'Rourke et al., 1992).<br>At low external Ca<sup>2+</sup> concentrations (0. adrenoceptor agonists to affect systolic Ca<sup>2+</sup> depends of the external Ca<sup>2+</sup> concentration (O'Rourke et al., 1992) At low external Ca<sup>2+</sup> concentrations (0.5 to 1 mM CaCl<sub>2</sub>)  $\alpha_1$ -adrenoceptor agonists appear to moder the external Ca<sup>2+</sup> concentration (O'Rourke et al., 1992).<br>At low external Ca<sup>2+</sup> concentrations (0.5 to 1 mM CaCl<sub>2</sub>),<br> $\alpha_1$ -adrenoceptor agonists appear to moderately increase<br>intracellular Ca<sup>2+</sup> transients (also see At low external Ca<sup>2+</sup> concentrations (0.5 to 1 mM CaC  $\alpha_1$ -adrenoceptor agonists appear to moderately incres intracellular Ca<sup>2+</sup> transients (also see Fedida and B chard, 1992). At 1.5 mM external CaCl<sub>2</sub>, 50% of myocy  $\alpha_1$ -adrenoceptor agonists appear to moderately increase<br>intracellular Ca<sup>2+</sup> transients (also see Fedida and Bou-<br>chard, 1992). At 1.5 mM external CaCl<sub>2</sub>, 50% of myocytes<br>show an increase in Ca<sup>2+</sup> transients followin chard, 1992). At 1.5 mM external CaCl<sub>2</sub>, 50% of myocytes<br>show an increase in Ca<sup>2+</sup> transients following  $\alpha_1$ -adre-<br>noceptor stimulation, whereas the other half do not<br>(Gambassi et al., 1992). At 2 mM external CaCl<sub>2</sub>, chard, 1992). At 1.5 mM external CaCl<sub>2</sub>, 50% of myocytes<br>show an increase in Ca<sup>2+</sup> transients following  $\alpha_1$ -adre-<br>noceptor stimulation, whereas the other half do not<br>(Gambassi et al., 1992). At 2 mM external CaCl<sub>2</sub>, show an increase in Ca<sup>2+</sup> transients following  $\alpha_1$ -adre-<br>noceptor stimulation, whereas the other half do not<br>(Gambassi et al., 1992). At 2 mM external CaCl<sub>2</sub>,  $\alpha_1$ -<br>adrenoceptor agonists no longer or inconsistently noceptor stimulation, whereas the other half do not (Gambassi et al., 1992). At 2 mM external CaCl<sub>2</sub>,  $\alpha_1$ -<br>adrenoceptor agonists no longer or inconsistently in-<br>crease intracellular Ca<sup>2+</sup> transients (O'Rourke, 1990;<br> (Gambassi et al., 1992). At 2 mM external CaCl<sub>2</sub>,  $\alpha_1$ -<br>adrenoceptor agonists no longer or inconsistently in-<br>crease intracellular Ca<sup>2+</sup> transients (O'Rourke, 1990;<br>Failli et al., 1992; cf. Jahnel et al., 1992b). Fail adrenoceptor agonists no longer or inconsistently in-<br>crease intracellular  $Ca^{2+}$  transients (O'Rourke, 1990;<br>Failli et al., 1992; cf. Jahnel et al., 1992b). Failli et al.<br>(1992) reported that, of 46 single cardiac cells crease intracellular Ca<sup>2+</sup> transients (O'Rourke, 1990;<br>Failli et al., 1992; cf. Jahnel et al., 1992b). Failli et al.<br>(1992) reported that, of 46 single cardiac cells exposed<br>to 2 mM CaCl<sub>2</sub>, only 12 myocytes (26%) respon Failli et al., 1992; cf. Jahnel et al., 1992b). Failli et al.<br>(1992) reported that, of 46 single cardiac cells exposed<br>to 2 mM CaCl<sub>2</sub>, only 12 myocytes (26%) responded to<br>phenylephrine (10 to 100  $\mu$ M). At higher extern (1992) reported that, of 46 single cardiac cells exposed<br>to 2 mM CaCl<sub>2</sub>, only 12 myocytes (26%) responded to<br>phenylephrine (10 to 100  $\mu$ M). At higher external Ca<sup>2+</sup><br>concentrations (5 mM),  $\alpha_1$ -adrenoceptor agonists to 2 mM CaCl<sub>2</sub>, only 12 myocytes (26%) responded<br>phenylephrine (10 to 100  $\mu$ M). At higher external Ca<br>concentrations (5 mM),  $\alpha_1$ -adrenoceptor agonists a<br>tually decreased Ca<sup>2+</sup> transients (Capogrossi et al., 199<br>O'R phenylephrine (10 to 100  $\mu$ M). At higher external Ca<sup>2</sup> concentrations (5 mM),  $\alpha_1$ -adrenoceptor agonists at tually decreased Ca<sup>2+</sup> transients (Capogrossi et al., 199<br>O'Rourke et al., 1992). Using spectromicrofluorom concentrations (5 mM),  $\alpha_1$ -adrenoceptor agonists actually decreased Ca<sup>2+</sup> transients (Capogrossi et al., 1991; O'Rourke et al., 1992). Using spectromicrofluorometry and adjusting the external Ca<sup>2+</sup> concentrations to tually decreased Ca<sup>2+</sup> transients (Capogrossi et al., 1991;<br>O'Rourke et al., 1992). Using spectromicrofluorometry<br>and adjusting the external Ca<sup>2+</sup> concentrations to phys-<br>iological levels (1.8 mM) for the rat, Terzic et O'Rourke et al., 1992). Using spectromicrofluce and adjusting the external Ca<sup>2+</sup> concentrations iological levels (1.8 mM) for the rat, Terzic et al. observed no change in Ca<sup>2+</sup> transients in elemotiven single cells supe *C. Metabolical levels* (1.8 mm<br> *C. Metabolic Effects*<br> *C. Metabolic Effects*<br> *C. Metabolic Effects*<br>
Epinephrine, in the served no change in  $Ca^{2+}$  transients in electrically<br>iven single cells superfused with phenylephrine.<br>Metabolic Effects<br>Epinephrine, in the presence of propranolol, can reg-<br>ate glycogen and glucose metabolism in cardia

driven single cells superfused with phenylephrine.<br>
C. Metabolic Effects<br>
Epinephrine, in the presence of propranolol, can regulate glycogen and glucose metabolism in cardiac muscle<br>
(for review, see Osnes et al., 1985). S C. Metabolic Effects<br>Epinephrine, in the presence of propranolol, can regulate glycogen and glucose metabolism in cardiac muscle<br>(for review, see Osnes et al., 1985). Stimulation of cardiac<br> $\alpha_1$ -adrenoceptors increases C. Metabolic Effects<br>
Epinephrine, in the presence of propranolol, can reg-<br>
ulate glycogen and glucose metabolism in cardiac muscle<br>
(for review, see Osnes et al., 1985). Stimulation of cardiac<br>  $\alpha_1$ -adrenoceptors incr Epinephrine, in the presence of propranolol, can regulate glycogen and glucose metabolism in cardiac muscle (for review, see Osnes et al., 1985). Stimulation of cardiac  $\alpha_1$ -adrenoceptors increases glucose uptake, the a ulate glycogen and glucose metabolism in cardiac muscle<br>(for review, see Osnes et al., 1985). Stimulation of cardiac  $\alpha_1$ -adrenoceptors increases glucose uptake, the activity<br>of phosphofructokinase (a rate-limiting glyc (for review, see Osnes et al., 1985). Stimulation of cardiac  $\alpha_1$ -adrenoceptors increases glucose uptake, the activity of phosphofructokinase (a rate-limiting glycolysis en-zyme), and lactate formation (Keely et al., 19 of phosphofructokinase (a rate-limiting glycolysis en-<br>zyme), and lactate formation (Keely et al., 1977; Clark<br>and Patten, 1984). Although stimulating glycolysis,  $\alpha_1$ -<br>adrenoceptor agonists inhibit the enzymatic activi and Patten, 1984). Although stimulating glycolysis,  $\alpha_1$ adrenoceptor agonists inhibit the enzymatic activity of

**a**spet

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phorylase *a* activity (Clark and Patten, 1984; Osnes et<br>
al., 1985). α<sub>1</sub>-Adrenoceptor agonists also modulate the 1 156 TERZIC ET<br>phorylase *a* activity (Clark and Patten, 1984; Osnes et na<br>al., 1985).  $\alpha_1$ -Adrenoceptor agonists also modulate the N,<br>pentose pathway which supplies precursors for adenine ne 156 TERZIC E<br>phorylase a activity (Clark and Patten, 1984; Osnes et ral., 1985).  $\alpha_1$ -Adrenoceptor agonists also modulate the rentose pathway which supplies precursors for adenine renucleotide synthesis. When injected f phorylase a activity (Clark and Patten, 1984; Osnes et al., 1985).  $\alpha_1$ -Adrenoceptor agonists also modulate the pentose pathway which supplies precursors for adenine nucleotide synthesis. When injected for 3 days into r phorylase *a* activity (Clark and Patten, 1984; Osnes et al., 1985).  $\alpha_1$ -Adrenoceptor agonists also modulate the pentose pathway which supplies precursors for adenine nucleotide synthesis. When injected for 3 days into al., 1985).  $\alpha_1$ -Adrenoceptor agonists also modulate the N, pentose pathway which supplies precursors for adenine nel nucleotide synthesis. When injected for 3 days into rats, rin norepinephrine and norfenefrine (in the pentose pathway which supplies precursors for adeninucleotide synthesis. When injected for 3 days into renorepinephrine and norfenefrine (in the presence of adrenoceptors antagonists) activate up to 8-fold (in dose-depende nucleotide synthesis. When injected for 3 days into rats, riference photon and norfenefrine (in the presence of  $\beta$ -<br>adrenoceptors antagonists) activate up to 8-fold (in a adose-dependent and prazosin-sensitive manner) g norepinephrine and norfenefrine (in the presence of  $\beta$ -<br>adrenoceptors antagonists) activate up to 8-fold (in a<br>dose-dependent and prazosin-sensitive manner) glucose-<br>6-phosphate dehydrogenase, the regulating enzyme of<br>t dose-dependent and prazosin-sensitive manner) glucose-6-phosphate dehydrogenase, the regulating enzyme of the pentose pathway (Zimmer et al., 1992). The increase in glucose-6-phosphate dehydrogenase is due to an en-hanceme dose-dependent and prazosin-sensitive manner) glucose-6-phosphate dehydrogenase, the regulating enzyme of the pentose pathway (Zimmer et al., 1992). The increase in glucose-6-phosphate dehydrogenase is due to an enhancemen 6-phosphate dehydrogenase, the regulating enzyme of public pentose pathway (Zimmer et al., 1992). The increase in glucose-6-phosphate dehydrogenase is due to an en-<br>in glucose-6-phosphate dehydrogenase is due to an en-<br>(1 the pentose pathway (Zimmer et al., 1992). The increase<br>in glucose-6-phosphate dehydrogenase is due to an en-<br>hancement of the enzyme's mRNA levels. Zimmer et al.<br>(1992) suggested that the stimulation of the pentose<br>pathw in glucose-6-phosphate dehydrogenase is due to an enhancement of the enzyme's mRNA levels. Zimmer et al. this (1992) suggested that the stimulation of the pentose megathway by catecholamines ( $\beta$ -adrenoceptor agonists ph hancement of the enzyme's mRNA levels. Zimmer et al. (1992) suggested that the stimulation of the pentose pathway by catecholamines ( $\beta$ -adrenoceptor agonists lalso stimulate glucose-6-phosphate dehydrogenase) could prov (1992) suggested that the stimulation of the pentose m<br>pathway by catecholamines ( $\beta$ -adrenoceptor agonists plase stimulate glucose-6-phosphate dehydrogenase) could convolve an adaptive mechanism to balance the energetic neurotransmitters. so stimulate glucose-6-phosphate dehydrogenase) covide an adaptive mechanism to balance the energ<br>penditure due to the positive inotropic effect of the<br>urotransmitters.<br>Mitochondrial functions, including oxygen consum<br>on, provide an adaptive mechanism to balance the energetic<br>expenditure due to the positive inotropic effect of these<br>neurotransmitters.<br>Mitochondrial functions, including oxygen consump-<br>tion, are affected by  $\alpha_1$ -adrenocep

expenditure due to the positive inotropic effect of these preund result of the rate of case is all the rate of Ca<sup>2+</sup> uptake et al., 1985). It was reported that the rate of Ca<sup>2+</sup> uptake the mitochondria, isolated from he meurotransmitters. solid Mitochondrial functions, including oxygen consump-<br>tion, are affected by  $\alpha_1$ -adrenoceptor stimulation (Osnes calc<br>et al., 1985). It was reported that the rate of Ca<sup>2+</sup> uptake "ph<br>by mitochondr Mitochondrial functions, including oxygen consump-<br>tion, are affected by  $\alpha_1$ -adrenoceptor stimulation (Osnes cal<br>et al., 1985). It was reported that the rate of  $Ca^{2+}$  uptake "pl<br>by mitochondria, isolated from hearts tion, are affected by  $\alpha_1$ -adrenoceptor stimulation (Osnes et al., 1985). It was reported that the rate of  $Ca^{2+}$  uptake by mitochondria, isolated from hearts perfused with an  $\alpha$ -adrenergic agonist, was significantly 1983).  $\alpha$ -adrenergic agonist, was significantly increased when<br>compared with control mitochondria (Crompton et al.,<br>1983).<br>In ATP-depleted rat cardiomyocytes, phenylephrine

 $\alpha$ -adrenergic agonist, was significantly increased whocompared with control mitochondria (Crompton et a 1983).<br>
In ATP-depleted rat cardiomyocytes, phenylephric enhances the deamination of AMP into inosine mono-<br>
phosph compared with control mitochondria (Crompton et al., 1983).<br>
In ATP-depleted rat cardiomyocytes, phenylephrine it<br>
enhances the deamination of AMP into inosine mono-<br>
phosphate (Hohl et al., 1989). This reaction is cataly 1983).<br>
In ATP-depleted rat<br>
enhances the deaminati<br>
phosphate (Hohl et al., 1<br>
by adenosine deaminase<br>  $\alpha_1$ -Adrenergic agonist In ATP-depleted rat cardiomyocytes, phenylephrine<br>hances the deamination of AMP into inosine mono-<br>osphate (Hohl et al., 1989). This reaction is catalyzed<br>adenosine deaminase.<br> $\alpha_1$ -Adrenergic agonists were also reported

enhances the deamination of AMP into inosine mono-<br>phosphate (Hohl et al., 1989). This reaction is catalyzed<br>by adenosine deaminase.<br> $\alpha_1$ -Adrenergic agonists were also reported to stimulate<br>protein synthesis in both iso phosphate (Hohl et al., 1989). This reaction is catalyzed<br>by adenosine deaminase.<br> $\alpha_1$ -Adrenergic agonists were also reported to stimulate<br>protein synthesis in both isolated myocytes and perfused<br>hearts (Fuller et al., by adenosine deaminase.<br>  $\alpha_1$ -Adrenergic agonists were also reported to stim<br>
protein synthesis in both isolated myocytes and peri<br>
hearts (Fuller et al., 1990). This effect appears to de<br>
on intracellular alkalinizatio  $\alpha_1$ -Adrenergic agonists were also reported to stimular protein synthesis in both isolated myocytes and perfuse hearts (Fuller et al., 1990). This effect appears to depen on intracellular alkalinization induced by  $\alpha_1$ protein synthesis in both isolated myocytes and perfused<br>hearts (Fuller et al., 1990). This effect appears to depend<br>on intracellular alkalinization induced by  $\alpha_1$ -adrenocep-<br>tor agonists and is associated with an incr hearts (Fuller et al., 1990). This effect appears to depe<br>on intracellular alkalinization induced by  $\alpha_1$ -adrenoc<br>tor agonists and is associated with an increase in int<br>cellular phosphocreatine concentration (Fuller et<br> on intracellular alkalinization induced by  $\alpha_1$ -adrenoceptor agonists and is associated with an increase in intracellular phosphocreatine concentration (Fuller et al., properties). It was suggested that the effects of t tor agonists and is associated with an increase in intractional cellular phosphocreatine concentration (Fuller et al., produced 1991). It was suggested that the effects of the  $\alpha_1$ -adre-<br>noceptor agonist in adult cardia cellular phosphocreatine concentration (Fuller et al.,  $1991$ ). It was suggested that the effects of the  $\alpha_1$ -adre-<br>noceptor agonist in adult cardiac tissue is exerted at the<br>level of translation because it was not prev 1991). It was suggested that the effects of the  $\alpha_1$ -adre-<br>noceptor agonist in adult cardiac tissue is exerted at the<br>level of translation because it was not prevented by<br>actinomycin D (Fuller et al., 1990). Thus, it ca noceptor agonist in adult cardiac tissue is exerted at the level of translation because it was not prevented by actinomycin D (Fuller et al., 1990). Thus, it can be postulated that these effects on protein synthesis can b level of translation because it was not prevented by<br>actinomycin D (Fuller et al., 1990). Thus, it can be<br>postulated that these effects on protein synthesis can be<br>dissociated from the effects of  $\alpha_1$ -adrenergic stimula actinomycin D (Fuller et al., 1990). Thus, it can<br>postulated that these effects on protein synthesis can<br>dissociated from the effects of  $\alpha_1$ -adrenergic stimulati<br>on cell growth and hypertrophy in neonatal cells whi<br>occ dissociated from the effects of  $\alpha_1$ -adrenergic stimulation<br>on cell growth and hypertrophy in neonatal cells which<br>occur at the level of transcription (see section V.D).<br>Mammalian atrial myocytes synthesize and secrete

on cell growth and hypertrophy in neonatal cells which<br>occur at the level of transcription (see section V.D).<br>Mammalian atrial myocytes synthesize and secrete a<br>potent natriuretic and vasoactive polypeptide hormone,<br>terme Mammalian atrial myocytes synthesize and secrete a other<br>potent natriuretic and vasoactive polypeptide hormone, of<br>termed ANP (Currie et al., 1983). Stimulation of  $\alpha_1$  pig<br>adrenoceptors enhances ANP secretion in adult termed ANP (Currie et al., 1983). Stimulation of  $\alpha_1$ - pig atria (Benfey and Varma, 1967; Govier, 1967).<br>adrenoceptors enhances ANP secretion in adult hearts<br>(Currie and Newman, 1986; Matsubara et al., 1987; Wong a posi termed ANP (Currie et al., 1983). Stimulation of a<br>adrenoceptors enhances ANP secretion in adult hear<br>(Currie and Newman, 1986; Matsubara et al., 1987; Wor<br>et al., 1988; Christensen et al., 1991). Using an in viv<br>model, La adrenoceptors enhances ANP secretion in adult hea<br>(Currie and Newman, 1986; Matsubara et al., 1987; We<br>et al., 1988; Christensen et al., 1991). Using an in v<br>model, Lachance and Garcia (1991) also observed a phe<br>ylephrine-(Currie and Newman, 1986; Matsubara et al., 1987; Won<br>et al., 1988; Christensen et al., 1991). Using an in viv<br>model, Lachance and Garcia (1991) also observed a phen<br>ylephrine-induced increase in circulating ANP concentrat et al., 1988; Christensen et al., 1991). Using an in vivo model, Lachance and Garcia (1991) also observed a phen-<br>ylephrine-induced increase in circulating ANP concentration. Furthermore, these authors showed that adre-<br>ne model, Lachance and Garcia (1991) also observed a phen-<br>ylephrine-induced increase in circulating ANP concen-<br>tration. Furthermore, these authors showed that adre-<br>nergic stimulation potentiates the ANP secretion trig-<br>19 ylephrine-induced increase in circulating ANP concertation. Furthermore, these authors showed that adentication potentiates the ANP secretion to gered by an increase in atrial wall tension. Sei a Glembotski (1990) reporte tration. Furthermore, these authors showed that adre-<br>nergic stimulation potentiates the ANP secretion trig-<br>gered by an increase in atrial wall tension. Sei and<br>Glembotski (1990) reported that  $\alpha_1$ -adrenergic stimula-<br> mergic stimulation potentiates the ANP secretion trig-<br>gered by an increase in atrial wall tension. Sei and Gam<br>Glembotski (1990) reported that  $\alpha_1$ -adrenergic stimula-<br>1985<br>tion also triggered ANP secretion from atrial

ET AL.<br>nM with ethyleneglycol bis( $\beta$ -aminoethyl ether)-<br>N,N,N',N'-tetraacetic acid or the blockade of Ca<sup>2+</sup> chan-FT AL.<br>
nM with ethyleneglycol bis( $\beta$ -aminoethyl ether<br>
N,N,N',N'-tetraacetic acid or the blockade of Ca<sup>2+</sup> chan-<br>
nels with nifedipine diminished by half the phenylep ET AL.<br>
nM with ethyleneglycol bis( $\beta$ -aminoethyl ether)-<br>
N,N,N',N'-tetraacetic acid or the blockade of Ca<sup>2+</sup> chan-<br>
nels with nifedipine diminished by half the phenyleph-<br>
rine-induced ANP secretion. Schiebinger et al nM with ethyleneglycol bis( $\beta$ -aminoethyl ether)<br>N,N,N',N'-tetraacetic acid or the blockade of Ca<sup>2+</sup> chan<br>nels with nifedipine diminished by half the phenyleph<br>rine-induced ANP secretion. Schiebinger et al. (1992<br>descri nels with nifedipine diminished by half the phenylephrine-induced ANP secretion. Schiebinger et al. (1992) described a Ca<sup>2+</sup> influx as mandatory for  $\alpha_1$ -adrenoceptor agonists to release ANP from rat isolated atria.<br>Li ls with nifedipine diminished by half the phenyleph-<br>ne-induced ANP secretion. Schiebinger et al. (1992)<br>scribed a Ca<sup>2+</sup> influx as mandatory for  $\alpha_1$ -adrenoceptor<br>onists to release ANP from rat isolated atria.<br>Lindeman

rine-induced ANP secretion. Schiebinger et al. (1992)<br>described a Ca<sup>2+</sup> influx as mandatory for  $\alpha_1$ -adrenoceptor<br>agonists to release ANP from rat isolated atria.<br>Lindemann (1986) showed that a sarcolemmal 15-kDa<br>prote described a Ca<sup>2+</sup> influx as mandatory for  $\alpha_1$ -adrenoceptor agonists to release ANP from rat isolated atria.<br>Lindemann (1986) showed that a sarcolemmal 15-kDa protein was phosphorylated following the stimulation of rat differentiative of the Hartmann (1986) showed that a sarcolemmal 15-kDa<br>protein was phosphorylated following the stimulation of<br>rat ventricles with  $\alpha_1$ -adrenoceptor agonists. Meij et al.<br>(1991) and Hartmann and Schrade Eindemann (1960) showed that a sarcolemmal 15-KD<br>protein was phosphorylated following the stimulation<br>rat ventricles with  $\alpha_1$ -adrenoceptor agonists. Meij et a<br>(1991) and Hartmann and Schrader (1992) reported the<br>this p protein was phosphorylated following the stimulation of<br>rat ventricles with  $\alpha_1$ -adrenoceptor agonists. Meij et al.<br>(1991) and Hartmann and Schrader (1992) reported that<br>this protein was also phosphorylated following th rat ventricles with  $\alpha_1$ -adrenoceptor agonists. Meij et al. (1991) and Hartmann and Schrader (1992) reported that this protein was also phosphorylated following the treatment of cultured neonatal and adult cardiomyocyte (1991) and Hartmann and Schrader (1992) reported this protein was also phosphorylated following the treement of cultured neonatal and adult cardiomyocytes we phorbol esters. It was proposed that this phosphorylatic could this protein was also phosphorylated following the treat-<br>ment of cultured neonatal and adult cardiomyocytes with<br>phorbol esters. It was proposed that this phosphorylation<br>could play a role in the down-regulation of the r phorbol esters. It was proposed that this phosphorylation<br>cold play a role in the down-regulation of the respon-<br>siveness of cardiac tissue to  $\alpha_1$ -adrenergic stimulation. A<br>protein with an apparent molecular mass of 15 siveness of cardiac tissue to  $\alpha_1$ -adrenergic stimulation. A could play a role in the down-regulation of the responsiveness of cardiac tissue to  $\alpha_1$ -adrenergic stimulation. A protein with an apparent molecular mass of 15 kDa in sodium dodecyl sulfate-polyacrylamide gel electroph siveness of cardiac tissue to  $\alpha_1$ -adrenergic stimulation. A<br>protein with an apparent molecular mass of 15 kDa in<br>sodium dodecyl sulfate-polyacrylamide gel electrophore-<br>sis has been purified, cloned, and sequenced. It protein with an apparent molecular mass of 15 kDa in<br>sodium dodecyl sulfate-polyacrylamide gel electrophore-<br>sis has been purified, cloned, and sequenced. It has a<br>calculated molecular mass of 8.4 kDa and was named<br>"phosph sodium dodecyl sulfate-polyacrylamide gel electrophore-<br>sis has been purified, cloned, and sequenced. It has a<br>calculated molecular mass of 8.4 kDa and was named<br>"phospholemman" (Palmer et al., 1991). It was speculated<br>tha sis has been purified, cloned, and sequenced. It has a calculated molecular mass of 8.4 kDa and was named "phospholemman" (Palmer et al., 1991). It was speculated that its phosphorylation could modulate the activity of col calculated molecular mass of 8.4 kDa and was named<br>"phospholemman" (Palmer et al., 1991). It was speculated<br>that its phosphorylation could modulate the activity of<br>colocalized channels, pumps, and/or antiporters by al-<br>ter "phospholemman" (Palmer et al., 1991). It was speculated<br>that its phosphorylation could modulate the activity of<br>colocalized channels, pumps, and/or antiporters by al-<br>tering sarcolemmal surface charges or, as recent data that its phosphorylation could modulate the activity of<br>colocalized channels, pumps, and/or antiporters by al-<br>tering sarcolemmal surface charges or, as recent data<br>indicate, that this protein could be a chloride channel b tering sarcolemmal surface charges or, as recent data indicate, that this protein could be a chloride channel by itself (Moorman et al., 1992). In contrast to the studies performed in rat ventricles or isolated cells, Edes kDa protein following  $\alpha_1$ -adrenergic or phorbol ester indicate, that this protein could be a chloride channel by<br>itself (Moorman et al., 1992). In contrast to the studies<br>performed in rat ventricles or isolated cells, Edes et al.<br>(1991) failed to observe any phosphorylation itself (Moorman et al., 1992). In contrast to the studie<br>performed in rat ventricles or isolated cells, Edes et a<br>(1991) failed to observe any phosphorylation of the 18<br>kDa protein following  $\alpha_1$ -adrenergic or phorbol e performed in rat ventrictes of isolated cens, Edes et al.<br>(1991) failed to observe any phosphorylation of the 15-<br>kDa protein following  $\alpha_1$ -adrenergic or phorbol ester<br>treatment of beating guinea pig hearts. This was p ADA protein following  $\alpha_1$ -adrenergic or phorbot es<br>treatment of beating guinea pig hearts. This was pro<br>ably related to the animal species they used becau<br>Talosi and Kranias (1992) showed a phosphorylation<br>this sarcole treatment of beating guinea pig hearts. This was probably related to the animal species they used because Talosi and Kranias (1992) showed a phosphorylation of this sarcolemmal protein following  $\alpha_1$ -adrenergic stimulat ably related to the animal species they used because<br>Talosi and Kranias (1992) showed a phosphorylation of<br>this sarcolemmal protein following  $\alpha_1$ -adrenergic stimu-<br>lation of rabbit hearts. In addition, a cytosolic 28-k Talosi and Kranias (1992)<br>this sarcolemmal protein<br>lation of rabbit hearts. I<br>protein was also found t<br>exposure to phenylephrir **In the Solution Algeben Control** in was also found to be phosphorylated<br>
in was also found to be phosphorylated<br>
ure to phenylephrine.<br> **V. Physiological and Pathophysiological and Pathophysiological and Pathophysiologic** otein was also found to be phosphorylated following<br>posure to phenylephrine.<br>V. Physiological and Pathophysiological<br>Consequences of  $\alpha_1$ -Adrenoceptor Stimulation<br> $\alpha_1$ -Adrenoceptors and Inotropy

## *A. a<sub>1</sub>-Adrenoceptors and Inotropy*<br>*A.*  $\alpha_1$ *-Adrenoceptors and Inotropy*<br>*A.*  $\alpha_1$ *-Adrenoceptors and Inotropy*<br>In 1966. Wenzel and Su were the V. Physiological and Pathophysiological<br>Consequences of  $\alpha_1$ -Adrenoceptor Stimulation<br> $\alpha_1$ -Adrenoceptors and Inotropy<br>In 1966, Wenzel and Su were the first to report a

postulated that these effects on protein synthesis can be<br>  $A. \alpha_1$ -Adrenoceptors and Inotropy<br>
dissociated from the effects of  $\alpha_1$ -adrenergic stimulation<br>
on cell growth and hypertrophy in neonatal cells which<br>
occur **Consequences of**  $\alpha_1$ **-Adrenoceptor Stimulation**<br>A.  $\alpha_1$ -Adrenoceptors and Inotropy<br>In 1966, Wenzel and Su were the first to report a<br>positive inotropic effect of an  $\alpha_1$ -adrenoceptor agonist,<br>phenylephrine, in rat v A.  $\alpha_1$ -Adrenoceptors and Inotropy<br>In 1966, Wenzel and Su were the first to report apositive inotropic effect of an  $\alpha_1$ -adrenoceptor agonist<br>phenylephrine, in rat ventricular strips. Soon thereafter<br>other investigato A.  $\alpha_1$ -Adrenbeeptors and Thotropy<br>In 1966, Wenzel and Su were the first to report a<br>positive inotropic effect of an  $\alpha_1$ -adrenoceptor agonist,<br>phenylephrine, in rat ventricular strips. Soon thereafter,<br>other investig In 1966, Wenzel and Su were the first to report a<br>positive inotropic effect of an  $\alpha_1$ -adrenoceptor agonist,<br>phenylephrine, in rat ventricular strips. Soon thereafter,<br>other investigators observed the positive inotropic positive inotropic effect of an  $\alpha_1$ -adrenoceptor ago<br>phenylephrine, in rat ventricular strips. Soon theree<br>other investigators observed the positive inotropic e<br>of various  $\alpha_1$ -adrenoceptor agonists in rabbit and gu<br> enylephrine, in rat ventricular strips. Soon thereafter,<br>her investigators observed the positive inotropic effect<br>various  $\alpha_1$ -adrenoceptor agonists in rabbit and guinea<br>g atria (Benfey and Varma, 1967; Govier, 1967).<br>S

a positive inotropic effect in different cardiac preparations (whole hearts, papillary muscles, ventricular strips, pig atria (Benfey and Varma, 1967; Govier, 1967).<br>Stimulation of myocardial  $\alpha_1$ -adrenoceptors produces<br>a positive inotropic effect in different cardiac prepara-<br>tions (whole hearts, papillary muscles, ventricular strip Stimulation of myocardial  $\alpha_1$ -adrenoceptors produces<br>a positive inotropic effect in different cardiac prepara-<br>tions (whole hearts, papillary muscles, ventricular strips,<br>atria, isolated cardiomyocytes) from several sp a positive inotropic effect in different cardiac prepara-<br>tions (whole hearts, papillary muscles, ventricular strips,<br>atria, isolated cardiomyocytes) from several species (rat,<br>rabbit, guinea pig, cat, lamb, cow, dog, monk tions (whole hearts, papillary muscles, ventricular strips,<br>atria, isolated cardiomyocytes) from several species (rat,<br>rabbit, guinea pig, cat, lamb, cow, dog, monkey) (Wagner<br>and Brodde, 1978; Shibata et al., 1980; Skomed atria, isolated cardiomyocytes) from several species (rat, rabbit, guinea pig, cat, lamb, cow, dog, monkey) (Wagner and Brodde, 1978; Shibata et al., 1980; Skomedal et al., 1983; Terzic and Vogel, 1990; Fedida and Bouchard rabbit, guinea pig, cat, lamb, cow, dog, monkey) (Wagner<br>and Brodde, 1978; Shibata et al., 1980; Skomedal et al.,<br>1983; Terzic and Vogel, 1990; Fedida and Bouchard, 1992;<br>Gambassi et al., 1992; for review, see Brückner et and Brodde, 1978; Shibata et al., 1980; Skomedal et al., 1983; Terzic and Vogel, 1990; Fedida and Bouchard, 1992; Gambassi et al., 1992; for review, see Brückner et al., 1985; Osnes et al., 1985; Endoh, 1986, 1991; Scholz 1983; Terzic and Vogel, 1990; Fedida and Bouchard, 1992;<br>Gambassi et al., 1992; for review, see Brückner et al.,<br>1985; Osnes et al., 1985; Endoh, 1986, 1991; Scholz et al.,<br>1986; Benfey, 1987; Nawrath, 1989; Pucéat et al.,

CARDIAC  $\alpha_1$ -AL<br>contribution of the  $\alpha_1$ -adrenoceptor to the inotropic re-<br>sponse of heart muscle to endogenous catecholamines in CARDIAC  $\alpha_1$ -ADRENC<br>contribution of the  $\alpha_1$ -adrenoceptor to the inotropic re-cours<br>sponse of heart muscle to endogenous catecholamines in 1964<br>the presence of unopposed  $\beta$ -adrenoceptors stimulation. al., CARDIAC  $\alpha_1$ -contribution of the  $\alpha_1$ -adrenoceptor to the inotropic response of heart muscle to endogenous catecholamines is<br>the presence of unopposed  $\beta$ -adrenoceptors stimulation.<br>These investigators estimated that contribution of the  $\alpha_1$ -adrenoceptor to the inotropic response of heart muscle to endogenous catecholamines in 19<br>the presence of unopposed  $\beta$ -adrenoceptors stimulation. al.<br>These investigators estimated that about 7 contribution of the  $\alpha_1$ -adrenoceptor to the inotropic sponse of heart muscle to endogenous catecholamines<br>the presence of unopposed  $\beta$ -adrenoceptors stimulation<br>These investigators estimated that about 75% of the<br>res sponse of heart muscle to endogenous catecholamines in<br>the presence of unopposed  $\beta$ -adrenoceptors stimulation.<br>These investigators estimated that about 75% of the<br>response to norepinephrine is mediated through  $\beta$ -adre These investigators estimated that about 75% of the<br>response to norepinephrine is mediated through  $\beta$ -adre-<br>noceptors and 25% via  $\alpha_1$ -adrenoceptor in rat cardiac<br>tissue. Concomitant muscarinic receptor stimulation in These investigators estimated that about 75% of the<br>response to norepinephrine is mediated through  $\beta$ -adre-<br>noceptors and 25% via  $\alpha_1$ -adrenoceptor in rat cardiac<br>tissue. Concomitant muscarinic receptor stimulation in response to norepinephrine is mediated through  $\beta$ -adre-noceptors and 25% via  $\alpha_1$ -adrenoceptor in rat cardiac tissue. Concomitant muscarinic receptor stimulation increases the  $\alpha_1$ -adrenoceptor component of the over 1987). sue. Concomitant muscarinic receptor stimulation in-<br>eases the  $\alpha_1$ -adrenoceptor component of the overall cotropic effect of norepinephrine (Christiansen et al., du<br>87).<br>As expected, selective  $\alpha_2$ -adrenoceptor agonis creases the  $\alpha_1$ -adrenoceptor component of the overall<br>inotropic effect of norepinephrine (Christiansen et al.,<br>1987). As expected, selective  $\alpha_2$ -adrenoceptor agonists cause<br>no positive inotropic effect (Williamson a

1987).<br>
As expected, selective  $\alpha_2$ -adrenoceptor agonists cau<br>
no positive inotropic effect (Williamson and Broadle<br>
1987; Housmans, 1990). The selective  $\alpha_1$ -adrenocept<br>
blocker, prazosin, in nanomolar concentrations As expected, selective  $\alpha_2$ -adrenoceptor agonists can o positive inotropic effect (Williamson and Broadl 1987; Housmans, 1990). The selective  $\alpha_1$ -adrenocep blocker, prazosin, in nanomolar concentrations, compitively 1987; Housmans, 1990). The selective  $\alpha_1$ -adrenoceptor persists for a long period (>20 min). A proportion (30%) blocker, prazosin, in nanomolar concentrations, compet-<br>itively inhibited the positive inotropic action of blocker, prazosin, in nanomolar concentrations, compet-<br>itively inhibited the positive inotropic action of phenyl-<br>ephrine (Skomedal et al., 1980). The nature of the  $\alpha_1$ -<br>adrenoceptor subtype(s) responsible for the pos blocker, prazosin, in nanomolar concentrations, compet-<br>itively inhibited the positive inotropic action of phenyl-<br>rangphrine (Skomedal et al., 1980). The nature of the  $\alpha_1$ -<br>adrenoceptor subtype(s) responsible for the itively inhibited the positive inotropic action of phenephrine (Skomedal et al., 1980). The nature of the *a*drenoceptor subtype(s) responsible for the positive inotropic effect is a matter of current investigation.<br>rabbi ephrine (Skomedal et al., 1980). The nature of the  $\alpha_1$ -<br>adrenoceptor subtype(s) responsible for the positive in-<br>otropic effect is a matter of current investigation. In<br>rabbit papillary muscle, the  $\alpha_1$ -adrenoceptoradrenoceptor-subtype(s) responsible for the positiotropic effect is a matter of current investigation-<br>rabbit papillary muscle, the  $\alpha_1$ -adrenoceptor-mechositive inotropic action is inhibited by the selective adrenocept otropic effect is a matter of current investigation. In was<br>rabbit papillary muscle, the  $\alpha_1$ -adrenoceptor-mediated On<br>positive inotropic action is inhibited by the selective  $\alpha_{1B}$ - ino<br>adrenoceptor-alkylating agent rabbit papillary muscle, the  $\alpha_1$ -adrenoceptor-mediated<br>positive inotropic action is inhibited by the selective  $\alpha_{1B}$ -<br>adrenoceptor-alkylating agent CEC in a concentration-<br>dependent manner (IC<sub>50</sub> = 2.4  $\mu$ M) and a positive inotropic action is inhibited by the selective  $\alpha_{11}$ <br>adrenoceptor-alkylating agent CEC in a concentration<br>dependent manner (IC<sub>50</sub> = 2.4  $\mu$ M) and abolished by 1<br> $\mu$ M CEC (Takanashi et al., 1991). Endoh et a adrenoceptor-alkylating agent CEC in a concentrat<br>dependent manner (IC<sub>50</sub> = 2.4  $\mu$ M) and abolished b<br> $\mu$ M CEC (Takanashi et al., 1991). Endoh et al. (1<br>recently reported that WB-4101, the  $\alpha_{1A}$ -subtype se<br>tive anta dependent manner (IC<sub>50</sub> = 2.4  $\mu$ M) and abolished by 10  $\mu$ M CEC (Takanashi et al., 1991). Endoh et al. (1992) recently reported that WB-4101, the  $\alpha_{1A}$ -subtype selective antagonist, shifted to a small extent the co  $\mu$ M CEC (Takanashi et al., 1991). Endoh et al. (1992)<br>recently reported that WB-4101, the  $\alpha_{1A}$ -subtype selec-<br>tive antagonist, shifted to a small extent the concentra-<br>tion-response curve of the positive inotropic e recently reported that WB-4101, the  $\alpha_{1A}$ -subtype selective antagonist, shifted to a small extent the concentra-<br>tion-response curve of the positive inotropic effect in-<br>duced by phenylephrine and suggested that the  $\$ tive antagonist, shifted to a small extent the concentra-<br>tion-response curve of the positive inotropic effect in-<br>duced by phenylephrine and suggested that the  $\alpha_{1A}$ - pa<br>subtype may also mediate the inotropic effect o tion-response curve of the positive inotropic effect in-<br>duced by phenylephrine and suggested that the  $\alpha_{1A}$ -<br>subtype may also mediate the inotropic effect of  $\alpha_1$ -<br>agonists, although to a much smaller extent than th duced by phenylephrine and suggested that the  $\alpha_{1A}$ - pap<br>subtype may also mediate the inotropic effect of  $\alpha_{1}$ - tim-<br>agonists, although to a much smaller extent than the que<br> $\alpha_{1B}$ -receptor. Michel et al. (1990) a subtype may also mediate the inotropic effect of  $\alpha_1$ -<br>agonists, although to a much smaller extent than the qu<br> $\alpha_{1B}$ -receptor. Michel et al. (1990) also implicated the  $\alpha_{1B}$ -<br>receptor subtype in mediating the inot  $\alpha_{1B}$ -receptor. Michel et al. (1990) also implicated the  $\alpha_{1B}$ -<br>receptor subtype in mediating the inotropic action. In<br>receptor subtype in mediating the inotropic action. In<br>contrast, preliminary recent reports sugg  $\alpha_{1B}$ -receptor. Michel et al. (1990) also implicated the  $\alpha_{1B}$ -<br>receptor subtype in mediating the inotropic action. In<br>contrast, preliminary recent reports suggest that the<br>stimulation of the  $\alpha_{1A}$ -subtype, at le receptor subtype in mediating the inotropic action. In Als<br>contrast, preliminary recent reports suggest that the eni<br>stimulation of the  $\alpha_{1A}$ -subtype, at least in rat tissue, is<br>responsible for the  $\alpha_1$ -adrenoceptorcontrast, preliminary recent reports suggest that the stimulation of the  $\alpha_{1A}$ -subtype, at least in rat tissue, is responsible for the  $\alpha_1$ -adrenoceptor-mediated positive inotropic effects in both papillary muscle (R stimulation of the  $\alpha_{1A}$ -subtype, at least in rat ti<br>responsible for the  $\alpha_1$ -adrenoceptor-mediated j<br>inotropic effects in both papillary muscle (Roko<br>Sulakhe, 1991) and isolated cells (Gambassi et al.<br>SZL-49 and WBresponsible for the  $\alpha_1$ -adrenoceptor-mediated positive a<br>inotropic effects in both papillary muscle (Rokosh and si<br>Sulakhe, 1991) and isolated cells (Gambassi et al., 1991).<br>SZL-49 and WB-4101 ihibited the norepinephri effect. nlakhe, 1991) and isolated cells (Gambassi et al., 1991)<br>ZL-49 and WB-4101 ihibited the norepinephrine-in-<br>ced increase in inotropy; CEC failed to prevent this<br>fect.<br>The positive inotropic effect resulting from the acti-<br> SZL-49 and WB-4101 ihibited the norepinephrine-in-<br>duced increase in inotropy; CEC failed to prevent this CP<br>effect. 19<br>The positive inotropic effect resulting from the acti-<br>vation of  $\alpha_1$ -adrenoceptors varies in magni

duced increase in inotropy; CEC failed to prevent this Cleffect.<br>
The positive inotropic effect resulting from the acti-<br>
in vation of  $\alpha_1$ -adrenoceptors varies in magnitude from one to<br>
species to another. Larger incre effect. 1988<br>The positive inotropic effect resulting from the activation of  $\alpha_1$ -adrenoceptors varies in magnitude from one to compete to another. Larger increases in developed force Sare found in the rat and rabbit tha The positive inotropic effect resulting from the acception of  $\alpha_1$ -adrenoceptors varies in magnitude from o species to another. Larger increases in developed for are found in the rat and rabbit than in the guinea  $\mu$  a vation of  $\alpha_1$ -adrenoceptors varies in magnitude from one to species to another. Larger increases in developed force are found in the rat and rabbit than in the guinea pig te and dog myocardium (Scholz et al., 1986). Th species to another. Larger increases in developed force<br>are found in the rat and rabbit than in the guinea pig<br>and dog myocardium (Scholz et al., 1986). The differ-<br>ences among species could be related to the density of<br>and dog myocardium (Scholz et al., 1986). The differences among species could be related to the density of  $\alpha_1$ -adrenceptors (Mukherjee et al., 1983; Endoh et al., 1991). Nakanishi et al. (1989) compared the positive in and dog myocardium (Scholz et al., 1960). The differences among species could be related to the density of  $\alpha_1$ -adrenoceptors (Mukherjee et al., 1983; Endoh et al., 1991). Nakanishi et al. (1989) compared the positive i ences among species could be related to the density of  $\alpha_1$ -adrenoceptors (Mukherjee et al., 1983; Endoh et al., 1991). Nakanishi et al. (1989) compared the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists in n  $\alpha_1$ -adrenoceptors (Mukherjee et al., 1983; Endoh et al. 1991). Nakanishi et al. (1989) compared the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists in newbor and adult rats, rabbits, and dogs. For a given ago 1991). Nakanishi et al. (1989) compared the positive trop inotropic effect of  $\alpha_1$ -adrenoceptor agonists in newborn stim and adult rats, rabbits, and dogs. For a given agonist stim concentration, the effect was greater inotropic effect of  $\alpha_1$ -adrenoceptor agonists in newborn st<br>and adult rats, rabbits, and dogs. For a given agonist st<br>concentration, the effect was greater in the adult. How-<br>sever, beyond middle age, an aging-associat concentration, the effect was greater in the adult. How-<br>ever, beyond middle age, an aging-associated decline in<br>the maximum positive inotropic effect of  $\alpha_1$ -agonists was<br>reported (Kimball et al., 1991).<br>1. Characteris

**Ever, beyond middle age, an aging-associated decime in** between the maximum positive inotropic effect of  $\alpha_1$ -agonists was time reported (Kimball et al., 1991).<br> *1. Characteristics of the*  $\alpha_1$ -adrenergic positive i

CARDIAC  $\alpha_1$ -ADRENOCEPTORS 157<br>
i inotropic re-course including a negative inotropic component (Govier, cholamines in 1968; Skomedal et al., 1983; Osnes et al., 1985; Tohse et al., 1987a; Otani et al., 1988; Ertl et al., 1991). For ENOCEPTORS 157<br>course including a negative inotropic component (Govier,<br>1968; Skomedal et al., 1983; Osnes et al., 1985; Tohse et<br>al., 1987a; Otani et al., 1988; Ertl et al., 1991). For<br>example, stimulation of  $\alpha_1$ -adre course including a negative inotropic component (Govier, 1968; Skomedal et al., 1983; Osnes et al., 1985; Tohse et al., 1987a; Otani et al., 1988; Ertl et al., 1991). For example, stimulation of  $\alpha_1$ -adrenoceptors in ra course including a negative inotropic component (Govier, 1968; Skomedal et al., 1983; Osnes et al., 1985; Tohse et al., 1987a; Otani et al., 1988; Ertl et al., 1991). For example, stimulation of  $\alpha_1$ -adrenoceptors in ra 1987a; Otani et al., 1988; Ertl et al., 1991). For<br>al., 1987a; Otani et al., 1988; Ertl et al., 1991). For<br>example, stimulation of  $\alpha_1$ -adrenoceptors in rat papillary<br>muscles results in a triphasic inotropic response. A example, stimulation of  $\alpha_1$ -adrenoceptors in rat papillary<br>muscles results in a triphasic inotropic response. An<br>initial increase in contractile force (phase 1) appears<br>immediately, reaching a maximum level within 30 s muscles results in a triphasic inotropic response. An initial increase in contractile force (phase 1) appears immediately, reaching a maximum level within 30 s. The contractile force then declines below the baseline, produ initial increase in contractile force (phase 1) appears<br>immediately, reaching a maximum level within 30 s. The<br>contractile force then declines below the baseline, pro-<br>ducing a negative inotropic phase (phase 2) that reach immediately, reaching a maximum level within 30 s. The<br>contractile force then declines below the baseline, pro-<br>ducing a negative inotropic phase (phase 2) that reaches<br>a maximum level at 80 to 90 s. The second increase in contractile force then declines below the baseline, pro-<br>ducing a negative inotropic phase (phase 2) that reaches<br>a maximum level at 80 to 90 s. The second increase in<br>contractile force (phase 3) is more pronounced than t a maximum level at 80 to 90 s. The second increase in contractile force (phase 3) is more pronounced than that of phase 1. It reaches a maximum level at 5 to 6 min and persists for a long period (>20 min). A proportion (3 contractile force (phase 3) is inferentiated that<br>of phase 1. It reaches a maximum level at 5 to 6 mi<br>persists for a long period (>20 min). A proportion<br>of frog atrial trabeculae responds to  $\alpha$ -stimulation<br>transient res phase 1. It reaches a maximum level at 5 to 6 min and<br>rsists for a long period (>20 min). A proportion (30%)<br>frog atrial trabeculae responds to  $\alpha$ -stimulation by a<br>ansient response (Niedergerke and Page, 1981).<br>A detail

bersists for a long period ( $>20$  mm). A proportion (30%)<br>of frog atrial trabeculae responds to  $\alpha$ -stimulation by a<br>transient response (Niedergerke and Page, 1981).<br>A detailed account of the characteristics of the stead of frog atrial trabecture responds to  $\alpha$ -stimulation by a<br>transient response (Niedergerke and Page, 1981).<br>A detailed account of the characteristics of the steady<br>state positive inotropic effect of  $\alpha_1$ -adrenoceptor-m A detailed account of the characteristics of the stea<br>state positive inotropic effect of  $\alpha_1$ -adrenoceptor agonis<br>was presented by Osnes et al. (1985) and Endoh (198<br>One property of the  $\alpha_1$ -adrenoceptor-mediated posi state positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists<br>was presented by Osnes et al. (1985) and Endoh (1986).<br>One property of the  $\alpha_1$ -adrenoceptor-mediated positive<br>inotropic effect is an increase in the contr was presented by Osnes et al. (1985) and Endoh (1986).<br>
One property of the  $\alpha_1$ -adrenoceptor-mediated positive<br>
inotropic effect is an increase in the contraction ampli-<br>
tude with no change or a slight prolongation in One property of the  $\alpha_1$ -adrenoceptor-mediated positive<br>inotropic effect is an increase in the contraction ampli-<br>tude with no change or a slight prolongation in the<br>duration of the contraction-relaxation cycle; there i inotropic effect is an increase in the contraction ampli-<br>tude with no change or a slight prolongation in the<br>duration of the contraction-relaxation cycle; there is also<br>no change or a slight increase in time to peak tens tude with no change or a slight prolongation in the<br>duration of the contraction-relaxation cycle; there is also<br>no change or a slight increase in time to peak tension<br>and relaxation time (Ledda et al., 1975; Endoh and<br>Blin duration of the contraction-relaxation cycle; there is also<br>no change or a slight increase in time to peak tension<br>and relaxation time (Ledda et al., 1975; Endoh and<br>Blinks, 1988; Skomedal et al., 1983; El Amrani et al.,<br>1 no change or a slight increase in time to peak tension<br>and relaxation time (Ledda et al., 1975; Endoh and<br>Blinks, 1988; Skomedal et al., 1983; El Amrani et al.,<br>1989). Li and Rouleau (1991) recently studied rabbit<br>papilla Blinks, 1988; Skomedal et al., 1970, Endon and Blinks, 1988; Skomedal et al., 1983; El Amrani et al., 1989). Li and Rouleau (1991) recently studied rabbit papillary muscle and reported a significant increase in time to pe 1989). Li and Rouleau (1991) recently studied rabbit papillary muscle and reported a significant increase in time to peak tension and in relaxation time. Consequently, all phases of the cycle are proportionally increased papillary muscle and reported a significant increase<br>time to peak tension and in relaxation time. Cons<br>quently, all phases of the cycle are proportionally i<br>creased in the presence of an  $\alpha_1$ -adrenoceptor agonii<br>Also, a quently, all phases of the cycle are propor<br>creased in the presence of an  $\alpha_1$ -adrenocep<br>Also, an increase in the V<sub>max</sub> of unloaded m<br>ening was observed (Li and Rouleau, 1991).<br>Phosphodiesterase inhibitors (e.g., theop quently, all phases of the cycle are proportionally increased in the presence of an  $\alpha_1$ -adrenoceptor agonist.<br>Also, an increase in the V<sub>max</sub> of unloaded muscle shortening was observed (Li and Rouleau, 1991).<br>Phosphodi A detailed account of the characteristics of the steady<br>state positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists)<br>since at al. (1985) and Endoh (1986).<br>We are response to al. (1985) and Endoh (1986).<br>One property o

ening was observed (Li and Rouleau, 1991).<br>
Phosphodiesterase inhibitors (e.g., theophylline) and<br>
adenylate cyclase inhibitors (i.e., muscarinic and adeno-<br>
sine agonists) do not affect the inotropic response of<br>
cardiac Phosphodiesterase inhibitors (e.g., theophylline) and<br>adenylate cyclase inhibitors (i.e., muscarinic and adeno-<br>sine agonists) do not affect the inotropic response of<br>cardiac muscle to  $\alpha_1$ -adrenoceptor stimulation (End adenyiate cyclose inhibitors (i.e., muscarint and adeno-<br>sine agonists) do not affect the inotropic response of<br>cardiac muscle to  $\alpha_1$ -adrenoceptor stimulation (Endoh<br>and Motomura, 1979; Endoh and Yamashita, 1980;<br>Chris sine agomsts) do not ariect the motropic response of cardiac muscle to  $\alpha_1$ -adrenoceptor stimulation (Endoh and Motomura, 1979; Endoh and Yamashita, 1980; Christiansen et al., 1987; for review, see Osnes et al., 1985; E to cAMP. Unistialised et al., 1567, for review, see Osnes et al., 1985; Endoh, 1991). This is expected because the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists is unrelated to cAMP.<br>Some experimental conditions (e.g.,

*i.* ever, beyond middle age, an aging-associated decline in bathing solution from 37°C to 32°C shifts the concentra-<br>the maximum positive inotropic effect of  $\alpha_1$ -agonists was tion-response curve for phenylephrine to t inotropic effect of  $\alpha_1$ -adrenoceptor agonists is unrelated<br>to cAMP.<br>Some experimental conditions (e.g., pacing frequency,<br>temperature, and Ca<sup>2+</sup> concentration of the bathing so-<br>lution) can affect the magnitude of the to cAMP.<br>Some experimental conditions (e.g., pacing frequency,<br>temperature, and Ca<sup>2+</sup> concentration of the bathing so-<br>lution) can affect the magnitude of the positive inotropic<br>response to  $\alpha_1$ -adrenoceptor agonists ( Some experimental conditions (e.g., pacing frequency,<br>temperature, and  $Ca^{2+}$  concentration of the bathing so-<br>lution) can affect the magnitude of the positive inotropic<br>response to  $\alpha_1$ -adrenoceptor agonists (reviewed temperature, and Ca<sup>2+</sup> concentration of the bathing so-<br>lution) can affect the magnitude of the positive inotropic<br>response to  $\alpha_1$ -adrenoceptor agonists (reviewed by En-<br>doh, 1986). The  $\alpha_1$ -adrenoceptor-mediated po lution) can affect the magnitude of the positive inotropic<br>response to  $\alpha_1$ -adrenoceptor agonists (reviewed by En-<br>doh, 1986). The  $\alpha_1$ -adrenoceptor-mediated positive ino-<br>tropic effect is most prominent at a low rate doh, 1986). The  $\alpha_1$ -adrenoceptor-mediated positive ino-<br>tropic effect is most prominent at a low rate of muscle<br>stimulation (0.5 Hz) and decreases or is absent at high<br>stimulating frequencies (Endoh and Schümann, 1975; doh, 1986). The  $\alpha_1$ -adrenoceptor-mediated positive ino-<br>tropic effect is most prominent at a low rate of muscle<br>stimulation (0.5 Hz) and decreases or is absent at high<br>stimulating frequencies (Endoh and Schümann, 1975; tropic effect is most prominent at a low rate of must<br>stimulation (0.5 Hz) and decreases or is absent at<br>stimulating frequencies (Endoh and Schümann, 1<br>Scholz et al., 1986). Lowering the temperature of<br>bathing solution fr stimulation (0.5 Hz) and decreases or is absent at high<br>stimulating frequencies (Endoh and Schümann, 1975;<br>Scholz et al., 1986). Lowering the temperature of the<br>bathing solution from 37°C to 32°C shifts the concentra-<br>tion stimulating frequencies (Endoh and Schümann, 1975;<br>Scholz et al., 1986). Lowering the temperature of the<br>bathing solution from 37°C to 32°C shifts the concentra-<br>tion-response curve for phenylephrine to the left (Endoh<br>et bathing solution from 37°C to 32°C shifts the concentrion-response curve for phenylephrine to the left (End<br>et al., 1977). An important modulator of the magnitu<br>of the positive inotropic response to  $\alpha_1$ -adrenocept<br>agon bathing solution from  $37 \text{ C}$  to  $32 \text{ C}$  shifts the concentration-response curve for phenylephrine to the left (Endoh et al., 1977). An important modulator of the magnitude of the positive inotropic response to  $\alpha_1$ 

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effect of phenylephrine in the lower concentration range<br>
(1 to 100 nM) requires the presence of an intact endocar-<br>
19 TE<br>(1 to 100 nM) requires in the lower concentration ra<br>(1 to 100 nM) requires the presence of an intact endoc<br>dial endothelium. Higher concentrations of phenyle The 158<br>effect of phenylephrine in the lower concentration re<br>(1 to 100 nM) requires the presence of an intact endo<br>dial endothelium. Higher concentrations of phenyle<br>rine destroy the endocardial endothelium and shift effect of phenylephrine in the lower concentration range<br>(1 to 100 nM) requires the presence of an intact endocar-<br>dial endothelium. Higher concentrations of phenyleph-<br>rine destroy the endocardial endothelium and shift t (1 to 100 nM) requires the presence of an intact endocar-<br>dial endothelium. Higher concentrations of phenyleph-<br>rine destroy the endocardial endothelium and shift the duced in number, by more than half, as compared with<br>d higher concentrations. al endothelium. Higher concentrations of phenyleph-<br>he destroy the endocardial endothelium and shift the<br>se-response curve of  $\alpha_1$ -adrenergic agonists toward<br>gher concentrations.<br>Increasing the Ca<sup>2+</sup> concentration of t

rine destroy the endocardial endothelium and shift the dose-response curve of  $\alpha_1$ -adrenergic agonists toward higher concentrations.<br>Increasing the Ca<sup>2+</sup> concentration of the bathing solution to 5 mM results, at least dose-response curve of  $\alpha_1$ -adrenergic agonists tows<br>higher concentrations.<br>Increasing the Ca<sup>2+</sup> concentration of the bathing<br>lution to 5 mM results, at least in isolated ventricu<br>cells, in a sustained negative inotrop higher concentrations.<br>Increasing the Ca<sup>2+</sup> concentration of the bathing so-<br>lution to 5 mM results, at least in isolated ventricular<br>cells, in a sustained negative inotropic effect to  $\alpha_1$ -adre-<br>noceptor agonists (Cap Increasing the Ca<sup>2+</sup> concentration of the bathing so-<br>lution to 5 mM results, at least in isolated ventricular<br>cells, in a sustained negative inotropic effect to  $\alpha_1$ -adre-<br>moceptor agonists (Capogrossi et al., 1991). lution to 5 mM results, at least in isolated ventricular cells, in a sustained negative inotropic effect to  $\alpha_1$ -adre-noceptor agonists (Capogrossi et al., 1991). This negative inotropic effect cannot be ascribed to  $Ca^{$ cells, in a sustained negative inotropic effect to  $\alpha_1$ -adre-<br>noceptor agonists (Capogrossi et al., 1991). This negative the<br>inotropic effect cannot be ascribed to Ca<sup>2+</sup> overload ob<br>because  $\alpha_1$ -adrenoceptor agonists noceptor agonists (Capogrossi et al., 1991). This negative<br>inotropic effect cannot be ascribed to  $Ca^{2+}$  overload<br>because  $\alpha_1$ -adrenoceptor agonists suppress spontaneous<br> $Ca^{2+}$  release from the sarcoplasmic reticulum because  $\alpha_1$ -adrenoceptor agonists suppress spontaneous<br>Ca<sup>2+</sup> release from the sarcoplasmic reticulum of isolated<br>cells usually observed under this experimental condition.<br>This negative inotropic effect was ascribed to Ca<sup>2+</sup> release from the sarcoplasmic reticulum of isolated whether endogenous catecholamines could support carcells usually observed under this experimental condition. diac function in heart failure via the myocardial  $\alpha$ Ca<sup>2+</sup> release from the sarcoplasmic reticulum of isolated<br>cells usually observed under this experimental condition.<br>This negative inotropic effect was ascribed to an en-<br>hanced  $\alpha_1$ -adrenoceptor-mediated activation of cells usually observed under this experimental condition. dia<br>This negative inotropic effect was ascribed to an en-<br>hanced  $\alpha_1$ -adrenoceptor-mediated activation of PKC l<br>when intracellular  $Ca^{2+}$  is increased by high e This negative inotropic effect was ascribed to an hanced  $\alpha_1$ -adrenoceptor-mediated activation of I<br>when intracellular Ca<sup>2+</sup> is increased by high exte<br>Ca<sup>2+</sup> (Capogrossi et al., 1991). However, it should<br>pointed out th hanced  $\alpha_1$ -adrenoceptor-mediated activation of<br>when intracellular  $Ca^{2+}$  is increased by high ext<br> $Ca^{2+}$  (Capogrossi et al., 1991). However, it shoul<br>pointed out that even at higher external  $Ca^{2+}$  conce<br>tions (>7.5 when intracellular  $Ca^{2+}$  is increased by high external  $Ca^{2+}$  (Capogrossi et al., 1991). However, it should be pointed out that even at higher external  $Ca^{2+}$  concentrations ( $>7.5$  mM) a positive inotropic effect of  $Ca^{2+}$  (Capogrossi et al., 1991). However, it should be pointed out that even at higher external  $Ca^{2+}$  concentrations ( $>7.5$  mM) a positive inotropic effect of phenylephrine, albeit small, was observed in papillary or pointed out that even at higher external Ca<sup>2+</sup> concentra-<br>tions (>7.5 mM) a positive inotropic effect of phenyleph-<br>rine, albeit small, was observed in papillary or atrial low<br>muscle (Meulemans et al., 1990; Li and Roulea tions (>7.5 mM) a positive inotropic effect of phenyleph-<br>rine, albeit small, was observed in papillary or atrial<br>muscle (Meulemans et al., 1990; Li and Rouleau, 1991;<br>Terzic and Vogel, 1991). It is not known what could<br>ex rine, albeit small, was observed in papillary or atrial muscle (Meulemans et al., 1990; Li and Rouleau, 1991; Terzic and Vogel, 1991). It is not known what could explain this difference between isolated cardiomyocytes and muscle (Meulemans et al., 1990; Li and Rouleau, 199<br>Terzic and Vogel, 1991). It is not known what cours<br>explain this difference between isolated cardiomyocyt<br>and intact muscle. A possible explanation could be the<br>isolated Terzic and Vogel, 1991). It is not known what could<br>explain this difference between isolated cardiomyocytes<br>and intact muscle. A possible explanation could be that<br>isolated cells have a diminished tolerance to  $Ca^{2+}$ . Mo explain this difference between isolated cardiomyocytes<br>and intact muscle. A possible explanation could be that<br>isolated cells have a diminished tolerance to  $Ca^{2+}$ . Mold-<br>erings and Schümann (1987) also reported that, u and intact muscle. A possible explanation could be that isolated cells have a diminished tolerance to  $Ca^{2+}$ . Molderings and Schümann (1987) also reported that, under some experimental conditions, the magnitude of the in isolated cells have a diminished tolerance to  $Ca^{2+}$ . Molerings and Schümann (1987) also reported that, und<br>some experimental conditions, the magnitude of the i<br>crease in inotropy induced by  $\alpha_1$ -adrenoceptor agonis<br>co erings and Schümann (1987) also reported that, under<br>some experimental conditions, the magnitude of the in-<br>crease in inotropy induced by  $\alpha_1$ -adrenoceptor agonists<br>could depend on the extracellular  $Ca^{2+}$  concentratio some experimental conditions, the magnitude of the in-<br>crease in inotropy induced by  $\alpha_1$ -adrenoceptor agonists<br>could depend on the extracellular  $Ca^{2+}$  concentration.<br>These authors showed that inhibition of cyclooxyge crease in inotropy induced by  $\alpha_1$ -adrenoceptor agonists not could depend on the extracellular  $Ca^{2+}$  concentration. These authors showed that inhibition of cyclooxygenase increased the  $\alpha_1$ -adrenoceptor-mediated pos could depend on the extracellular  $Ca^{2+}$  concentration.<br>These authors showed that inhibition of cyclooxygenase<br>increased the  $\alpha_1$ -adrenoceptor-mediated positive ino-<br>tropic effect at low agonist concentrations when the These authors showed that inhibition of cyclooxygenase<br>increased the  $\alpha_1$ -adrenoceptor-mediated positive ino-<br>tropic effect at low agonist concentrations when the atria-<br>were bathed in 1.2 mM Ca<sup>2+</sup>. This effect was not creased the  $\alpha_1$ -adrenoceptor-mediated positive ino-<br> *2. apic* effect at low agonist concentrations when the atria ifice<br> *2. a<sub>1</sub>-Adrenoceptor-mediated positive inotropic effect in* adre<br> *2. a<sub>1</sub>-Adrenoceptor-mediate* 

tropic effect at low agonist concentrations when the atria if<br>were bathed in 1.2 mM Ca<sup>2+</sup>. This effect was not further<br>observed when external Ca<sup>2+</sup> was elevated to 2.5 mM.<br>2.  $\alpha_1$ -Adrenoceptor-mediated positive inotro observed when external Ca<sup>2+</sup> was elevated to 2.5 mM.<br>2.  $\alpha_1$ -Adrenoceptor-mediated positive inotropic effect in<br>pathological conditions. It has been proposed that  $\alpha_1$ -<br>adrenoceptors might serve as a reserve mechanis 2.  $\alpha_1$ -Adrenoceptor-mediated positive inotropic effect in pathological conditions. It has been proposed that  $\alpha_1$ -adrenoceptors might serve as a reserve mechanism to maintain myocardial responsiveness to catecholamin pathological conditions. It has been proposed that a adrenoceptors might serve as a reserve mechanism maintain myocardial responsiveness to cate cholaming under conditions in which the  $\beta$ -adrenoceptor is block functiona adrenoceptors might serve as a reserve mechanism to<br>maintain myocardial responsiveness to cate cholamines<br>under conditions in which the  $\beta$ -adrenoceptor is blocked,<br>functionally antagonized, reduced in number, or uncou-<br> maintain myocardial responsiveness to catecholami<br>under conditions in which the  $\beta$ -adrenoceptor is block<br>functionally antagonized, reduced in number, or unc<br>pled from its transduction pathway (Brückner et<br>1985; Osnes et under conditions in which the  $\beta$ -adrenoceptor is blocked, co<br>functionally antagonized, reduced in number, or uncou-<br>pled from its transduction pathway (Brückner et al., H<br>1985; Osnes et al., 1985; Homcy et al., 1991). F functionally antagonized, reduced in number, or uncou-<br>pled from its transduction pathway (Brückner et al., How<br>1985; Osnes et al., 1985; Homcy et al., 1991). Further- in the<br>more, several pathological and clinical situat pled from its transduction pathway (Brückner et al., 1985; Osnes et al., 1985; Homcy et al., 1991). Furthermore, several pathological and clinical situations modify f the density of  $\alpha_1$ -adrenergic receptors in the myoc 1985; Osnes et al., 1985; Homcy et al., 1991). Furthemore, several pathological and clinical situations modit the density of  $\alpha_1$ -adrenergic receptors in the myocardiu which could be associated with an increase in the p the density of  $\alpha_1$ -adrenergic receptors in the myocardium<br>which could be associated with an increase in the positive<br>inotropic effect induced by  $\alpha_1$ -adreneceptors agonists.<br>For example, chronic treatment with  $\beta$ -a inotropic effect induced by  $\alpha_1$ -adrenoceptors agonists.

tagonists augments the number of myocardial  $\alpha_1$ -adrenoceptors (Mügge et al., 1985). This propranolol-induced increase in the density of  $\alpha_1$ -adrenoceptors is inhibited For example, chronic treatment with  $\beta$ -adrenergic an-<br>tagonists augments the number of myocardial  $\alpha_1$ -adre-<br>noceptors (Mügge et al., 1985). This propranolol-induced The effect of dietary fish oil on cardiac function For example, chronic treatment with  $\beta$ -adrenergic antagonists augments the number of myocardial  $\alpha_1$ -adrenoceptors (Mügge et al., 1985). This propranolol-induced increase in the density of  $\alpha_1$ -adrenoceptors is inhi tagonists augments the number of myocardial  $\alpha_1$ -adre-noceptors (Mügge et al., 1985). This propranolol-induced increase in the density of  $\alpha_1$ -adrenoceptors is inhibited by cycloheximide, an inhibitor of protein synth moceptors (Mügge et al., 1985). This propranolol-induced<br>increase in the density of  $\alpha_1$ -adrenoceptors is inhibited res<br>by cycloheximide, an inhibitor of protein synthesis, sug-<br>ingesting that it was due to de novo rece increase in the density of  $\alpha_1$ -adrenoceptors is inhibity cycloheximide, an inhibitor of protein synthesis, sugesting that it was due to de novo receptor synthe (Steinkraus et al., 1989). At least in rat hearts, tuncrea by cycloheximide, an inhibitor of protein synthesis, suggesting that it was due to de novo receptor synthesis (Steinkraus et al., 1989). At least in rat hearts, the increase in  $\alpha_1$ -adrenoceptors density was not accompa

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AL.<br>sponse to  $\alpha_1$ -adrenergic agonists (Steinkraus et al., 89).<br>In congestive heart failure,  $\beta$ -adrenoceptors are re-<br>ced in number, by more than half, as compared with response to  $\alpha_1$ -adrenergic agonists (Steinkraus et al., 1989).<br>In congestive heart failure,  $\beta$ -adrenoceptors are re-<br>duced in number, by more than half, as compared with<br>normally functioning hearts (Bristow et al., 1 response to  $\alpha_1$ -adrenergic agonists (Steinkraus et al., 1989).<br>In congestive heart failure,  $\beta$ -adrenoceptors are re-<br>duced in number, by more than half, as compared with<br>normally functioning hearts (Bristow et al., 1 1989).<br>In congestive heart failure,  $\beta$ -adrenoceptors are<br>duced in number, by more than half, as compared w<br>normally functioning hearts (Bristow et al., 1982). T<br>reduction is accompanied by a decrease in the bioche<br>ical In congestive heart failure,  $\beta$ -adrenoceptors are re-<br>duced in number, by more than half, as compared with<br>normally functioning hearts (Bristow et al., 1982). This<br>reduction is accompanied by a decrease in the biochem-<br> reduction is accompanied by a decrease in the biochemical and inotropic responsiveness of cardiac tissue to  $\beta$ -<br>adrenoceptor agonists (Bristow et al., 1985). No difference in the absolute density of  $\alpha_1$ -adrenoceptors or in the  $\alpha_1$ -adrenoceptor-mediated effects on PIs has been reduction is accompanied by a decrease in the biochemical and inotropic responsiveness of cardiac tissue to  $\beta$ -adrenoceptor agonists (Bristow et al., 1985). No difference in the absolute density of  $\alpha_1$ -adrenoceptors ical and inotropic responsiveness of cardiac tissue to  $\beta$ -<br>adrenoceptor agonists (Bristow et al., 1985). No differ-<br>ence in the absolute density of  $\alpha_1$ -adrenoceptors or in<br>the  $\alpha_1$ -adrenoceptor-mediated effects on adrenoceptor agonists (Bristow et al., 1985). No difference in the absolute density of  $\alpha_1$ -adrenoceptors or in the  $\alpha_1$ -adrenoceptor-mediated effects on PIs has been observed in the failing when compared to the nonfa ence in the absolute density of  $\alpha_1$ -adrenoceptors or in<br>the  $\alpha_1$ -adrenoceptor-mediated effects on PIs has been<br>observed in the failing when compared to the nonfailing<br>heart (Bristow et al., 1988). The question remain the  $\alpha_1$ -adrenoceptor-mediated effects on PIs has been<br>observed in the failing when compared to the nonfailing<br>heart (Bristow et al., 1988). The question remains<br>whether endogenous catecholamines could support car-<br>diac heart (Bristow et al., 1988). The question remains

Hearts isolated from cardiomyopathic Syrian hamsters show an enhanced positive inotropic response to  $\alpha_1$ diac function in heart failure via the myocardial  $\alpha_1$ -<br>adrenoceptor (Schmitz et al., 1987a).<br>Hearts isolated from cardiomyopathic Syrian hamsters<br>show an enhanced positive inotropic response to  $\alpha_1$ -<br>adrenoceptors (B adrenoceptor (Schmitz et al., 1987a).<br>Hearts isolated from cardiomyopathic Syrian hamsters<br>show an enhanced positive inotropic response to  $\alpha_1$ -<br>adrenoceptors (Böhm et al., 1986; Sen et al., 1990).<br>Horackova et al. (199 Hearts isolated from cardiomyopathic Syrian hamsters<br>show an enhanced positive inotropic response to  $\alpha_1$ -<br>adrenoceptors (Böhm et al., 1986; Sen et al., 1990).<br>Horackova et al. (1991) showed that the EC<sub>50</sub> for the  $\alpha_$ show an enhanced positive inotropic response to  $\alpha_1$ -<br>adrenoceptors (Böhm et al., 1986; Sen et al., 1990).<br>Horackova et al. (1991) showed that the EC<sub>50</sub> for the  $\alpha_1$ -<br>adrenoceptor-mediated positive inotropic effect w adrenoceptors (Böhm et al., 1986; Sen et al., 1990).<br>Horackova et al. (1991) showed that the  $EC_{50}$  for the  $\alpha_1$ -<br>adrenoceptor-mediated positive inotropic effect was 50%<br>lower in cardiomyopathic than in normal hamsters Horackova et al. (1991) showed that the EC<sub>50</sub> for the  $\alpha_1$ -<br>adrenoceptor-mediated positive inotropic effect was 50%<br>lower in cardiomyopathic than in normal hamsters. With<br>the progression of cardiomyopathy,  $\beta$ -adrenoc adrenoceptor-mediated positive inotropic effect was 50%<br>lower in cardiomyopathic than in normal hamsters. With<br>the progression of cardiomyopathy,  $\beta$ -adrenoceptor<br>gradually disappear, whereas  $\alpha_1$ -adrenoceptor density lower in cardiomyop<br>the progression of<br>gradually disappear<br>mains high, even w<br>giya et al., 1991a).<br>An increase in tl e progression of cardiomyopathy,  $\beta$ -adrenoceptors<br>adually disappear, whereas  $\alpha_1$ -adrenoceptor density re-<br>ains high, even when heart failure develops fully (Ka-<br>ya et al., 1991a).<br>An increase in the  $\alpha_1$ -adrenocept

gradually disappear, whereas  $\alpha_1$ -adrenoceptor density remains high, even when heart failure develops fully (Ka-<br>giya et al., 1991a).<br>An increase in the  $\alpha_1$ -adrenoceptor density was also<br>observed in cardiac hypoxia ( mains high, even when heart failure develops fully (Ka-<br>giya et al., 1991a).<br>An increase in the  $\alpha_1$ -adrenoceptor density was also<br>observed in cardiac hypoxia (Heathers et al., 1988; Ka-<br>giya et al., 1991b). An explanat giya et al., 1991a).<br>
An increase in the  $\alpha_1$ -adrenoceptor density was also<br>
observed in cardiac hypoxia (Heathers et al., 1988; Ka-<br>
giya et al., 1991b). An explanation for this increase is<br>
not yet forthcoming. This c An increase in the  $\alpha_1$ -adrenoceptor density was also<br>observed in cardiac hypoxia (Heathers et al., 1988; Ka-<br>giya et al., 1991b). An explanation for this increase is<br>not yet forthcoming. This change in density could be observed in cardiac hypoxia (Heathers et al., 1988; Ka-<br>giya et al., 1991b). An explanation for this increase is not yet forthcoming. This change in density could be explained by the incorporation in the sarcolemma of newly synthesized receptors or, as previously suggested, by an unmasking of covert receptors following the modificati not yet forthcoming. This change in density could be explained by the incorporation in the sarcolemma of newly synthesized receptors or, as previously suggested by an unmasking of covert receptors following the modificatio newly synthesized receptors or, as previously suggested, by an unmasking of covert receptors following the mod-

were bathed in 1.2 mM Ca<sup>2+</sup>. This effect was not further In hypertensive animals, both the number of cardiac observed when external Ca<sup>2+</sup> was elevated to 2.5 mM.  $\beta$ -adrenoceptors and the positive inotropic effect of by an unmasking of covert receptors following the modification of membrane fluidity (Heathers et al., 1988).<br>In hypertensive animals, both the number of cardiac  $\beta$ -adrenoceptors and the positive inotropic effect of  $\beta$ ification of membrane fluidity (Heathers et al., 1988).<br>In hypertensive animals, both the number of cardiac  $\beta$ -adrenoceptors and the positive inotropic effect of  $\beta$ -adrenergic agonists are reduced (Böhm et al., 1988a) In hypertensive animals, both the number of cardiac  $\beta$ -adrenoceptors and the positive inotropic effect of  $\beta$ -adrenergic agonists are reduced (Böhm et al., 1988a). The positive inotropic effect of phenylephrine appears p-autenoceptors and the positive inotropic effect of p-<br>adrenergic agonists are reduced (Böhm et al., 1988a).<br>The positive inotropic effect of phenylephrine appears<br>not to differ between normotensive and hypertensive<br>anim The positive inotropic effect of phenylephrine appears<br>not to differ between normotensive and hypertensive<br>animals (Fujiwara et al., 1972). Also, the total cardiac<br>content of  $\alpha_1$ -adrenoceptors is similar in hypertensiv not to differ between normotensive and hypertensive<br>animals (Fujiwara et al., 1972). Also, the total cardiac<br>content of  $\alpha_1$ -adrenoceptors is similar in hypertensive<br>and normotensive animals (Limas and Limas, 1987).<br>How content of  $\alpha_1$ -adrenoceptors is similar in hypertensive<br>and normotensive animals (Limas and Limas, 1987).<br>However, the distribution of  $\alpha_1$ -adrenoceptors is higher<br>in the sarcolemma and lower in the cytosolic vesicul content of  $\alpha_1$ -adrenoceptors is similar in hypertensive<br>and normotensive animals (Limas and Limas, 1987).<br>However, the distribution of  $\alpha_1$ -adrenoceptors is higher<br>in the sarcolemma and lower in the cytosolic vesicul and normotensive animals (Limas and Limas, 1987).<br>However, the distribution of  $\alpha_1$ -adrenoceptors is higher<br>in the sarcolemma and lower in the cytosolic vesicular<br>fraction of the myocardium obtained from hypertensive<br>an However, the distribution of  $\alpha_1$ -adrenoceptors is highe<br>in the sarcolemma and lower in the cytosolic vesicula<br>fraction of the myocardium obtained from hypertensive<br>animals when compared with normotensive controls (Li<br>m in the sarcolemma and lower in the cytosolic vesic<br>fraction of the myocardium obtained from hyperten<br>animals when compared with normotensive controls<br>mas and Limas, 1987). Therefore, the  $\alpha/\beta$  ratio of p<br>malemmal cardiac animals when compared with normotensive controls (Limas and Limas, 1987). Therefore, the  $\alpha/\beta$  ratio of plasanimals when compared with normoten<br>mas and Limas, 1987). Therefore, the<br>malemmal cardiac adrenoceptors is chas<br>sive animals, with the  $\alpha_1$ -adrenocepto<br>coming more important in hypertension<br>The effect of dietary fish oi as and Limas, 1987). Therefore, the  $\alpha/\beta$  ratio of plas-<br>alemmal cardiac adrenoceptors is changed in hyperten-<br>ve animals, with the  $\alpha_1$ -adrenoceptor component be-<br>ming more important in hypertension.<br>The effect of die

malemmal cardiac adrenoceptors is changed in hypertensive animals, with the  $\alpha_1$ -adrenoceptor component becoming more important in hypertension.<br>The effect of dietary fish oil on cardiac function and responsiveness to a sive animals, with the  $\alpha_1$ -adrenoceptor component be-<br>coming more important in hypertension.<br>The effect of dietary fish oil on cardiac function and<br>responsiveness to adrenoceptor agonists has been studies<br>in perfused r The enect of dietary hish on on cardiac runction and<br>responsiveness to adrenoceptor agonists has been studies<br>in perfused rat hearts. The inotropic response to  $\alpha$ -<br>agonists is reduced following a 4-week diet containing<br> agonists is reduced following a 4-week diet containing 5% menhaden oil, whereas the cardiac responsiveness to  $\beta$ -adrenoceptor agonists is not affected by dietary fish oil (Reibel et al., 1988).

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CARDIAC  $\alpha_1$ -ADRENOCEPTORS<br>In hypothyroidism the inotropic response to  $\alpha_1$ -adre- of inositol ph<br>nergic stimulation is increased (Nakashima et al., 1971; myofibrillar r CARDIAC  $\alpha_1$ -ADRENC<br>
In hypothyroidism the inotropic response to  $\alpha_1$ -adre- of in-<br>
nergic stimulation is increased (Nakashima et al., 1971; myc<br>
Kunos et al., 1974; reviewed by Osnes et al., 1985). In<br>
the hypothyroi In hypothyroidism the inotropic response to  $\alpha_1$ -adre-<br>nergic stimulation is increased (Nakashima et al., 1971<br>Kunos et al., 1974; reviewed by Osnes et al., 1985). In<br>the hypothyroid state the number of  $\alpha_1$ -adrenocep In hypothyronusm the motropic response to  $a_1$ -adre-<br>nergic stimulation is increased (Nakashima et al., 1971;<br>Kunos et al., 1974; reviewed by Osnes et al., 1985). In<br>the hypothyroid state the number of  $\alpha_1$ -adrenceptor Kunos et al., 1974; reviewed by Osnes et al., 1985). In<br>the hypothyroid state the number of  $\alpha_1$ -adrenoceptor<br>has been reported to be unchanged (Williams and Lef<br>kowitz, 1979) or even reduced (Groß and Lues, 1985)<br>Thyro the mypothyroid state the humber of  $\alpha_1$ -adrenocepticals been reported to be unchanged (Williams and L<br>kowitz, 1979) or even reduced (Groß and Lues, 198<br>Thyroid hormones modulate isozyme transition of my<br>sin in the mamm has been reported to be unchanged (Williams and Lef-<br>kowitz, 1979) or even reduced (Groß and Lues, 1985). the<br>Thyroid hormones modulate isozyme transition of myo-<br>sin in the mammalian ventricular myocardium (Wine-<br>congrad kowitz, 1979) or even reduced (Groß and Lues, 1985).<br>Thyroid hormones modulate isozyme transition of myo-<br>sin in the mammalian ventricular myocardium (Wine-<br>grad, 1984). Hypothyroidism causes a transition to the<br>V3 isozym I hyrota normones modulate isozyme transition of myo-<br>
sin in the mammalian ventricular myocardium (Wine-<br>
grad, 1984). Hypothyroidism causes a transition to the<br>
V3 isozyme, which responds to  $\alpha$ - but not to  $\beta$ -adrene V3 isozyme, which responds to  $\alpha$ - but not to  $\beta$ -adrenergic<br>stimulation (Endoh, 1986). In addition, the transition<br>from the V1 to the V3 myosin isoform leads to a decrease<br>in the maximal actomyosin ATPase activity.<br>Exp vs isozyme, which responds to  $\alpha$ - but not to p-adrenergic in<br>stimulation (Endoh, 1986). In addition, the transition<br>from the V1 to the V3 myosin isoform leads to a decrease<br>in the maximal actomyosin ATPase activity.<br>Exp

From the V1 to the V5 myoshi isolorm leads to a decrease volume in the maximal actomyosin ATPase activity.<br>
Experimentally induced diabetes mellitus is also char-<br>
acterized by an increased inotropic responsiveness of the Experimentally induced diabetes mellitus is also char-<br>acterized by an increased inotropic responsiveness of this<br>olated cardiac muscle or whole working hearts to  $\alpha_1$ -<br>podernoceptor agonists (Downing et al., 1983; Cang acterized by an increased inotropic responsiveness of the isolated cardiac muscle or whole working hearts to  $\alpha_1$ -<br>adrenoceptor agonists (Downing et al., 1983; Canga and  $I_{\text{to}}$ , Sterin-Borda, 1986; Heijnis and van Zw isolated cardiac muscle or whole working hearts to  $\alpha_1$ -<br>adrenoceptor agonists (Downing et al., 1983; Canga and  $I_u$ <br>Sterin-Borda, 1986; Heijnis and van Zwieten, 1992). The po<br>dose response to  $\alpha_1$ -adrenoceptor agonis adrenoceptor agomsts (Downing et al., 1983, Canga and<br>Sterin-Borda, 1986; Heijnis and van Zwieten, 1992). The<br>dose response to  $\alpha_1$ -adrenoceptor agonists shows both a<br>leftward and an upward shift in diabetic animals. Bi dose response to  $\alpha_1$ -adrenoceptor agonists shows both a (leftward and an upward shift in diabetic animals. Binding fitulies reveal a reduced number of  $\alpha_1$ -adrenoceptor-binding sites associated with no change (Tanaka leftward and an upward shift in diabetic animals. Binding festudies reveal a reduced number of  $\alpha_1$ -adrenoceptor-<br>binding sites associated with no change (Tanaka et al., ag<br>1992) or an increase in their affinity constan studies reveal a reduced number of  $\alpha_1$ -adrenoceptor-<br>binding sites associated with no change (Tanaka et al., agor<br>1992) or an increase in their affinity constants (Wald et et a<br>al., 1988). The decrease in cell surface binding sites associated with no change (Tanaka et al., 1992) or an increase in their affinity constants (Wald et al., 1988). The decrease in cell surface receptor density has been suggested to be linked to a high cardiac 1992). *3. 1988*). The decrease in cell surface receptor density due to a high cardiac PKC nuity, also observed in diabetic models (Tanaka et al., s 92).<br>3. Proposed mechanisms of the  $\alpha_1$ -adrenergic positive illustropic effec

activity, also observed in diabetic models (Tanaka et al., such 1992).<br>
3. Proposed mechanisms of the  $\alpha_1$ -adrenergic positive ille-<br>
inotropic effect. Do  $\alpha_1$ -adrenoceptor agonists belong to a<br>
traditional positive i 1992).<br>3. Proposed mechanisms of the  $\alpha_1$ -adrenergic positive<br>inotropic effect. Do  $\alpha_1$ -adrenoceptor agonists belong to a<br>traditional positive inotropic group of agents? They do<br>not (Pucéat et al., 1992). They differ 3. Proposed mechanisms of the  $\alpha_1$ -darenergic positive<br>inotropic effect. Do  $\alpha_1$ -adrenoceptor agonists belong to a<br>traditional positive inotropic group of agents? They do<br>not (Pucéat et al., 1992). They differ from  $\$ *inotropic effect*. Do  $\alpha_1$ -adrenoceptor agonists belong to a traditional positive inotropic group of agents? They do not (Pucéat et al., 1992). They differ from  $\beta$ -adrenoceptor agonists, phosphodiesterase inhibitors, Fraditional positive inotropic group of agents: They do<br>not (Pucéat et al., 1992). They differ from  $\beta$ -adrenoceptor<br>agonists, glucagon, and other positive inotropic agents that<br>increase contractile force by elevating cA hot (Puceat et al., 1992). They unfer from p-autenoceptor<br>agonists, phosphodiesterase inhibitors,  $H_2$ -histamine ag-<br>onists, glucagon, and other positive inotropic agents that<br>increase contractile force by elevating cAMP agonists, phosphodesterase inhibitors,  $112$ -installine agonists, glucagon, and other positive inotropic agents that<br>increase contractile force by elevating cAMP levels. Unlike dihydropyridine agonists (e.g., Bay K 8644), binists, glucagon, and other positive inotropic agents that<br>increase contractile force by elevating cAMP levels. Un-<br>like dihydropyridine agonists (e.g., Bay K 8644),  $\alpha_1$ -<br>adrenoceptor agonists do not directly activate mechanism with cardiotonic glycosides because they do<br>not inhibit Na<sup>+</sup>/K<sup>+</sup> pumping. Several mechanisms have<br>been proposed to participate in the positive inotropic<br>mechanism with cardiotonic glycosides because they do<br>th adrenoceptor agonists do not directly activate  $ic_a$ . Also,<br>  $\alpha_1$ -adrenoceptor agonists do not share the inotropic<br>
mechanism with cardiotonic glycosides because they do<br>
not inhibit Na<sup>+</sup>/K<sup>+</sup> pumping. Several mechanism  $\alpha_1$ -adrenoceptor agonists do not share the inotropic<br>mechanism with cardiotonic glycosides because they do<br>not inhibit Na<sup>+</sup>/K<sup>+</sup> pumping. Several mechanisms have<br>these proposed to participate in the positive inotropic mechanism with cardiotonic givessides because they do<br>not incredirect of  $\alpha_1$ -adrenoceptor agonists,<br>been proposed to participate in the positive inotropic<br>effect of  $\alpha_1$ -adrenoceptor agonists (fig. 1). Currently,<br>thr indirect increase in  $I_{Ca}$  inward current, (*b*) a stimulation<br> $a_t$ -adrenoceptor stimulation



FIG. 1. Proposed mechanisms underlying the positive inotropic action of  $\alpha_1$ -adrenoceptor agonists.

ENOCEPTORS 159<br>of inositol phosphate turnover, and *(c)* an increase in<br>myofibrillar responsiveness to  $Ca^{2+}$ .

has been suggested to be linked to a high cardiac PKC noceptor agonists on an increase in Ca<sup>2+</sup> influx. However, activity, also observed in diabetic models (Tanaka et al., such an explanation should be viewed with cautio ENOCEPTORS<br>
of inositol phosphate turnover, and (c) an increase<br>
myofibrillar responsiveness to Ca<sup>2+</sup>.<br>
a. EVIDENCE FOR AND AGAINST A CAUSAL RELATI<br>SHIP BETWEEN  $\alpha_1$ -ADRENERGIC EFFECTS ON THE ACT of inositol phosphate turnover, and  $(c)$  an increase in<br>myofibrillar responsiveness to  $Ca^{2+}$ .<br>a. EVIDENCE FOR AND AGAINST A CAUSAL RELATION-<br>SHIP BETWEEN  $\alpha_1$ -ADRENERGIC EFFECTS ON THE ACTION<br>POTENTIAL AND POSITIVE IN myofibrillar responsiveness to  $Ca^{2+}$ .<br>a. EVIDENCE FOR AND AGAINST A CAUSAL RELATION-<br>SHIP BETWEEN  $\alpha_1$ -ADRENERGIC EFFECTS ON THE ACTION<br>POTENTIAL AND POSITIVE INOTROPIC EFFECT. Because<br>there is a known relationship be a. EVIDENCE FOR AND AGAINST A CAUSAL RELATION-<br>SHIP BETWEEN  $\alpha_1$ -ADRENERGIC EFFECTS ON THE ACTION<br>POTENTIAL AND POSITIVE INOTROPIC EFFECT. Because<br>there is a known relationship between the duration of<br>action potentials a. EVIDENCE FOR AND AGAINST A CAUSAL RELATION-<br>SHIP BETWEEN  $\alpha_1$ -ADRENERGIC EFFECTS ON THE ACTION<br>POTENTIAL AND POSITIVE INOTROPIC EFFECT. Because<br>there is a known relationship between the duration of<br>action potentials SHIP BETWEEN  $\alpha_1$ -ADRENERGIC EFFECTS ON THE ACTION POTENTIAL AND POSITIVE INOTROPIC EFFECT. Becausthere is a known relationship between the duration action potentials and contractile force, it is natural consider that t POTENTIAL AND POSITIVE INOTROPIC EFFECT. Because<br>there is a known relationship between the duration of<br>action potentials and contractile force, it is natural to<br>consider that the two are related when the action poten-<br>tia there is a known relationship between the duration of action potentials and contractile force, it is natural to consider that the two are related when the action potential is prolonged by  $\alpha_1$ -adrenoceptor agonists. A p action potentials and contractile force, it is natural to consider that the two are related when the action potential is prolonged by  $\alpha_1$ -adrenoceptor agonists. A prolonged action potential due to the inhibition of  $I_{$ consider that the two are related when the action potential is prolonged by  $\alpha_1$ -adrenoceptor agonists. A prolonged action potential due to the inhibition of  $I_{\text{to}}$  by  $\alpha_1$ -adrenoceptor agonists will increase  $Ca^{2+$ tial is prolonged by  $\alpha_1$ -adrenoceptor agonists. A pro-<br>longed action potential due to the inhibition of  $I_{to}$  by  $\alpha_1$ -<br>adrenoceptor agonists will increase  $Ca^{2+}$  influx through<br>voltage-dependent  $Ca^{2+}$  channels (F longed action potential due to the inhibition of  $I_{to}$  by  $\alpha_1$ -<br>adrenoceptor agonists will increase  $Ca^{2+}$  influx through<br>voltage-dependent  $Ca^{2+}$  channels (Fedida et al., 1989).<br>Because of the properties of  $I_{to}$ , adrenoceptor agonists will increase  $Ca^{2+}$  influx throus voltage-dependent  $Ca^{2+}$  channels (Fedida et al., 1988)<br>Because of the properties of  $I_{\omega}$ , such a mechanism couprovide an explanation for the frequency depende voltage-dependent Ca<sup>2+</sup> channels (Fedida et al., 1989).<br>Because of the properties of  $I_{\omega}$ , such a mechanism could<br>provide an explanation for the frequency dependency of<br>the positive inotropic effect of  $\alpha_1$ -agonists Because of the properties of  $I_{\omega}$ , such a mechanism could<br>the positive inotropic effect of  $\alpha_1$ -agonists. Indeed, pres-<br>posure of cardiac cells to 4-aminopyridine, a blocker of<br>posure of cardiac cells to 4-aminopyrid provide an explanation for the frequency dependency of<br>the positive inotropic effect of  $\alpha_1$ -agonists. Indeed, preex-<br>positive inotropic effect (Tohse et al., 1990). In addition,<br>Ca<sup>2+</sup> channel antagonists (verapamil, d posure of cardiac cells to 4-aminopyridine, a blocker of  $I_{\text{to}}$ , appears to prevent  $\alpha_1$ -agonists from producing a positive inotropic effect (Tohse et al., 1990). In addition,  $Ca^{2+}$  channel antagonists (verapamil,  $I_{\text{to}}$ , appears to prevent  $\alpha_1$ -agonists from producing positive inotropic effect (Tohse et al., 1990). In addition Ca<sup>2+</sup> channel antagonists (verapamil, diltiazem, and nifedipine) have been shown to block, at least  $Ca^{2+}$  channel antagonists (verapamil, diltiazem, and nifedipine) have been shown to block, at least to some extent, the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists (Tohse et al., 1987a; Kushida et al., 199 Ca<sup>2+</sup> channel antagonists (verapamil, diltiazem, and nifedipine) have been shown to block, at least to some extent, the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists (Tohse et al., 1987a; Kushida et al., 1990 fedipine) have been shown to block, at least to so<br>extent, the positive inotropic effect of  $\alpha_1$ -adrenocep<br>agonists (Tohse et al., 1987a; Kushida et al., 1990; Enc<br>et al., 1991). These findings could be explained by<br>dep extent, the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists (Tohse et al., 1987a; Kushida et al., 1990; Endou et al., 1991). These findings could be explained by a dependency of the positive inotropic effect of such also inside the anti-<br>such an explained by a dependency of the positive inotropic effect of  $\alpha_1$ -adre-<br>noceptor agonists on an increase in Ca<sup>2+</sup> influx. However,<br>such an explanation should be viewed with caution b dependency of the positive inotropic effect of  $\alpha_1$ -a<br>noceptor agonists on an increase in Ca<sup>2+</sup> influx. Howe<br>such an explanation should be viewed with caution<br>cause Ca<sup>2+</sup> channel blockers also decrease basal contr<br>ile moceptor agonists on an increase in  $Ca^{2+}$  influx. However, moceptor agonists on an increase in  $Ca^{2+}$  influx. However, where  $Ca^{2+}$  channel blockers also decrease basal condie force and exhibit an affinity for cardiac moceptor agons is on an increase in  $Ca$ <br>such an explanation should be viewed w<br>cause  $Ca^{2+}$  channel blockers also decrease<br>ile force and exhibit an affinity for cardia<br>tor-binding sites (Kushida et al., 1990).<br>Recently, En an explanation should be viewed with caltion be-<br>use  $Ca^{2+}$  channel blockers also decrease basal contract-<br>force and exhibit an affinity for cardiac  $\alpha_1$ -adrenocep-<br>r-binding sites (Kushida et al., 1990).<br>Recently,

cause can exhibit an affinity for cardiac  $\alpha_1$ -adrenoceptor-binding sites (Kushida et al., 1990).<br>Recently, Fedida and Bouchard (1992), using the whole<br>cell voltage clamp technique to control the duration of<br>depolarizat ile force and exhibit an affinity for cardiac  $\alpha_1$ -adrenoceptor-binding sites (Kushida et al., 1990).<br>Recently, Fedida and Bouchard (1992), using the whole<br>cell voltage clamp technique to control the duration of<br>depolar tor-binding sites (Kushida et al., 1990).<br>Recently, Fedida and Bouchard (1992), using the whole<br>cell voltage clamp technique to control the duration of<br>depolarization, provided evidence that, at least under the<br>experiment Recently, Fedida and Bouchard (1992), using the whole<br>cell voltage clamp technique to control the duration of<br>depolarization, provided evidence that, at least under the<br>experimental conditions used, the increase in contra cell voltage clamp technique to control the duration of depolarization, provided evidence that, at least under the experimental conditions used, the increase in contractile force produced by  $\alpha_1$ -agonists can be observe repolarization, provided evidence that, at least didently<br>experimental conditions used, the increase in contractor<br>force produced by  $\alpha_1$ -agonists can be observed only with<br>the action potential duration is increased. Al Experimental conductions used, the increase in contractive<br>force produced by  $\alpha_1$ -agonists can be observed only when<br>the action potential duration is increased. Although the<br>results of these experiments point out that t the action potential duration is increased. Although the<br>results of these experiments point out that the prolon-<br>gation of the action potential plays an important role in<br>the positive inotropic effect of  $\alpha_1$ -adrenocept mesures of these experiments point out that the proformation of the action potential plays an important role in the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists, they do not necessarily mean that additional i gation of the action potential plays an important role if<br>the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists<br>they do not necessarily mean that additional inotropi<br>mechanisms do not also participate in the inotr the positive inotropic effect of  $\alpha_1$ -adrehoceptor agonists,<br>they do not necessarily mean that additional inotropic<br>mechanisms do not also participate in the inotropic<br>action of  $\alpha_1$ -agonists. A potential limitation o mechanisms do not also participate in the motropic<br>action of  $\alpha_1$ -agonists. A potential limitation of the tech-<br>nique used could have been that the internal dialysis of<br>myocytes through the patch pipette may have preven nique used could have been that the internal dialysis of<br>myocytes through the patch pipette may have prevented<br>the mechanisms leading to myofibrillar sensitization to<br>Ca<sup>2+</sup> to take place.<br>Several reports suggest that the myocytes through the patch pipette may have prevented

of K<sup>r</sup>currents<br>
in normally polarized myocardial preparations exposed<br>
to Mn<sup>2+</sup>, which causes a suppression of the slow inward<br>
PROLONGATION<br>
THE ACTION POTENTIAL of the action potential duration without an increase in the mechanisms leading to myofibrillar sensitization to  $Ca^{2+}$  to take place.<br>Several reports suggest that the electrophysiological effects caused by  $\alpha_1$ -adrenoceptor agonists can be disso-ciated from their positive i the mechanisms leading to myofibrillar sensitization to  $Ca^{2+}$  to take place.<br>Several reports suggest that the electrophysiological<br>effects caused by  $\alpha_1$ -adrenoceptor agonists can be disso-<br>ciated from their positive Ca<sup>2+</sup> to take place.<br>Several reports suggest that the electrophysiological<br>effects caused by  $\alpha_1$ -adrenoceptor agonists can be disso-<br>ciated from their positive inotropic effects. For example,<br>in normally polarized myo Several reports suggest that the electrophyshological<br>effects caused by  $\alpha_1$ -adrenoceptor agonists can be disso-<br>ciated from their positive inotropic effects. For example,<br>in normally polarized myocardial preparations e effects caused by  $a_1$ -autenoceptor agonists can be usso-<br>ciated from their positive inotropic effects. For example,<br>in normally polarized myocardial preparations exposed<br>to  $Mn^{2+}$ , which causes a suppression of the sl clated from their positive inotropic effects. For example,<br>in normally polarized myocardial preparations exposed<br>to  $Mn^{2+}$ , which causes a suppression of the slow inward<br>current, phenylephrine produced a marked prolonga In normany polarized injocardial preparations exposed<br>to  $Mn^{2+}$ , which causes a suppression of the slow inward<br>current, phenylephrine produced a marked prolongation<br>of the action potential duration without an increase i current, phenylephrine produced a marked prolongation<br>of the action potential duration without an increase in<br>contractile force (Handa et al., 1982). In addition, for<br>concentrations of  $\alpha_1$ - and  $\beta$ -adrenoceptor agonis of the action potential duration without an increase in<br>contractile force (Handa et al., 1982). In addition, for<br>concentrations of  $\alpha_1$ - and  $\beta$ -adrenoceptor agonists that<br>produce the same magnitude of positive inotrop

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the maximum rate of depolarization of slow action po-<br>
tentials as compared to  $\beta$ -adrenoceptor agonists (Brück-160 TEI<br>the maximum rate of depolarization of slow action<br>tentials as compared to  $\beta$ -adrenoceptor agonists (Brück-<br>ner and Scholz, 1984). Furthermore, for a given depol 160<br>the maximum rate of depolarization of slow action<br>tentials as compared to  $\beta$ -adrenoceptor agonists (Brü<br>ner and Scholz, 1984). Furthermore, for a given depol<br>izing pulse (i.e., under voltage clamp conditions), at le the maximum rate of depolarization of slow action potentials as compared to  $\beta$ -adrenoceptor agonists (Brückner and Scholz, 1984). Furthermore, for a given depolarizing pulse (i.e., under voltage clamp conditions), at le the maximum rate of depolarization of slow action po-<br>tentials as compared to  $\beta$ -adrenoceptor agonists (Brück-<br>ner and Scholz, 1984). Furthermore, for a given depolar-<br>izing pulse (i.e., under voltage clamp conditions), tentials as compared to  $\beta$ -adrenoceptor agonists (Brück-nitr ner and Scholz, 1984). Furthermore, for a given depolar-hibitizing pulse (i.e., under voltage clamp conditions), at least agon in feline cardiac cells,  $\alpha_1$ ner and Scholz, 1984). Furthermore, for a given depolar-<br>izing pulse (i.e., under voltage clamp conditions), at least<br>in feline cardiac cells,  $\alpha_1$ -adrenoceptor stimulation pro-<br>duces an increase in contractile force wi izing pulse (i.e., under voltage clamp conditions), at limit feline cardiac cells,  $\alpha_1$ -adrenoceptor stimulation duces an increase in contractile force with no increas  $Ca^{2+}$  current (Hartmann et al., 1988). Dirksen et in feline cardiac cells,  $\alpha_1$ -adrenoceptor stimulation produces an increase in contractile force with no increase in Ca<sup>2+</sup> current (Hartmann et al., 1988). Dirksen et al. (1991) reported that, in guinea pig ventricle, duces an increase in contractile force with no increase in Ca<sup>2+</sup> current (Hartmann et al., 1988). Dirksen et al. (1991) reported that, in guinea pig ventricle,  $\alpha_1$ -adrenoceptor stimulation produces a positive inotropi Ca<sup>2+</sup> current (Hartmann et al., 1988). Dirksen et al. C. (1991) reported that, in guinea pig ventricle,  $\alpha_1$ -adreno-<br>ceptor stimulation produces a positive inotropic effect pro<br>even when the Ca<sup>2+</sup> transient and the ac (1991) reported that, in guinea pig ventricle,  $\alpha_1$ -adreno-<br>ceptor stimulation produces a positive inotropic effect<br>even when the Ca<sup>2+</sup> transient and the action potential<br>duration are decreased. Similarly, in rat cardi ceptor stimulation produces a positive inotropic effect peven when the  $Ca^{2+}$  transient and the action potential the duration are decreased. Similarly, in rat cardiac cells, a spositive inotropic effect of phenylephrine positive inotropic effect of phenylephrine can be ob-<br>served, at least in some cells, in the absence of an increase<br>in intracellular Ca<sup>2+</sup> (Gambassi et al., 1992). It might be<br>margued on these grounds that the prolongati served, at least in some cells, in the absence of an increase<br>in intracellular Ca<sup>2+</sup> (Gambassi et al., 1992). It might be<br>argued on these grounds that the prolongation of the<br>action potential might participate, but is no in intracellular (argued on these<br>action potential<br>origin, of the  $\alpha_1$ <br>diac contractility<br>b. IS THERE tion potential might participate, but is not the sole higin, of the  $\alpha_1$ -adrenoceptor-mediated increase in car-<br>ac contractility.<br>b. IS THERE A CAUSAL RELATIONSHIP BETWEEN  $\alpha_1$ - am<br>RENOCEPTOR-MEDIATED STIMULATION OF T

BREAKDOWN OF PHOSPHATIDYL INOSITOLS AND CONdiac contractility.  $\begin{array}{ll}\n\text{c}}\n\text{c}\n\text{d}\$ b. IS THERE A CAUSAL RELATIONSHIP BETWEEN  $\alpha_1$ -<br>ADRENOCEPTOR-MEDIATED STIMULATION OF THE<br>BREAKDOWN OF PHOSPHATIDYL INOSITOLS AND CON-<br>TRACTILE FORCE? As reviewed above, the stimulation of<br>cardiac  $\alpha_1$ -adrenoceptors pr ADRENOCEPTOR-MEDIATED STIMULATION OF THE CAN<br>BREAKDOWN OF PHOSPHATIDYL INOSITOLS AND CON-<br>TRACTILE FORCE? As reviewed above, the stimulation of can<br>cardiac  $\alpha_1$ -adrenoceptors promotes the breakdown of PI, card<br>producing **BREAKDOWN OF PHOSPHATIDYL INOSITOLS AND CON-**<br>TRACTILE FORCE? As reviewed above, the stimulation of ca<br>cardiac  $\alpha_1$ -adrenoceptors promotes the breakdown of PI, ca<br>producing IP<sub>3</sub> and DAG. The role of these molecules in cardiac  $\alpha_1$ -adrenoceptors promotes the breakdor<br>producing IP<sub>3</sub> and DAG. The role of these mol<br>the excitation-contraction process in heart m<br>well as in mediating the positive inotropic effe<br>adrenoceptor agonists, is no oducing IP<sub>3</sub> and DAG. The role of these molecules in and<br>e excitation-contraction process in heart muscle, as (198<br>ell as in mediating the positive inotropic effect of  $\alpha_1$ - to 5<br>renoceptor agonists, is not yet fully c

the excitation-contraction process in heart muscle, as (19)<br>well as in mediating the positive inotropic effect of  $\alpha_1$ -<br>adrenoceptor agonists, is not yet fully clarified. Under<br>A prerequisite for a second-messenger role well as in mediating the positive inotropic effect of  $\alpha_1$ -<br>adrenoceptor agonists, is not yet fully clarified. Unlet a prerequisite for a second-messenger role of IP<sub>3</sub> in N<sub>6</sub><br>the  $\alpha_1$ -adrenoceptor-mediated inotropic adrenoceptor agonists, is not yet fully clarified.<br>A prerequisite for a second-messenger role of IP<sub>3</sub> in<br>the  $\alpha_1$ -adrenoceptor-mediated inotropic action is that the<br> $\alpha_1$ -adrenoceptor agonist-induced increase in IP<sub>3</sub> A prerequisite for a second-messenger role of  $IP_3$  in<br>the  $\alpha_1$ -adrenoceptor-mediated inotropic action is that the<br> $\alpha_1$ -adrenoceptor agonist-induced increase in  $IP_3$  should<br>precede the increase in the force of contra the  $\alpha_1$ -adrenoceptor-mediated inotropic action is that the  $\alpha_1$ -adrenoceptor agonist-induced increase in IP<sub>3</sub> should by precede the increase in the force of contraction. Indeed, the Schmitz et al. (1987b) and Scholz  $\alpha_1$ -adrenotepton agomst-moded increase in 11 3 should<br>precede the increase in the force of contraction. Indeed,<br>Schmitz et al. (1987b) and Scholz et al. (1988) found that<br>the positive inotropic effect of phenylephrine precede the increase in the force of contraction. Indeed, the Schmitz et al. (1987b) and Scholz et al. (1988) found that strothe positive inotropic effect of phenylephrine in rat atria In is preceded by a decrease in  $\text{$ Schmitz et al. (1987b) and Scholz et al. (1988) found that<br>the positive inotropic effect of phenylephrine in rat atria<br>is preceded by a decrease in  $\text{PIP}_2$  and an increase in  $\text{IP}_3$ .<br>Whereas the decrease in  $\text{PIP}_2$  the positive inotropic effect of phenylephrine in rat atria Ii<br>is preceded by a decrease in  $\text{PIP}_2$  and an increase in IP<sub>3</sub>.<br>Whereas the decrease in  $\text{PIP}_2$  and the increase in IP<sub>3</sub> w<br>could already be detected at 30 is preceded by a decrease in  $\text{PIP}_2$  and an increase i<br>Whereas the decrease in  $\text{PIP}_2$  and the increase is<br>could already be detected at 30 s, the increase in fo<br>contraction did not start before 1 min. In rat par<br>muscl could already be detected at 30 s, the increase in force of contraction did not start before 1 min. In rat papillary muscles, Otani et al. (1988) showed that concentration-response curves for  $\alpha_1$ -adrenoceptor-mediated sitol phosphate formation and inotropic responses were being in accordance with the view that concentration-<br>sitol phosphate formation and inotropic responses were being in accordance with the view that the breakdown in<br>o muscles, Otani et al. (1988) showed that concentration-<br>response curves for  $\alpha_1$ -adrenoceptor-mediated [<sup>3</sup>H]ino-<br>sitol phosphate formation and inotropic responses were by<br>similar. In accordance with the view that the b response curves for  $\alpha_1$ -adrenoceptor-mediated [<sup>3</sup>H]ino-<br>sitol phosphate formation and inotropic responses were by<br>similar. In accordance with the view that the breakdown in<br>of PI may be involved in the positive inotro sitol phosphate formation and inotropic responses were<br>similar. In accordance with the view that the breakdown<br>of PI may be involved in the positive inotropic effect of<br> $\alpha_1$ -agonists is the finding that lithium, an inhi inder. In accordance with the view that the breakdown<br>of PI may be involved in the positive inotropic effect of<br> $\alpha_1$ -agonists is the finding that lithium, an inhibitor of<br>inositol phosphate hydrolysis, potentiates the p -agonists is the finding that lithium, an inhibitor of ino<br>ositol phosphate hydrolysis, potentiates the positive fib<br>otropic effect of  $\alpha_1$ -adrenoceptor agonists (Molderings med<br>Schümann, 1987; Skomedal et al., 1991).<br>I inositol phosphate hydrolysis, potentiates the positive filinotropic effect of  $\alpha_1$ -adrenoceptor agonists (Molderings m and Schümann, 1987; Skomedal et al., 1991). to If the hydrolysis of PIP<sub>2</sub> is an essential link in

inotropic effect of  $\alpha_1$ -adrenoceptor agonists (Molderings<br>and Schümann, 1987; Skomedal et al., 1991).<br>If the hydrolysis of PIP<sub>2</sub> is an essential link in the<br>pharmacomechanical coupling that follows the binding<br>of the and Schümann, 1987; Skomedal et al., 1991).<br>
If the hydrolysis of PIP<sub>2</sub> is an essential link in the<br>
pharmacomechanical coupling that follows the binding<br>
of the agonist to cardiac  $\alpha_1$ -adrenoceptors, then the in-<br>
hib If the hydrolysis of  $F1F_2$  is an essential fink in<br>pharmacomechanical coupling that follows the bind<br>of the agonist to cardiac  $\alpha_1$ -adrenoceptors, then the<br>hibition of  $\text{PIP}_2$  hydrolysis should block the inotre<br>effe pharmacomechanical coupling that follows the binding (13<br>of the agonist to cardiac  $\alpha_1$ -adrenoceptors, then the in-<br>hibition of PIP<sub>2</sub> hydrolysis should block the inotropic trig<br>effect of  $\alpha_1$ -adrenoceptor agonists. T effect of  $\alpha_1$ -adrenoceptor agonists. To test this hypothe-<br>sis, Otani et al. (1988) exposed papillary muscles labeled for<br>with [<sup>3</sup>H]inositol to 0.1 mM neomycin, a blocker of PIP<sub>2</sub> d<br>degradation. Neomycin inhibited [<sup></sup> sis, Otani et al. (1988) exposed papillary muscles labeled<br>with [<sup>3</sup>H]inositol to 0.1 mM neomycin, a blocker of  $\text{PIP}_2$ <br>degradation. Neomycin inhibited [<sup>3</sup>H]inositol phosphate<br>formation and diminished the inotropic eff

ST AL.<br>showed that another inhibitor of phospholipase C, 2-<br>nitro-4-carboxyphenyl-N,N diphenylcarbamate, also in-<br>hibits the positive inotropic effect of the  $\alpha_1$ -adrenoceptor ET AL.<br>showed that another inhibitor of phospholipase C,<br>nitro-4-carboxyphenyl-N,N diphenylcarbamate, also i<br>hibits the positive inotropic effect of the  $\alpha_1$ -adrenocept<br>agonist, methoxamine, in rat ventricular strips. H showed that another inhibitor of phospholipase C, 2 nitro-4-carboxyphenyl-N,N diphenylcarbamate, also inhibits the positive inotropic effect of the  $\alpha_1$ -adrenoceptoi agonist, methoxamine, in rat ventricular strips. Howe nitro-4-carboxyphenyl-N,N diphenylcarbamate, also inhibits the positive inotropic effect of the  $\alpha_1$ -adrenoceptor agonist, methoxamine, in rat ventricular strips. However, nitro-4-carboxyphenyl-N,N diphenylcarbamate, also inhibits the positive inotropic effect of the  $\alpha_1$ -adrenoceptor agonist, methoxamine, in rat ventricular strips. However, neither neomycin nor 2-nitro-4-carboxyphenyl-N, C. onist, methoxamine, in rat ventricular strips. However,<br>ither neomycin nor 2-nitro-4-carboxyphenyl-N,N di-<br>eenylcarbamate are specific inhibitors of phospholipase<br>In rat papillary muscle,  $\alpha_1$ -adrenoceptor stimulation<br>o phenylcarbamate are specific inhibitors of phospholipase<br>C.<br>In rat papillary muscle,  $\alpha_1$ -adrenoceptor stimulation

even when the Ca<sup>2+</sup> transient and the action potential the specific role of the two limbs of the PI turnover (IP<sub>3</sub> duration are decreased. Similarly, in rat cardiac cells, a and DAG-PKC) in the  $\alpha_1$ -adrenoceptor-media positive inotropic effect of phenylephrine can be ob-<br>served, at least in some cells, in the absence of an increase<br>in phoglyceric acid which inhibits IP<sub>3</sub> degradation; this<br>in intracellular Ca<sup>2+</sup> (Gambassi et al., 1992 origin, of the  $\alpha_1$ -adrenoceptor-mediated increase in car-<br>diac contractility.<br>b. IS THERE A CAUSAL RELATIONSHIP BETWEEN  $\alpha_1$ -<br>b. IS THERE A CAUSAL RELATIONSHIP BETWEEN  $\alpha_1$ -<br>adrenergic stimulation but that enhanced phenylcarbamate are specific inhibitors of phospholipase C.<br>
In rat papillary muscle,  $\alpha_1$ -adrenoceptor stimulation<br>
produces a triphasic inotropic response. To investigate<br>
the specific role of the two limbs of the PI C.<br>In rat papillary muscle,  $\alpha_1$ -adrenoceptor stimulation<br>produces a triphasic inotropic response. To investiga<br>the specific role of the two limbs of the PI turnover (I<br>and DAG-PKC) in the  $\alpha_1$ -adrenoceptor-mediated p In rat papillary muscle,  $\alpha_1$ -adrenoceptor stimula<br>produces a triphasic inotropic response. To investit<br>the specific role of the two limbs of the PI turnover<br>and DAG-PKC) in the  $\alpha_1$ -adrenoceptor-mediated p<br>tive inotr photonces a triphasic motropic response. To investigate<br>the specific role of the two limbs of the PI turnover (IP<sub>3</sub><br>and DAG-PKC) in the  $\alpha_1$ -adrenoceptor-mediated posi-<br>tive inotropic effect, Otani et al. (1988) used 2 the specific role of the two films of the F1 turnover (IF<sub>3</sub> and DAG-PKC) in the  $\alpha_1$ -adrenoceptor-mediated positive inotropic effect, Otani et al. (1988) used 2,3-diphos-phoglyceric acid which inhibits IP<sub>3</sub> degradatio tive inotropic effect, Otani et al. (1988) used 2,3-diphostive inotropic effect, Otani et al. (1988) used 2,3-diphos-<br>phoglyceric acid which inhibits  $IP_3$  degradation; this<br>molecule potentiated the  $\alpha_1$ -adrenergic mediated initial<br>phases (the transient positive and negative p phoglyceric acid which inhibits if  $_3$  degradation, this<br>molecule potentiated the  $\alpha_1$ -adrenergic mediated initial<br>phases (the transient positive and negative phases) but<br>had no effect on the sustained positive inotrop molecule potentiated the  $\alpha_1$ -adrenergic mediated initial<br>phases (the transient positive and negative phases) but<br>had no effect on the sustained positive inotropic re-<br>sponse. These authors concluded that  $\text{PIP}_2$  degr phases (the transient positive and negative phases) but<br>had no effect on the sustained positive inotropic re-<br>sponse. These authors concluded that  $\text{PIP}_2$  degradation<br>could play a role in the early inotropic response to onse. These authors concluded that  $\text{PIP}_2$  degradation<br>uld play a role in the early inotropic response to  $\alpha_1$ -<br>renergic stimulation but that enhanced IP<sub>3</sub> formation<br>mot explain the sustained positive inotropic respo

cardiac  $\alpha_1$ -adrenoceptors promotes the breakdown of PI, cardiac muscle cells. Studying saponin-skinned myocytes<br>producing IP<sub>3</sub> and DAG. The role of these molecules in and isolated sarcoplasmic reticulum, Movsesian et effect of  $\alpha_1$ -adrenoceptor agonists. To test this hypothe-<br>sis, Otani et al. (1988) exposed papillary muscles labeled following the flash impulse. However, the magnitude of<br>with [<sup>3</sup>H]inositol to 0.1 mM neomycin, a blo There is some controversy as to whether or not  $IP_3$ could play a role in the early inotropic response to  $\alpha_1$ -<br>adrenergic stimulation but that enhanced IP<sub>3</sub> formation<br>cannot explain the sustained positive inotropic response.<br>There is some controversy as to whether or no adrenergic stimulation but that enhanced IP<sub>3</sub> formation<br>cannot explain the sustained positive inotropic response.<br>There is some controversy as to whether or not IP<sub>3</sub><br>can release  $Ca^{2+}$  from the sarcoplasmic reticulum o cannot explain the sustained positive inotropic response.<br>There is some controversy as to whether or not  $IP_3$ <br>can release  $Ca^{2+}$  from the sarcoplasmic reticulum of<br>cardiac muscle cells. Studying saponin-skinned myocytes There is some controversy as  $\omega$  whether or not II 3<br>can release Ca<sup>2+</sup> from the sarcoplasmic reticulum of<br>cardiac muscle cells. Studying saponin-skinned myocytes<br>and isolated sarcoplasmic reticulum, Movsesian et al.<br>(19 cardiac muscle cells. Studying saponin-skinned myocytes<br>and isolated sarcoplasmic reticulum, Movsesian et al.<br>(1986) found no evidence that IP<sub>3</sub> (at concentrations up<br>to 50  $\mu$ M) can release Ca<sup>2+</sup> from the sarcoplasmic (1986) found no evidence that  $IP_3$  (at concentrations up<br>to 50  $\mu$ M) can release  $Ca^{2+}$  from the sarcoplasmic retic-<br>ulum. In saponin-skinned guinea pig papillary muscles,<br>Nosek et al. (1986) demonstrated that  $Ca^{2+}$ -(1580) found no evidence that If 3 (at concentrations up<br>to 50  $\mu$ M) can release  $Ca^{2+}$  from the sarcoplasmic retic<br>ulum. In saponin-skinned guinea pig papillary muscles<br>Nosek et al. (1986) demonstrated that  $Ca^{2+}$ -ind ulum. In saponin-skinned guinea pig papillary muscles,<br>Nosek et al. (1986) demonstrated that  $Ca^{2+}$ -induced force<br>oscillations are enhanced, in magnitude and frequency,<br>by IP<sub>3</sub> at concentrations as low as 1  $\mu$ M. IP<sub>3</sub> the magnitude of caffeine contractures,<br>Nosek et al. (1986) demonstrated that  $Ca^{2+}$ -induced force<br>oscillations are enhanced, in magnitude and frequency,<br>by IP<sub>3</sub> at concentrations as low as  $1 \mu$ M. IP<sub>3</sub> also increased<br> strose<br>a et al. (1500) demonstrated that Ca<sup>2</sup>-induced force<br>oscillations are enhanced, in magnitude and frequency<br>by IP<sub>3</sub> at concentrations as low as  $1 \mu$ M. IP<sub>3</sub> also increase<br>the magnitude of caffeine contractures, c by IP<sub>3</sub> at concentrations as low as  $1 \mu$ M. IP<sub>3</sub> also increased<br>the magnitude of caffeine contractures, caffeine being a<br>strong releaser of Ca<sup>2+</sup> from the sarcoplasmic reticulum.<br>In mechanically skinned cardiac cells, by II 3 at concentrations as tow as 1  $\mu$ m. II 3 also increased<br>the magnitude of caffeine contractures, caffeine being a<br>strong releaser of Ca<sup>2+</sup> from the sarcoplasmic reticulum.<br>In mechanically skinned cardiac cells, F the magnitude of caffeine contractures, caffeine being a strong releaser of  $Ca^{2+}$  from the sarcoplasmic reticulum.<br>In mechanically skinned cardiac cells, Fabiato (1986) showed that  $1,4,5$ -IP<sub>3</sub> induces a slow release o strong releaser of Ca<sup>2+</sup> from the sarcoplasmic reticulum.<br>In mechanically skinned cardiac cells, Fabiato (1986)<br>showed that 1,4,5-IP<sub>3</sub> induces a slow release of Ca<sup>2+</sup><br>which causes a tension transient. This tension tran In mechanically skinned cardiac cells, Fabiato (1986)<br>showed that  $1,4,5$ -IP<sub>3</sub> induces a slow release of Ca<sup>2+</sup><br>which causes a tension transient. This tension transient<br>increased from 3 to 15% of maximum tension when the showed that 1,4,5-IP<sub>3</sub> induces a slow release of Ca<br>which causes a tension transient. This tension transient<br>increased from 3 to 15% of maximum tension when the<br>concentration of 1,4,5-IP<sub>3</sub> was increased from 2 to 30  $\mu$ increased from 3 to 13% of maximum tension when the<br>concentration of  $1,4,5$ -IP<sub>3</sub> was increased from 2 to 30  $\mu$ M.<br>This author suggested that  $1,4,5$ -IP<sub>3</sub>-induced release of<br>Ca<sup>2+</sup> may play a role in the modulation of concentration of 1,4,5-1F<sub>3</sub> was increased from 2 to 3d.<br>This author suggested that  $1,4,5$ -IF<sub>3</sub>-induced releas<br>Ca<sup>2+</sup> may play a role in the modulation of Ca<sup>2+</sup> rel<br>by hormones or pharmacological agents. Recently, ina-This author suggested that  $1,4,5$ -IP<sub>3</sub>-induced release Ca<sup>2+</sup> may play a role in the modulation of Ca<sup>2+</sup> relea<br>by hormones or pharmacological agents. Recently, Mc<br>ina-Viamonte et al. (1990) explored whether phospholo<br>p  $Ca^{2+}$  may play a role in the modulation of  $Ca^{2+}$  release<br>by hormones or pharmacological agents. Recently, Mol-<br>ina-Viamonte et al. (1990) explored whether phospholi-<br>pase C (0.05 units/ml), when applied extracellularl by normones or pharmacological agents. Recentry, Mol-<br>ina-Viamonte et al. (1990) explored whether phospholi-<br>pase C (0.05 units/ml), when applied extracellularly,<br>increased Ca<sup>2+</sup> transients in isolated, paced Purkinje<br>fi pase C (0.05 units/ml), when applied extracellularly,<br>increased  $Ca^{2+}$  transients in isolated, paced Purkinje<br>fibers. Extracellularly applied phospholipase C aug-<br>mented intracellular IP<sub>3</sub>, suggesting a relationship beincreased Ca transients in isolated, paced rurking<br>fibers. Extracellularly applied phospholipase C aug-<br>mented intracellular IP<sub>3</sub>, suggesting a relationship be-<br>tween IP<sub>3</sub> generation and the size of the intracellular<br>Ca meers. Extracentuarly applied phosphonpase  $\sim$  augmented intracellular IP<sub>3</sub>, suggesting a relationship be-<br>tween IP<sub>3</sub> generation and the size of the intracellular<br>Ca<sup>2+</sup> transient in intact cardiac tissue. Kentish et a tween IP<sub>3</sub> generation and the size of the intracellular  $Ca^{2+}$  transient in intact cardiac tissue. Kentish et al. (1990) using the caged compound technique showed that photorelease of IP<sub>3</sub> in rat cardiac ventricular tr tween IP<sub>3</sub> generation and the size of the intracellula  $Ca^{2+}$  transient in intact cardiac tissue. Kentish et a (1990) using the caged compound technique showed the photorelease of IP<sub>3</sub> in rat cardiac ventricular trabec  $Ca^{2+}$  transient in intact cardiac tissue. Kentish et al. (1990) using the caged compound technique showed that photorelease of  $IP_3$  in rat cardiac ventricular trabeculae triggers the release of  $Ca^{2+}$  from the sarcopl (1990) using the caged compound technique showed that<br>photorelease of  $IP_3$  in rat cardiac ventricular trabeculae<br>triggers the release of  $Ca^{2+}$  from the sarcoplasmic retic-<br>ulum as indicated by the tension developed by photorelease of IP<sub>3</sub> in rat cardiac ventricular trabeculae<br>triggers the release of  $Ca^{2+}$  from the sarcoplasmic retic-<br>ulum as indicated by the tension developed by the muscle<br>following the flash impulse. However, the m ulum as indicated by the tension developed by the muscle<br>following the flash impulse. However, the magnitude of<br>developed tension was much smaller than that developed<br>in response to flashes that trigger  $Ca^{2+}$ -induced  $Ca$ ulum as indicated by the tension developed by the muscle following the flash impulse. However, the magnitude of developed tension was much smaller than that developed in response to flashes that trigger  $Ca^{2+}$ -induced  $Ca$ following the flash impulse. However, the magnitude of developed tension was much smaller than that developed in response to flashes that trigger  $Ca^{2+}$ -induced  $Ca^{2+}$ release. It was concluded that  $IP_3$  does not trigge

 $\begin{array}{cccc}\n\text{CARDIAC} & \alpha_1\text{-ADREN}\n\text{conclusions were drawn from saponin-skinned chick} & \text{the\n atrial muscle by Vites and Pappano (1990) who reported} & \text{size} & \text{size}$ CARDIAC  $\alpha_1$ -ADRE<br>conclusions were drawn from saponin-skinned chick the<br>atrial muscle by Vites and Pappano (1990) who reported site<br>that the tension developed in response to 20  $\mu$ M IP<sub>3</sub> il CARDIAC  $\alpha_1$ -ADRENC<br>conclusions were drawn from saponin-skinned chick the<br>atrial muscle by Vites and Pappano (1990) who reported sien<br>that the tension developed in response to 20  $\mu$ M IP<sub>3</sub> illar<br>(maximal effect) was h atrial muscle by Vites and Pappano (1990) who reported<br>that the tension developed in response to 20  $\mu$ M IP<sub>3</sub><br>(maximal effect) was half of the force amplitude recorded<br>in response to caffeine. Recently, Zhu and Nosek (1 atrial muscle by vies and rappano (1550) who reported<br>that the tension developed in response to 20  $\mu$ M IP<sub>3</sub> illary<br>(maximal effect) was half of the force amplitude recorded micro<br>in response to caffeine. Recently, Zhu that the tension developed in response to 20  $\mu$ M IP<sub>3</sub> (maximal effect) was half of the force amplitude recorded in response to caffeine. Recently, Zhu and Nosek (1991) investigated the effects of IP<sub>3</sub> on Ca<sup>2+</sup> releas (maximal effect) was half of the force amplitude recorded mid-<br>in response to caffeine. Recently, Zhu and Nosek (1991) pro<br>investigated the effects of  $IP_3$  on  $Ca^{2+}$  release from inc-<br>sarcoplasmic reticulum in skinned r in response to caffeine. Recently, Zhu and Nosek (199<br>investigated the effects of  $IP_3$  on  $Ca^{2+}$  release fre<br>sarcoplasmic reticulum in skinned rat papillary musc<br>Based on the notion that  $Ca^{2+}$ -induced  $Ca^{2+}$  release mvestigated the effects of  $\text{H}_3^3$  on Ca<sup>2</sup> release from increase same space. The sarcoplasmic reticulum shared ca<sup>2+</sup> release were distinct mechanisms for Ca<sup>2+</sup> release from the sarcoplasmic reticulum chanisms for Ca Based on the notion that  $Ca^{2+}$ -induced  $Ca^{2+}$  release and transpontaneous cyclic  $Ca^{2+}$  release were distinct mechanisms for  $Ca^{2+}$  release from the sarcoplasmic reticulum chifectlike change of  $Fa$  facilitates the sp spontaneous cyclic  $Ca^{2+}$  release from<br>(Fabiato, 1985), these aut<br>facilitates the spontaneous<br> $Ca^{2+}$ -induced  $Ca^{2+}$  release.<br>Even if  $IP_3$  could modula sms for Ca<sup>2+</sup> release from the sarcoplasmic reticului<br>abiato, 1985), these authors demonstrated that II<br>cilitates the spontaneous Ca<sup>2+</sup> release rather than th<br><sup>2+</sup>-induced Ca<sup>2+</sup> release.<br>Even if IP<sub>3</sub> could modulate th

(Fabiato, 1985), these authors demonstrated that facilitates the spontaneous Ca<sup>2+</sup> release rather than Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release.<br>Even if IP<sub>3</sub> could modulate the mobilization of in cellular Ca<sup>2+</sup>, the positive inot facilitates the spontaneous  $Ca^{2+}$  release rather than the<br>  $Ca^{2+}$ -induced  $Ca^{2+}$  release.<br>
Even if IP<sub>3</sub> could modulate the mobilization of intra-<br>
cellular  $Ca^{2+}$ , the positive inotropic effect of  $\alpha_1$ -adreno-<br>
ce Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release.<br>Even if IP<sub>3</sub> could modulate the mobilization of in<br>cellular Ca<sup>2+</sup>, the positive inotropic effect of  $\alpha_1$ -adre<br>ceptor agonists has been dissociated, at least in s<br>experimental conditions, Even if  $H_3$  could modulate the mobilization of intra-<br>cellular Ca<sup>2+</sup>, the positive inotropic effect of  $\alpha_1$ -adreno-<br>ceptor agonists has been dissociated, at least in some<br>experimental conditions, from an increase in 1992; Terzic et al., 1992a). Furthermore,  $\alpha_1$ -adrenoceptor experimental conditions, from an increase in intracellu-<br>lar Ca<sup>2+</sup> transients (Dirksen et al., 1991; Gambassi et al., 1992; Terzic et al., 1992a). Furthermore,  $\alpha_1$ -adrenoceptor<br>agonists are able to increase contractil lar Ca<sup>2+</sup> transients (Dirksei<br>1992; Terzic et al., 1992a). lagonists are able to increase<br>levels that can be achieved<br>(Terzic and Vogel, 1991).<br>In skeletal muscle, IP<sub>3</sub> ca 92; Terzic et al., 1992a). Furthermore,  $\alpha_1$ -adrenoceptor onists are able to increase contractile force above the vels that can be achieved by stimulators of Ca<sup>2+</sup> influx erzic and Vogel, 1991). In skeletal muscle, IP<sub></sub>

sensitivity of contractions in the above the levels that can be achieved by stimulators of  $Ca^{2+}$  influ (Terzic and Vogel, 1991).<br>In skeletal muscle, IP<sub>3</sub> can modulate the apparent Ca<sup>3</sup> sensitivity of contractile prote meyer, 1986). However, in rabbit papillary muscle, Nosek<br>
et al. (1990). However, in rabbit papillary muscle, Nosek<br>
et al. (1990) failed to demonstrate any effect of 30  $\mu$ M<br>
IP<sub>3</sub> on the Ca<sup>2+</sup> sensitivity of myofilame In skeletal muscle, IP<sub>3</sub> can modulate the apparent Ca<sup>2+</sup><br>sensitivity of contractile proteins (Thieleczek and Heil-<br>meyer, 1986). However, in rabbit papillary muscle, Nosek<br>et al. (1990) failed to demonstrate any effect et al. (1990). However, in rabbit papillary muscle, Nosek<br>et al. (1990) failed to demonstrate any effect of 30  $\mu$ M<br>IP<sub>3</sub> on the Ca<sup>2+</sup> sensitivity of myofilaments (cf. Scholz<br>et al., 1992a). Pucéat et al., (1990) obtain meyer, 15880). However, in rabolt papinary muscle, Nose<br>et al. (1990) failed to demonstrate any effect of 30  $\mu$ <br>IP<sub>3</sub> on the Ca<sup>2+</sup> sensitivity of myofilaments (cf. Scho<br>et al., 1992a). Pucéat et al., (1990) obtained si IP<sub>3</sub> on the Ca<sup>2+</sup> sensitivity of myofilaments (cf. Scholz<br>et al., 1992a). Pucéat et al., (1990) obtained similar<br>results in single isolated chemically skinned rat ventric-<br>ular cells, a model in which molecular diffusio mediate in single isolated chemically skinned rat ventricular cells, a model in which molecular diffusion is facilitated. In summary, it appears that  $IP_3$  alone cannot mediate the sustained positive inotropic effect of tated. In summary, it appears that  $IP_3$  alone cannot mediate the sustained positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists. This conclusion is also supported by the observation that  $IP_3$  is only transiently in adrenoceptor agonists. This conclusion is also supported<br>by the observation that IP<sub>3</sub> is only transiently increased<br>following  $\alpha_1$ -adrenoceptor stimulation, whereas the pos-<br>itive inotropic effect is sustained.<br>In frog renoceptor agonists. This conclusion is also supported<br>the observation that IP<sub>3</sub> is only transiently increased<br>llowing  $\alpha_1$ -adrenoceptor stimulation, whereas the pos-<br>ve inotropic effect is sustained.<br>In frog heart cel

by the observation that IP<sub>3</sub> is only transiently increased<br>following  $\alpha_1$ -adrenoceptor stimulation, whereas the pos-<br>itive inotropic effect is sustained.<br>In frog heart cells, the  $\alpha_1$ -adrenergic response occurs<br>witho following  $\alpha_1$ -adrenoceptor stimulation, whereas the positive inotropic effect is sustained.<br>In frog heart cells, the  $\alpha_1$ -adrenergic response occusition at change in the action potential overshoot a with a less prono itive inotropic effect is sustained.<br>
In frog heart cells, the  $\alpha_1$ -adrenergic response occurs<br>
without a change in the action potential overshoot and<br>
with a less pronounced lengthening of the action poten-<br>
tial durat with a less pronounced lengthening of the action potential duration than during the  $\beta$ -adrenergic action. Based<br>on the observation that caffeine prevents the  $\alpha_1$ -adre-<br>nergic inotropic response, Niedergerke and Page without a change in the action potential overshoot and<br>with a less pronounced lengthening of the action poten-<br>tial duration than during the  $\beta$ -adrenergic action. Based<br>on the observation that caffeine prevents the  $\alpha_$ with a less pronounced lengthening of the action potential duration than during the  $\beta$ -adrenergic action. Based<br>on the observation that caffeine prevents the  $\alpha_1$ -adrenergic inotropic response, Niedergerke and Page (1 tial duration than during the  $\beta$ -adrenergic action. Based<br>on the observation that caffeine prevents the  $\alpha_1$ -adre-<br>nergic inotropic response, Niedergerke and Page (1989) oper<br>proposed that adrenoceptors facilitate  $Ca^{$ on the observation that caffeine prevents the  $\alpha_1$ -adre-<br>nergic inotropic response, Niedergerke and Page (1989)<br>proposed that adrenoceptors facilitate  $Ca^{2+}$  discharge<br>from the sarcoplasmic reticulum without requiring nergic inotropic response, Niedergerke and Page (198<br>proposed that adrenoceptors facilitate  $Ca^{2+}$  dischar<br>from the sarcoplasmic reticulum without requiring<br>increase in the  $I_{Ca}$  or in the process of  $Ca^{2+}$ -induced Ca<br> proposed that adrenoceptors facilitate  $Ca^{2+}$  discharge<br>from the sarcoplasmic reticulum without requiring an<br>increase in the  $I_{Ca}$  or in the process of  $Ca^{2+}$ -induced  $Ca^{2+}$ <br>release; such a facilitation would result f from the sarcoplasmic reticulum without requiring an estation increase in the  $I_{Ca}$  or in the process of  $Ca^{2+}$ -induced  $Ca^{2+}$  presponsiveness; such a facilitation would result from the forma-<br>vertion of IP<sub>3</sub>. However increase in the  $I_{Ca}$  or in the process of  $Ca^{2+}$ -induced  $Ca^{2+}$  Frelease; such a facilitation would result from the formation of IP<sub>3</sub>. However, it should be kept in mind that the caffeine also increases myofibrillar conclusion. ffeine also increases myofibrillar responsiveness to left that  $a^{2+}$ , a phenomenon that could lead to a misleading medicion.<br>
c. EVIDENCE THAT  $\alpha_1$ -ADRENOCEPTOR STIMULATION WEREASES THE MYOFIBRILLAR RESPONSIVENESS TO

Ca<sup>2+</sup>, a phenomenon that could lead to a misleading meas<br>conclusion.<br>c. EVIDENCE THAT  $\alpha_1$ -ADRENOCEPTOR STIMULATION which<br>INCREASES THE MYOFIBRILLAR RESPONSIVENESS TO with<br>CA<sup>2+</sup>. COULD THE DIACYLGLYCEROL LIMB PLAY A R conclusion. <br>
c. EVIDENCE THAT  $\alpha_1$ -ADRENOCEPTOR STIMULATION wh<br>
INCREASES THE MYOFIBRILLAR RESPONSIVENESS TO wit<br>
CA<sup>2+</sup>. COULD THE DIACYLGLYCEROL LIMB PLAY A ROLE wh<br>
IN MEDIATING THE EFFECTS OF  $\alpha_1$ -ADRENOCEPTOR AG C. EVIDENCE THAT  $\alpha_1$ -ADRENOCEPTOR STIMULATION<br>INCREASES THE MYOFIBRILLAR RESPONSIVENESS TO<br>CA<sup>2+</sup>. COULD THE DIACYLGLYCEROL LIMB PLAY A ROLE<br>IN MEDIATING THE EFFECTS OF  $\alpha_1$ -ADRENOCEPTOR AG-<br>ONISTS ON CONTRACTILE FOR INCREASES THE MYOFIBRILLAR RESPONSIVENESS TO<br>CA<sup>2+</sup>. COULD THE DIACYLGLYCEROL LIMB PLAY A ROLE<br>IN MEDIATING THE EFFECTS OF  $\alpha_1$ -ADRENOCEPTOR AG-<br>ONISTS ON CONTRACTILE FORCE AND MYOFIBRILLAR<br>SENSITIZATION? Endoh and Blin

ENOCEPTORS 16<br>the effects of sympathomimetic amines on  $Ca^{2+}$  tran-<br>sients and isometric contractions in isolated rabbit pap ENOCEPTORS 161<br>the effects of sympathomimetic amines on  $Ca^{2+}$  tran-<br>sients and isometric contractions in isolated rabbit pap-<br>illary muscles in which multiple superficial cells had been<br>microinjected with the  $Ca^{2+}$ -se the effects of sympathomimetic amines on  $Ca^{2+}$  transients and isometric contractions in isolated rabbit paillary muscles in which multiple superficial cells had been<br>microinjected with the  $Ca^{2+}$ -sensitive bioluminesce the effects of sympathomimetic amines on  $Ca^{2+}$  transients and isometric contractions in isolated rabbit papillary muscles in which multiple superficial cells had been microinjected with the  $Ca^{2+}$ -sensitive bioluminesc illary muscles in which multiple superficial cells had been<br>microinjected with the  $Ca^{2+}$ -sensitive bioluminescent<br>protein aequorin. These authors found that the modest<br>increase in  $Ca^{2+}$  transient produced by phenyleph mary muscles in which mattiple superficial cents had been<br>microinjected with the  $Ca^{2+}$ -sensitive bioluminescen<br>protein aequorin. These authors found that the modes<br>increase in  $Ca^{2+}$  transient produced by phenylephrino protein aequorin. These authors found that the modest<br>increase in Ca<sup>2+</sup> transient produced by phenylephrine<br>was associated with a prominent increase in twitch con-<br>tractile force. For a given increase in the force of con increase in  $Ca^{2+}$  transient produced by phenylephrine<br>was associated with a prominent increase in twitch con-<br>tractile force. For a given increase in the force of con-<br>traction,  $\alpha_1$ -adrenoceptor stimulation induces a tractile force. For a given increase in the force of contractile force. For a given increase in the force of con-<br>traction,  $\alpha_1$ -adrenoceptor stimulation induces a smaller<br>change in the amplitude of the  $Ca^{2+}$  transient than did<br>other positive inotropic interventions. That traction,  $\alpha_1$ -adrenoceptor stimulation induces a smaller<br>change in the amplitude of the Ca<sup>2+</sup> transient than did<br>other positive inotropic interventions. That is, the rela-<br>tion between the force developed and the ampl tion between the force developed and the amplitude of the aequorin signal is much steeper when the force is<br>increased by  $\alpha_1$ -adrenergic stimulation than when it is<br>altered by other positive inotropic interventions. The<br>suggestion was that the  $\alpha_1$ -adrenoceptor agonists increased by  $\alpha_1$ -adrenergic stimulation than when it is<br>altered by other positive inotropic interventions. The<br>suggestion was that the  $\alpha_1$ -adrenoceptor agonists should<br>increase the myofibrillar  $Ca^{2+}$  sensitivity ( altered by other positive in<br>suggestion was that the  $\alpha_1$ -ad<br>increase the myofibrillar C<sub>4</sub><br>Blinks, 1988; Endoh, 1986).<br>Subsequently, Capogrossi

other positive inotropic interventions. That is, the rela-<br>tion between the force developed and the amplitude of<br>the aequorin signal is much steeper when the force is<br>increased by  $\alpha_1$ -adrenergic stimulation than when i Subsequently, Capogrossi et al. (1988) simultaneously<br>measured cytosolic  $Ca^{2+}$  and twitch amplitude in Indo-<br>1-loaded cardiomyocytes. For a given  $Ca^{2+}$  transient,  $\alpha_1$ increase the myofibrillar  $Ca^{2+}$  sensitivity (Endoh and Blinks, 1988; Endoh, 1986).<br>
Subsequently, Capogrossi et al. (1988) simultaneously<br>
measured cytosolic  $Ca^{2+}$  and twitch amplitude in Indo-<br>
1-loaded cardiomyocyte Blinks, 1988; Endoh, 1986).<br>
Subsequently, Capogrossi et al. (1988) simultaneously<br>
measured cytosolic Ca<sup>2+</sup> and twitch amplitude in Indo-<br>
1-loaded cardiomyocytes. For a given Ca<sup>2+</sup> transient,  $\alpha_1$ -<br>
adrenoceptor ago dissequently, capogrossi et al. (1505) simulatieously<br>measured cytosolic Ca<sup>2+</sup> and twitch amplitude in Indo<br>1-loaded cardiomyocytes. For a given Ca<sup>2+</sup> transient,  $\alpha_1$ <br>adrenoceptor agonists increased, whereas  $\beta$ -adre measured cytosolic Ca<sup>2+</sup> and twitch amplitude in Indo-<br>1-loaded cardiomyocytes. For a given Ca<sup>2+</sup> transient,  $\alpha_1$ -<br>adrenoceptor agonists increased, whereas  $\beta$ -adrenoceptor<br>agonists decreased, twitch amplitude. These adrenoceptor agonists increased, whereas  $\beta$ -adrenoceptor agonists decreased, twitch amplitude. These authors coluded that  $\alpha_1$ - and  $\beta$ -adrenoceptor stimulation produpposite effects on myofibrillar sensitivity to Ca<sup></sup> agonists decreased, twitch amplitude. These authors concluded that  $\alpha_1$ - and  $\beta$ -adrenoceptor stimulation produce opposite effects on myofibrillar sensitivity to  $Ca^{2+}$  (Gambassi et al., 1992). Thus, the principle tha diately and  $\beta$ -difference the responsive opposite effects on myofibrillar sensitivity to Ca<sup>2+</sup> (Gam-<br>bassi et al., 1992). Thus, the principle that  $\alpha_1$ -adrenergic<br>stimulation increases the responsiveness of myofibril cluded that  $\alpha_1$ - and  $\beta$ -adrenoceptor stimulation<br>opposite effects on myofibrillar sensitivity to bassi et al., 1992). Thus, the principle that  $\alpha_1$ <br>stimulation increases the responsiveness of m<br>Ca<sup>2+</sup> was confirmed besic crices on myomorinal schictivity to Ca<sup>1</sup> (Gansilver) since that  $\alpha_1$ -adrenerg mulation increases the responsiveness of myofibrils  $1^{2+}$  was confirmed for single cardiac cells.<br>It also has been postulated that

bassis et al., 1992). Thus, the principle that  $\alpha_1$ -adrentergies<br>stimulation increases the responsiveness of myofibrils to<br>Ca<sup>2+</sup> was confirmed for single cardiac cells.<br>It also has been postulated that  $\alpha_1$ -adrencept Ca<sup>2+</sup> was confirmed for single cardiac cells.<br>Ca<sup>2+</sup> was confirmed for single cardiac cells.<br>It also has been postulated that  $\alpha_1$ -adrenoceptor ago<br>mists increase the myofibrillar response to Ca<sup>2+</sup> based on<br>the effect re also has been posturated that  $\alpha_1$  addenberghor age<br>mists increase the myofibrillar response to  $Ca^{2+}$  based on<br>the effects of  $\alpha_1$ -agonists on the parameters of the con-<br>traction-relaxation cycle (see section V.A the effects of  $\alpha_1$ -agonists on the parameters of the contraction-relaxation cycle (see section V.A.1) which strikingly resemble those induced by an increase in the length of the sarcomeres. The latter has been associat traction-relaxation cycle (see section V.A.1) which<br>ingly resemble those induced by an increase in the<br>of the sarcomeres. The latter has been associate<br>an enhancement of myofibrillar sensitivity to<br>(Meulemans et al., 1990 gly resemble those induced by an increase in the length<br>the sarcomeres. The latter has been associated with<br>enhancement of myofibrillar sensitivity to  $Ca^{2+}$ <br>feulemans et al., 1990; Li and Rouleau, 1991).<br>Definite eviden

of the sarcomeres. The latter has been associated with<br>an enhancement of myofibrillar sensitivity to Ca<sup>2+</sup><br>(Meulemans et al., 1990; Li and Rouleau, 1991).<br>Definite evidence that  $\alpha_1$ -adrenoceptor agonists indeed<br>produc an enhancement of myofibrillar sensitivity to  $Ca^{2+}$ <br>(Meulemans et al., 1990; Li and Rouleau, 1991).<br>Definite evidence that  $\alpha_1$ -adrenoceptor agonists indeed<br>produce a myofibrillar sensitization to  $Ca^{2+}$  ions was<br>obt (we<br>use mains et al., 1550, Li and Rouleau, 1551).<br>Definite evidence that  $\alpha_1$ -adrenoceptor agonists inde<br>produce a myofibrillar sensitization to Ca<sup>2+</sup> ions we<br>obtained by Pucéat et al (1990). A preparation of isolat<br>c produce a myohorinal sensulation  $\omega$  Ca rolls was<br>obtained by Pucéat et al (1990). A preparation of isolated<br>chemically skinned cells was used, and the force devel-<br>oped by a single cell in response to various  $Ca^{2+}$ -co chemically skinned cells was used, and the force devel-<br>oped by a single cell in response to various  $Ca^{2+}$ -contain-<br>ing solutions was measured. This protocol was used to<br>establish a tension-pCa relationship in the absen oped by a single cell in response to various  $Ca^{2+}$ -containing solutions was measured. This protocol was used to establish a tension-pCa relationship in the absence or presence of phenylephrine pretreatment. When cells w ing solutions was measured. This protocol was used to<br>establish a tension-pCa relationship in the absence or<br>presence of phenylephrine pretreatment. When cells<br>were preexposed to phenylephrine before skinning, the<br>tensionestablish a tension-pCa relationship in the absence or<br>presence of phenylephrine pretreatment. When cells<br>were preexposed to phenylephrine before skinning, the<br>tension-pCa curve was significantly shifted toward the<br>left. presence of phenylephrine pretreatment. When cells<br>were preexposed to phenylephrine before skinning, the<br>tension-pCa curve was significantly shifted toward the<br>left. Thereby, it was demonstrated independently of<br>measuring were preexposed to phenylephrine before skinning, the tension-pCa curve was significantly shifted toward the left. Thereby, it was demonstrated independently of measuring intracellular  $Ca^{2+}$  that phenylephrine increased tension-pCa curve was significantly shifted toward the left. Thereby, it was demonstrated independently of measuring intracellular  $Ca^{2+}$  that phenylephrine increased the  $Ca^{2+}$  sensitivity of myofilaments. The pCa<sub>50</sub>, left. Thereby, it was demonstrated independently of measuring intracellular  $Ca^{2+}$  that phenylephrine increased the  $Ca^{2+}$  sensitivity of myofilaments. The pCa<sub>50</sub>, which is increased following the treatment of the cell creased the Ca<sup>2+</sup> sensitivity of myofilaments. The pCa<sub>50</sub>, which is increased following the treatment of the cells with  $\alpha_1$ -adrenoceptor agonists, returned to control values when alkaline phosphatase was applied to s creased the Ca<sup>2+</sup> sensitivity of myofilaments. The pCa<sub>50</sub>,<br>which is increased following the treatment of the cells<br>with  $\alpha_1$ -adrenoceptor agonists, returned to control values<br>when alkaline phosphatase was applied to s which is increased following the treatment of the cells<br>with  $\alpha_1$ -adrenoceptor agonists, returned to control values<br>when alkaline phosphatase was applied to skinned cells.<br>Thus, contrary to  $\beta$ -adrenoceptor agonists, w with  $\alpha_1$ -adrenoceptor agonists, returned to control values<br>when alkaline phosphatase was applied to skinned cells.<br>Thus, contrary to  $\beta$ -adrenoceptor agonists, which are<br>known to decrease the Ca<sup>2+</sup> sensitivity of myo

nists are "sensitizing" cardiotonic agents (Pucéat et al., 1990, 1992; Terzic et al., 1992a).<br>
Some evidence suggests that PKC activators mimic

TERZIC ET<br>sts are "sensitizing" cardiotonic agents (Pucéat et al., w<br>90, 1992; Terzic et al., 1992a).<br>Some evidence suggests that PKC activators mimic W<br>ceptor-mediated myofibrillar sensitization. Pucéat et  $\alpha$ receptor-mediated myofibrical materials. The evidence suggests that PKC activators mimic<br>
Some evidence suggests that PKC activators mimic<br>
receptor-mediated myofibrillar sensitization. Pucéat et<br>
al. (1990) demonstrated, nists are "sensitizing" cardiotonic agents (Pucéat et al., 1990, 1992; Terzic et al., 1992a).<br>
Some evidence suggests that PKC activators mimic<br>
receptor-mediated myofibrillar sensitization. Pucéat et<br>
al. (1990) demonstra 1990, 1992; Terzic et al., 1992a).<br>
Some evidence suggests that PKC activators mimic<br>
receptor-mediated myofibrillar sensitization. Pucéat et<br>
al. (1990) demonstrated, in skinned rat myocardial cells,<br>
that the application Some evidence suggests that PKC activators m<br>receptor-mediated myofibrillar sensitization. Pucée<br>al. (1990) demonstrated, in skinned rat myocardial c<br>that the application of PKC cell-permeant active<br>prior to skinning incr neceptor-ineurated informal sensitization. I detail et  $a_1$ -<br>al. (1990) demonstrated, in skinned rat myocardial cells, Na<br>that the application of PKC cell-permeant activators 199<br>prior to skinning increases the myofibril that the application of PKC cell-permeant activators 1999;<br>prior to skinning increases the myofibrillar responsive-<br>ness to  $Ca^{2+}$ , as indicated by a leftward shift of the port<br>tension-pCa relationship. The leftward shif prior to skinning increases the myofibrillar responsiveness to  $Ca^{2+}$ , as indicated by a leftward shift of the ptension-pCa relationship. The leftward shift was also creversed by the application of alkaline phosphatase t ness to  $Ca^{2+}$ , as indicated by a leftward shift of the tension-pCa relationship. The leftward shift was also reversed by the application of alkaline phosphatase to the skinned cells. This would imply that PKC activation tension-pCa relationship. The leftward shift was also reversed by the application of alkaline phosphatase to the skinned cells. This would imply that PKC activation causes a phosphorylation of the contractile proteins, th reversed by the application of alkaline phosphatase to ex-<br>the skinned cells. This would imply that PKC activation ide<br>causes a phosphorylation of the contractile proteins, tra-<br>thereby producing the observed increase in causes a phosphorylation of the contractile proteins, tractile force produced by phenylephrine in multicellular<br>thereby producing the observed increase in myofibrillar (Terzic and Vogel, 1990, 1991; Otani et al., 1990) or causes a phosphorylation of the contractile proteins,<br>thereby producing the observed increase in myofibrillar<br>Ca<sup>2+</sup> responsiveness. It is important to note that the<br>direct application of PKC, purified from bovine brain, thereby producing the observed increase in myofibrillar ( $\text{Ca}^{2+}$  responsiveness. It is important to note that the undirect application of PKC, purified from bovine brain, to by skinned fibers was ineffective in alteri  $Ca^{2+}$  responsiveness. It is important to note that direct application of PKC, purified from bovine brain, skinned fibers was ineffective in altering the myofibril responsiveness to  $Ca^{2+}$ , whereas the application  $cAMP$ direct application of FKC, purified from bovine brain, to by skinned fibers was ineffective in altering the myofibrillar ion responsiveness to  $Ca^{2+}$ , whereas the application of edical cAMP-dependent protein kinase decrea cAMP-dependent protein kinase decreased the myofila-<br>ment response. Hence, PKC per se appeared not to<br>directly cause the enhanced responsiveness of myofibrils.<br>However, the authors could not totally exclude the hy-<br>pothesi cAMP-dependent protein kinase decreased the myofila-<br>ment response. Hence, PKC per se appeared not to lin<br>directly cause the enhanced responsiveness of myofibrils. pl<br>However, the authors could not totally exclude the hy-<br> the brain PKC per se appeared not to the<br>directly cause the enhanced responsiveness of myofibrils. pl<br>However, the authors could not totally exclude the hy-<br>pothesis that the lack of effect of PKC could be related<br>in to th However, the authors could not totally exclude the hy-<br>pothesis that the lack of effect of PKC could be related ius<br>to the brain PKC preparation they used. Indeed, the<br>or PKC isozyme profile is different in brain and hear pothesis that the lack of effect of PKC could be rel<br>to the brain PKC preparation they used. Indeed,<br>PKC isozyme profile is different in brain and heart<br>review, see Kikkawa et al., 1989). More specifically,<br>preparation use we the brain PKC preparation they used. Indeed, the one<br>PKC isozyme profile is different in brain and heart (for<br>review, see Kikkawa et al., 1989). More specifically, the the<br>preparation used did not contain the minor  $Ca^{$ PKC isozyme profile is different in brain and heart (review, see Kikkawa et al., 1989). More specifically, the preparation used did not contain the minor  $Ca^{2+}$ -insestive isoforms of the kinase. In harmony with such hypo review, see Kikkawa et al., 1989). More specifically, the preparation used did not contain the minor  $Ca^{2+}$ -insensitive isoforms of the kinase. In harmony with such an hypothesis, Collins et al. (1992), using a PKC pseud preparation used did not contain the minor Ca<sup>2+</sup>-inses<br>sitive isoforms of the kinase. In harmony with such a<br>hypothesis, Collins et al. (1992), using a PKC pseud<br>substrate inhibitor, showed that a Ca<sup>2+</sup>-independent i<br>of sitive isoforms of the kinase. In harmony with such an hypothesis, Collins et al. (1992), using a PKC pseudo-substrate inhibitor, showed that a Ca<sup>2+</sup>-independent isoform of PKC mediated the  $\alpha_1$ -adrenoceptor-induced co exponses. Coming et al. (1992), using a 1 NC pseudo-<br>substrate inhibitor, showed that a Ca<sup>2+</sup>-independent is-<br>oform of PKC mediated the  $\alpha_1$ -adrenoceptor-induced B<br>contraction in ferret aorta cells. Moreover, Khalil et substrate inhibitor, showed that a Ca<sup>2+</sup>-independent is-<br>oform of PKC mediated the  $\alpha_1$ -adrenoceptor-induced Bountra and Vaughan-Jones, 1989; Lagadic-Gossmann<br>contraction in ferret aorta cells. Moreover, Khalil et al., contraction in ferret aorta cells. Moreover, Khalil et al., contraction in ferret aorta cells. Moreover, Khalil et al.,<br>(1992), using the same preparation, reported that the<br>translocation of the Ca<sup>2+</sup>-independent isozyme  $\epsilon$  of PKC<br>was involved in the Ca<sup>2+</sup>-independent contract (1992), using the same preparation, reported that the translocation of the Ca<sup>2+</sup>-independent isozyme  $\epsilon$  of PKC e was involved in the Ca<sup>2+</sup>-independent contraction in-<br>duced by phenylephrine in this tissue. It was post was involved in the  $Ca^{2+}$ -independent contraction in-<br>duced by phenylephrine in this tissue. It was postulated<br>that an additional protein kinase that may be activated<br>by PKC could be responsible for the myofibrillar sen duced by phenylephrine in this tissue. It was postulated<br>that an additional protein kinase that may be activated<br>by PKC could be responsible for the myofibrillar sensi-<br>tization. MLC kinase could be this additional kinase. that an additional protein kinase that may be activated<br>by PKC could be responsible for the myofibrillar sensi-<br>tization. MLC kinase could be this additional kinase.<br>Indeed, this kinase which specifically phosphorylates<br>ML that an additional protein kinase that may be activated<br>by PKC could be responsible for the myofibrillar sensi-<br>tization. MLC kinase could be this additional kinase.<br>Indeed, this kinase which specifically phosphorylates<br>ML by PKC could be responsible for the myofibrillar sensi-<br>tization. MLC kinase could be this additional kinase.<br>Indeed, this kinase which specifically phosphorylates<br>MLC-2 (for review, see Barany and Barany, 1980) in-<br>creas tization. MLC kinase could be this additional kinase. di-<br>Indeed, this kinase which specifically phosphorylates  $\alpha_1$ <br>MLC-2 (for review, see Barany and Barany, 1980) in-<br>creases the Ca<sup>2+</sup> sensitivity of cardiac myofilam Indeed, this kinase which specifically phosphoryla MLC-2 (for review, see Barany and Barany, 1980) creases the  $Ca^{2+}$  sensitivity of cardiac myofilame:<br>(Morano et al., 1985; Clément et al., 1992). The abile of PKC to enh xation of the mystem of the mystem of the myofilaments dependence al., 1985; Clément et al., 1992). The ability of PKC to enhance MLC kinase-induced Ca<sup>2+</sup> sensitization of the myofilaments has been reported in skinned th (Morano et al., 1985; Clément et al., 1992). The ability<br>of PKC to enhance MLC kinase-induced  $Ca^{2+}$  sensiti-<br>zation of the myofilaments has been reported in skinned<br>cardiomyocytes (Clément et al., 1992).<br>In addition to of PKC to enhance MLC kinase-induced  $Ca^{2+}$  sensiti-

of PKC to enhance MLC kinase-induced Ca<sup>2+</sup> sensitization of the myofilaments has been reported in skinned cardiomyocytes (Clément et al., 1992).<br>In addition to sensitizing the myofibrils via phosphor-<br>ylation,  $\alpha_1$ -adr zation of the myofilaments has been reported in skinned<br>
cardiomyocytes (Clément et al., 1992). int<br>
In addition to sensitizing the myofibrils via phosphor-<br>
ylation,  $\alpha_1$ -adrenoceptor agonists also could conceivably Ma cardiomyocytes (Clément et al., 1992).<br>
In addition to sensitizing the myofibrils via phosphor-<br>
ylation,  $\alpha_1$ -adrenoceptor agonists also could conceivably<br>
augment myofibrillar responsiveness to Ca<sup>2+</sup> through an<br>
intr In addition to sensitizing the myofibrils via phosphor-<br>ylation,  $\alpha_1$ -adrenoceptor agonists also could conceivably<br>augment myofibrillar responsiveness to  $Ca^{2+}$  through an<br>intracellular alkalinization. An increase in p augment myofibrillar responsiveness to  $Ca^{2+}$  through an intracellular alkalinization. An increase in pH<sub>i</sub> produces a positive inotropic effect (Vaughan-Jones et al., 1987) which is, in part, due to an increase in myofi augment myofibrillar responsiveness to  $Ca^{2+}$  through an<br>intracellular alkalinization. An increase in pH<sub>i</sub> produces<br>in<br>a positive inotropic effect (Vaughan-Jones et al., 1987) 19<br>which is, in part, due to an increase in intracellular alkalinization. An increase in pH<sub>i</sub> produces in a positive inotropic effect (Vaughan-Jones et al., 1987) 198 which is, in part, due to an increase in myofibrillar Ca<sup>2+</sup> 199 sensitivity (Fabiato and Fabiato sensitivity (Fabiato and Fabiato, 1978). Although pH<sub>i</sub> is in rabbit (Kushida et al., 1988) or rat papillary muscles<br>a major regulator of cardiac excitation-contraction cou-<br>pling (Kurachi, 1982; Solaro et al., 1988; Orch Kentish, 1990), pharmacological modulation of  $pH_i$  has

<sup>e</sup><br>which cardiac contractility could be regulated (Terzic<br>and Vogel, 1990; Krämer et al., 1991; Terzic et al., 1992a; <sup>er</sup> AL.<br>which cardiac contractility could be regulated (Terzic<br>and Vogel, 1990; Krämer et al., 1991; Terzic et al., 1992a;<br>Wang and Morgan, 1992). As described in section IV.B, ET AL.<br>which cardiac contractility could be regulated (Terzic<br>and Vogel, 1990; Krämer et al., 1991; Terzic et al., 1992a;<br>Wang and Morgan, 1992). As described in section IV.B,<br> $\alpha_1$ -adrenoceptor agonists elevate pH<sub>i</sub> by which cardiac contractility could be regulated (Terzic and Vogel, 1990; Krämer et al., 1991; Terzic et al., 1992a; Wang and Morgan, 1992). As described in section IV.B,  $\alpha_1$ -adrenoceptor agonists elevate pH<sub>i</sub> by activa winch caluat contractinty could be regulated (Terzic<br>and Vogel, 1990; Krämer et al., 1991; Terzic et al., 1992a;<br>Wang and Morgan, 1992). As described in section IV.B,<br> $\alpha_1$ -adrenoceptor agonists elevate pH<sub>i</sub> by activati ang and Morgan, 1992). As described in section IV.B -adrenoceptor agonists elevate pH<sub>i</sub> by activating the a<sup>+</sup>/H<sup>+</sup> antiport (Iwakura et al., 1990; Terzic et al. 92a; Wallert and Fröhlich, 1992; Pucéat et al., 1993a) Sev

 $\alpha_1$ -adrenoceptor agonists elevate pH<sub>i</sub> by activating the Na<sup>+</sup>/H<sup>+</sup> antiport (Iwakura et al., 1990; Terzic et al., 1992a; Wallert and Fröhlich, 1992; Pucéat et al., 1993a). Several findings indicate that the activity 1992a; Wallert and Fröhlich, 1992; Pucéat et al., 1993a).<br>Several findings indicate that the activity of the anti-<br>porter could participate in the positive inotropic effects<br>of  $\alpha_1$ -adrenoceptor agonists. First, inhibit 1992a; Wallert and Fröhlich, 1992; Pucéat et al.,<br>Several findings indicate that the activity of the<br>porter could participate in the positive inotropic<br>of  $\alpha_1$ -adrenoceptor agonists. First, inhibition of  $\Gamma$ <br>exchange b Several findings indicate that the activity of the anti-<br>porter could participate in the positive inotropic effects<br>of  $\alpha_1$ -adrenoceptor agonists. First, inhibition of Na<sup>+</sup>/H<sup>+</sup><br>exchange by selective blockers (e.g., he porter could participate in the positive inotropic enects<br>of  $\alpha_1$ -adrenoceptor agonists. First, inhibition of Na<sup>+</sup>/H<sup>+</sup><br>exchange by selective blockers (e.g., hexamethylamilor-<br>ide, ethylisopropylamiloride) inhibits the exchange by selective blockers (e.g., hexamethylamiloride, ethylisopropylamiloride) inhibits the increase in contractile force produced by phenylephrine in multicellular (Terzic and Vogel, 1990, 1991; Otani et al., 1990) o de, emynsopropyrammorde) inmotes the increase in con-<br>tractile force produced by phenylephrine in multicellular<br>(Terzic and Vogel, 1990, 1991; Otani et al., 1990) or<br>unicellular cardiac preparations (Gambassi et al., 1992 That is that cannot be produced by phenylephrime in mutteentum<br>
(Terzic and Vogel, 1990, 1991; Otani et al., 1990)<br>
unicellular cardiac preparations (Gambassi et al., 1990)<br>
by at least 50%. Similarly, ionic substitution (Terzic and Vogel, 1990, 1991; Otani et al., 1990<br>unicellular cardiac preparations (Gambassi et al., 1<br>by at least 50%. Similarly, ionic substitution of Na<sup>+</sup><br>ions that cannot replace Na<sup>+</sup> in Na<sup>+</sup>/H<sup>+</sup> exchange m<br>edly r unicellular cardiac preparations (Gambassi et al., 1992)<br>by at least 50%. Similarly, ionic substitution of Na<sup>+</sup> with<br>ions that cannot replace Na<sup>+</sup> in Na<sup>+</sup>/H<sup>+</sup> exchange mark-<br>edly reduces the positive inotropic action ions that cannot replace Na<sup>+</sup> in Na<sup>+</sup>/H<sup>+</sup> exchange markedly reduces the positive inotropic action of phenylephrine. Specifically, it is known that lithium, but not choline, will exchange for H<sup>+</sup> via the Na<sup>+</sup>/H<sup>+</sup> ant ions that cannot replace Na<sup>+</sup> in Na<sup>+</sup>/H<sup>+</sup> exchange mark-<br>edly reduces the positive inotropic action of phenyleph-<br>rine. Specifically, it is known that lithium, but not cho-<br>line, will exchange for H<sup>+</sup> via the Na<sup>+</sup>/H<sup></sup> edivergences the positive interiopte action of phenylephricine. Specifically, it is known that lithium, but not choline, will exchange for  $H^+$  via the Na<sup>+</sup>/H<sup>+</sup> antiport phenylephrine-induced positive inotropic effects ime. Specincally, it is allown that fitnum, but not choline, will exchange for  $H^+$  via the Na<sup>+</sup>/H<sup>+</sup> antiport phenylephrine-induced positive inotropic effects in choline-substituted solutions averaged 37% of that in li line-substituted solutions averaged 37% of that in lith-<br>ium-substituted solutions (Terzic and Vogel, 1991). Sec-<br>ond, the time course and magnitude of the  $\alpha_1$ -adrenocep-<br>tor-mediated alkalinization closely correlates line-substituted solutions averaged 37% of that in lith-<br>ium-substituted solutions (Terzic and Vogel, 1991). Sec-<br>ond, the time course and magnitude of the  $\alpha_1$ -adrenocep-<br>tor-mediated alkalinization closely correlates ham-substituted solutions (1 erzic and Vogel, 1991). Second, the time course and magnitude of the  $\alpha_1$ -adrenoceptor-mediated alkalinization closely correlates to that of the positive inotropic effect (Terzic et al., 199 (ond, the time course and magnitude of the  $\alpha_1$ -adrenoceptor-mediated alkalinization closely correlates to that of the positive inotropic effect (Terzic et al., 1991, 1992a;<br>Gambassi et al., 1992). Third, the degree of the positive indition effect (Terzic et al., 1991, 1992a, Gambassi et al., 1992). Third, the degree of alkalinization (0.1 pH unit) caused by  $\alpha_1$ -adrenoceptor agonists (Terzic et al., 1992a) is known to increase contra (0.1 pH unit) caused by  $\alpha_1$ -adrenoceptor agonists (Terzic et al., 1992a) is known to increase contractile force by al., 1992a) is known to increase contractile force by<br>veral-fold in cardiac tissue (Vaughan-Jones et al., 1987;<br>vuntra and Vaughan-Jones, 1989; Lagadic-Gossmann<br>d Feuvray, 1990).<br>Although PKC analogs may mimic some  $\alpha_1$ 

Bountra and Vaughan-Jones, 1989; Lagadic-Gossmann<br>and Feuvray, 1990).<br>Although PKC analogs may mimic some  $\alpha_1$ -adrenergic<br>effects, Yuan et al. (1987), Capogrossi et al. (1990), and<br>Otani et al. (1992) showed that phorbo Bountra and Vaughan-Jones, 1989; Lagadic-Gossmann<br>and Feuvray, 1990).<br>Although PKC analogs may mimic some  $\alpha_1$ -adrenergic<br>effects, Yuan et al. (1987), Capogrossi et al. (1990), and<br>Otani et al. (1992) showed that phorbo Although PKC analogs may mimic some  $\alpha_1$ -adrenergic<br>effects, Yuan et al. (1987), Capogrossi et al. (1990), and<br>Otani et al. (1992) showed that phorbol esters and 1,2-<br>dioctanoylglycerol produce a negative inotropic resp Although FRC analogs may mimic some  $\alpha_1$ -adrenergic<br>effects, Yuan et al. (1987), Capogrossi et al. (1990), and<br>Otani et al. (1992) showed that phorbol esters and 1,2-<br>dioctanoylglycerol produce a negative inotropic resp enects, ruan et al. (1987), Capogrossi et al. (1990), and<br>Otani et al. (1992) showed that phorbol esters and 1,2-<br>dioctanoylglycerol produce a negative inotropic response<br>in perfused beating hearts, papillary muscle, or is Otani et al. (1992) showed that phorbol esters and 1,2-dioctanoylglycerol produce a negative inotropic response<br>in perfused beating hearts, papillary muscle, or isolated<br>rat ventricular myocytes. This result would not be dioctality apply the product a hegative inotropic response<br>in perfused beating hearts, papillary muscle, or isolated<br>rat ventricular myocytes. This result would not be pre-<br>dicted if PKC mediates the positive inotropic ef rat ventricular myocytes. This result would not be pre-<br>dicted if PKC mediates the positive inotropic effect of<br> $\alpha_1$ -agonists, unless an opposing effect of PKC activation<br>was present in intact myocytes; this latter effe dicted if FKC mediates the positive inotropic effect of  $\alpha_1$ -agonists, unless an opposing effect of PKC activation was present in intact myocytes; this latter effect would lead to an overall negative inotropic effect. I was present in intact myocytes; this latter effect would<br>lead to an overall negative inotropic effect. Indeed, in<br>single cardiomyocytes loaded with the  $Ca^{2+}$  indicator<br>Indo-1, phorbol-12-myristate-13-acetate and 1,2-dio lead to an overall negative inotropic effect. Indeed, in<br>single cardiomyocytes loaded with the  $Ca^{2+}$  indicator<br>Indo-1, phorbol-12-myristate-13-acetate and 1,2-dioc-<br>tanoylglycerol markedly reduce the amplitude of the<br>in Indo-1, phorbol-12-myristate-13-acetate and 1,2-dioc-<br>tanoylglycerol markedly reduce the amplitude of the<br>intracellular  $Ca^{2+}$  transient. This finding could explain<br>why PKC activators produce a negative inotropic effect. Indo-1, phorbol-12-myristate-13-acetate and 1,2-dioc-<br>tanoylglycerol markedly reduce the amplitude of the<br>intracellular Ca<sup>2+</sup> transient. This finding could explain<br>why PKC activators produce a negative inotropic effect.<br> tanoylglycerol markedly reduce the amplitude of the<br>intracellular Ca<sup>2+</sup> transient. This finding could explain<br>why PKC activators produce a negative inotropic effect.<br>Moreover, other groups have described a positive ino-<br> why PKC activators produce a negative inotropic effect.<br>Moreover, other groups have described a positive ino-<br>tropic effect with 1,2-dioctanoylglycerol (10 to 100  $\mu$ M)<br>in electrically driven guinea pig atria (Teutsch et Moreover, other groups have described a positive ino-<br>
tropic effect with 1,2-dioctanoylglycerol (10 to 100  $\mu$ M)<br>
in electrically driven guinea pig atria (Teutsch et al.<br>
1987) and rat cardiac myocytes (McLeod and Hardi Moreover, other groups have described a positive ino-<br>tropic effect with 1,2-dioctanoylglycerol (10 to 100  $\mu$ M)<br>in electrically driven guinea pig atria (Teutsch et al.,<br>1987) and rat cardiac myocytes (McLeod and Harding in electrically driven guinea pig atria (Teutsch et al., 1987) and rat cardiac myocytes (McLeod and Harding, 1991) or no effect of phorbol esters on contractile force in rabbit (Kushida et al., 1988) or rat papillary musc 1991) or no effect of phorbol esters on contractile force 1991) or no enect of phorbot esters on contractile force<br>in rabbit (Kushida et al., 1988) or rat papillary muscle<br>(Otani et al., 1988). Whether the application of a PK<br>activator results in a positive, negative, or no inotr In rabolt (Kushida et al., 1566) or rat papinary muscles<br>(Otani et al., 1988). Whether the application of a PKC<br>activator results in a positive, negative, or no inotropic<br>effect may depend on the net effect of the intracel

CARDIAC  $\alpha_1$ -ADRE<br>fibrils, the size of the intracellular Ca<sup>2+</sup> transient (related cor<br>or not to the external Ca<sup>2+</sup> concentration), the state of m<br>Ca<sup>2+</sup> loading and cellular tolerance to Ca<sup>2+</sup>, and other n CARDIAC  $\alpha_1$ -ADR<br>fibrils, the size of the intracellular Ca<sup>2+</sup> transient (related<br>or not to the external Ca<sup>2+</sup> concentration), the state of<br>Ca<sup>2+</sup> loading and cellular tolerance to Ca<sup>2+</sup>, and other<br>unknown factor(s). fibrils, the size of the intracellular  $Ca^{2+}$  transient (related cover on to the external  $Ca^{2+}$  concentration), the state of metal  $Ca^{2+}$  loading and cellular tolerance to  $Ca^{2+}$ , and other nisunknown factor(s). als

 $Ca^{2+}$  loading and cellular tolerance to  $Ca^{2+}$ , and other unknown factor(s).<br>There have been contradictory reports regarding the ability of PKC blockers to prevent the positive inotropic effect of  $\alpha_1$ -adrenoceptor a et al. (1988, 1992) reported that staurosporine and H7 There have been contradictory reports regarding the<br>ability of PKC blockers to prevent the positive inotropic zate<br>effect of  $\alpha_1$ -adrenoceptor agonists. On one hand, Otani point<br>et al. (1988, 1992) reported that stauros inhere have been contradictory reports regarding the<br>ability of PKC blockers to prevent the positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists. On one hand, Otani<br>et al. (1988, 1992) reported that staurosporine and ability of FRC blockers to prevent the positive inotropic zate<br>effect of  $\alpha_1$ -adrenoceptor agonists. On one hand, Otani potential<br>et al. (1988, 1992) reported that staurosporine and H7 pointhibited the sustained positiv effect of  $\alpha_1$ -adrenoceptor agomsts. On one hand, Otam<br>et al. (1988, 1992) reported that staurosporine and H7<br>inhibited the sustained positive inotropic effect induced<br>by  $\alpha_1$ -adrenoceptor agonists in rat papillary mu et al. (1566, 1592) reported that staurosporme and  $\overline{H}$  inhibited the sustained positive inotropic effect induced<br>by  $\alpha_1$ -adrenoceptor agonists in rat papillary muscles. On<br>the other hand, Endou et al. (1991) showed by  $\alpha_1$ -adrenoceptor agonists in rat papillary muscles. On<br>the other hand, Endou et al. (1991) showed that H7 does<br>not affect the contractile response of rat papillary muscle<br>to phenylephrine, and that neither phorbol 1 the other hand, Endou et al. (1991) showed that H7 does<br>not affect the contractile response of rat papillary muscle<br>to phenylephrine, and that neither phorbol 12,13-dibu-<br>tyrate or 12-O-tetradecanoylphorbol-13-acetate rep the other hand, Endou et al. (1991) showed that H7 does<br>not affect the contractile response of rat papillary muscle<br>to phenylephrine, and that neither phorbol 12,13-dibu-<br>tyrate or 12-O-tetradecanoylphorbol-13-acetate rep not affect the contractile response of rat papillary muscle<br>to phenylephrine, and that neither phorbol 12,13-dibu-<br>tyrate or 12-O-tetradecanoylphorbol-13-acetate repro-<br>duced the effects of  $\alpha_1$ -adrenergic stimulation. to phenylephrine, and that neither phorbol 12,13-dibutyrate or 12-O-tetradecanoylphorbol-13-acetate reproduced the effects of  $\alpha_1$ -adrenergic stimulation. Hence there are discrepancies in the findings which, in part dep tyrate or 12-O-tetradecanoylphorbol-13-acetate repro-<br>duced the effects of  $\alpha_1$ -adrenergic stimulation. Hence,<br>there are discrepancies in the findings which, in part,<br>depend on whether PKC was activated through the adre there are discrepancies in the findings which, in part,<br>there are discrepancies in the findings which, in part,<br>depend on whether PKC was activated through the adre-<br>noceptor or phorbol esters. It should be kept in mind n depend on whether PKC was activated through the adre-<br>noceptor or phorbol esters. It should be kept in mind<br>that the diacylglycerol pathway represents only one limb<br>of the PI signal transduction system and that receptor<br>ac depend on whether FKC was activated through the a<br>noceptor or phorbol esters. It should be kept in n<br>that the diacylglycerol pathway represents only one l<br>of the PI signal transduction system and that rece<br>activation may g that the diacylglycerol pathway represents only one limb 1978; Osnes et al., 1985). Thus, in contrast with many<br>of the PI signal transduction system and that receptor other positive inotropic drugs, such as  $\beta$ -adrenocep specific isozymes of PKC (Ryves et al., 1991; Otani et out concomitant tachycardia. This result is at first sur-<br>al., 1992; Pucéat et al., 1993b) that are not activated prising knowing that  $\alpha_1$ -adrenoceptor stimulation of the PI signal transduction system and that receptor of activation may generate additional cofactors. Furthermore, exogenously applied PKC activators may stimulate consection is al., 1992; Pucéat et al., 1993b) that are activation may generate additional colactors. Further<br>more, exogenously applied PKC activators may stimulat<br>specific isozymes of PKC (Ryves et al., 1991; Otani  $\epsilon$ <br>al., 1992; Pucéat et al., 1993b) that are not activate<br>fo more, exogenously applied FKC activators may stimula<br>specific isozymes of PKC (Ryves et al., 1991; Otani<br>al., 1992; Pucéat et al., 1993b) that are not activat<br>following receptor occupation. Non-PKC-dependent a<br>tions of pho specific isozymes of PKC (Kyves et al., 1991; Otani<br>al., 1992; Pucéat et al., 1993b) that are not activat<br>following receptor occupation. Non-PKC-dependent at<br>tions of phorbol esters cannot be excluded either (Wa<br>son and K

brillar Ca<sup>2+</sup> sensitivity but do not always mimic the specified positive inotropic effects of  $\alpha_1$ -adrenoceptor agonists. It also always mimic the specified positive inotropic effects of  $\alpha_1$ -adrenoceptor agonists. I son and Karmazyn, 1991).<br>In summary, activators of PKC can increase myofi-<br>brillar Ca<sup>2+</sup> sensitivity but do not always mimic the<br>positive inotropic effects of  $\alpha_1$ -adrenoceptor agonists. It<br>is not clear whether there a In summary, activators of PKC can increase my<br>brillar Ca<sup>2+</sup> sensitivity but do not always mimic<br>positive inotropic effects of  $\alpha_1$ -adrenoceptor agonists<br>is not clear whether there are other intracellular mess<br>gers, in in summary, activators of 1 KC can increase inyont-<br>brillar Ca<sup>2+</sup> sensitivity but do not always mimic the<br>positive inotropic effects of  $\alpha_1$ -adrenoceptor agonists. It<br>is not clear whether there are other intracellular bind a sensitivity but do not always mimic the positive inotropic effects of  $\alpha_1$ -adrenoceptor agonists.<br>is not clear whether there are other intracellular messee<br>gers, in addition to PKC, that mediate the inotrop<br>effec positive inctropic effects of  $\alpha_1$ -adrenoceptor agonists. It and<br>is not clear whether there are other intracellular messen-<br>gers, in addition to PKC, that mediate the inotropic ra<br>effects of  $\alpha_1$ -adrenoceptor agonists is not clear whether there are other intracellular messen-<br>gers, in addition to PKC, that mediate the inotropic rateffects of  $\alpha_1$ -adrenoceptor agonists or whether the phar-<br>macological tools used are imperfect. Thus, i gers, in addition to FRC, that metallie the inotropic<br>effects of  $\alpha_1$ -adrenoceptor agonists or whether the phar-<br>macological tools used are imperfect. Thus, it may be<br>premature to draw any definite conclusion regarding enects of  $\alpha_1$ -adrenoceptor a<br>macological tools used are<br>premature to draw any defin<br>role of the PI pathway in t<br>of  $\alpha_1$ -adrenoceptor agonists<br>Unlike traditional "Ca<sup>2+</sup> macological tools used are imperiect. Thus, it may be premature to draw any definite conclusion regarding the 1<br>role of the PI pathway in the positive inotropic effects (of  $\alpha_1$ -adrenoceptor agonists.<br>Unlike traditional

role of the PI pathway in the positive inotropic effects (for  $\alpha_1$ -adrenoceptor agonists. include to contractile proteins,  $\alpha_1$ -adrenoceptor agonists fibincrease the responsiveness of myofilaments to  $Ca^{2+}$  via the t bind to contractile proteins,  $\alpha_1$ -adrenoceptor agonists the contractive process,  $\alpha_1$ -attendeeptor agometers<br>increase the responsiveness of myofilaments to  $Ca^{2+}$  via the<br>two receptor-mediated mechanisms: (a) intracellular al-<br>kalinization and (b) phosphorylation of contrac leftware the responsiveness of injoint<br>angles to Ca Via the pconceptor-mediated mechanisms: (a) intracellular al-<br>kalinization and (b) phosphorylation of contractile pro-<br>tein(s). As previously argued (Terzic et al., 1992 two receptor-metricular metricularisms. (a) intractential areal halo and kalinization and (b) phosphorylation of contractile produced by the leftward shift of the pCa-tension curve produced by the phosphorylation of the c tein(s). As previously argued (Terzic et al., 1992a), the<br>leftward shift of the pCa-tension curve produced by the<br>phosphorylation of the contractile protein(s) reaches 0.13 maticity of isolated (normally polarized) Purkin betward shift of the pca-tension curve produced by the<br>phosphorylation of the contractile protein(s) reaches 0.13 maint. pCa (Pucéat et al., 1990), whereas the shift expected de<br>from the alkalinization (approximately 0.1 phosphorylation of the contractile protein(s) reaches 0.13<br>unit  $\cdot$  pCa (Pucéat et al., 1990), whereas the shift expected<br>from the alkalinization (approximately 0.1 unit  $\cdot$  pH) can<br>be calculated to amount to 0.07 unit unit PCa (Fuceat et al., 1990), whereas the shirt expected<br>from the alkalinization (approximately 0.1 unit PH) can<br>be calculated to amount to 0.07 unit PCa (Fabiato and<br>Fabiato, 1978). The phosphorylation of contractile p From the antimization (approximately 0.1 unit  $\cdot$  pH) can<br>be calculated to amount to 0.07 unit  $\cdot$  pCa (Fabiato and fi<br>Fabiato, 1978). The phosphorylation of contractile pro-<br>tein(s) is not dependent on the alkalinizati be calculated to amount to 0.07 time-pea (Fabiato and Fabiato, 1978). The phosphorylation of contractile precision is not dependent on the alkalinization because is not affected by  $\text{Na}^+/H^+$  antiport inhibitors whic co rabiato, 1978). The phosphorylation of contractie pro<br>tein(s) is not dependent on the alkalinization because is<br>is not affected by  $Na^+/H^+$  antiport inhibitors whic<br>completely abolish the intracellular increase in pH<sub>i</sub> ( beints) is not dependent on the anxaninzation because it<br>is not affected by  $Na^+/H^+$  antiport inhibitors which an<br>completely abolish the intracellular increase in pH<sub>i</sub> (Ter-<br>zic et al., 1992a; reviewed by Pucéat et al., is not anected by YNA /H antiport inimitions which<br>completely abolish the intracellular increase in pH<sub>i</sub> (Ter-<br>zic et al., 1992a; reviewed by Pucéat et al., 1992). Con-<br>sequently, a total pCa<sub>50</sub> shift of 0.2 unit pCa co completely abolish the intracement increase in pri<sub>i</sub> (1 er zic et al., 1992a; reviewed by Pucéat et al., 1992). Con sequently, a total pCa<sub>50</sub> shift of 0.2 unit pCa could be expected following  $\alpha_1$ -adrenoceptor stimula

ENOCEPTORS<br>could account for a major portion of the  $\alpha_1$ -adrenoceptor-<br>mediated positive inotropic effect, albeit other r ENOCEPTORS<br>could account for a major portion of the  $\alpha_1$ -adrenocept<br>mediated positive inotropic effect, albeit other mech<br>nisms (e.g., prolongation of the action potential) co ENOCEPTORS 163<br>could account for a major portion of the  $\alpha_1$ -adrenoceptor-<br>mediated positive inotropic effect, albeit other mecha-<br>nisms (e.g., prolongation of the action potential) could<br>also be important (fig. 1). The could account for a major portion of the  $\alpha_1$ -adrenoceptor-<br>mediated positive inotropic effect, albeit other mecha-<br>nisms (e.g., prolongation of the action potential) could<br>also be important (fig. 1). The intracellular mediated positive inotropic effect, aftern other mechanisms (e.g., prolongation of the action potential) could also be important (fig. 1). The intracellular balance between phosphorylation/dephosphorylation and alkalinizat msins (e.g., prolongation of the action potential) could<br>also be important (fig. 1). The intracellular balance be-<br>tween phosphorylation/dephosphorylation and alkalini-<br>zation/buffer capacity may determine the respective also be important (iig. 1). The intracement balance be-<br>tween phosphorylation/dephosphorylation and alkalini-<br>zation/buffer capacity may determine the respective im-<br>portance of the two sensitizing mechanisms in the overa Exation/buffer capacity may determine the respective in<br>portance of the two sensitizing mechanisms in the overa<br>positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists.<br>addition, the intracellular control of the degree zation/burier capacity may determine the respective<br>portance of the two sensitizing mechanisms in the ov<br>positive inotropic effect of  $\alpha_1$ -adrenoceptor agonist<br>addition, the intracellular control of the degree of p<br>phor portance of the two sensitizing mechanisms in the overall<br>positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists. In<br>addition, the intracellular control of the degree of phos-<br>phorylation and alkalinization produced by positive inotropic effect of  $\alpha_1$ -adrenoceptor agonists. In<br>addition, the intracellular control of the degree of phos-<br>phorylation and alkalinization produced by  $\alpha_1$ -adreno-<br>ceptor agonists may prevent an oversensiti addition, the intracemental control of the degree of phos-<br>phorylation and alkalinization produced by  $\alpha_1$ -adreno-<br>ceptor agonists may prevent an oversensitization of the<br>myofilaments to  $Ca^{2+}$ , an undesirable effect o phorylation and algorithmical<br>ceptor agonists may preven<br>myofilaments to  $Ca^{2+}$ , an<br>served with conventional (<br>bind to contractile proteins myofilaments to Ca<sup>2+</sup>, an<br>served with conventional<br>bind to contractile protein<br>*B. Chronotropic Effects*<br>Usually, in normal adul served with conventional  $Ca^{2+}$  sensitizers that directly<br>bind to contractile proteins.<br>B. Chronotropic Effects<br>Usually, in normal adult hearts,  $\alpha_1$ -adrenoceptor ago-<br>nists induce no chronotropic action (Wagner and Br

B. Chronotropic Effects<br>
Usually, in normal adult hearts,  $\alpha_1$ -adrenoceptor ago-<br>
nists induce no chronotropic action (Wagner and Brodde,<br>
1978; Osnes et al., 1985). Thus, in contrast with many B. Chronotropic Effects<br>Usually, in normal adult hearts,  $\alpha_1$ -adrenoceptor ago-<br>nists induce no chronotropic action (Wagner and Brodde,<br>1978; Osnes et al., 1985). Thus, in contrast with many<br>other positive inotropic dru Usually, in normal adult hearts,  $\alpha_1$ -adrenoceptor ag<br>nists induce no chronotropic action (Wagner and Brodd<br>1978; Osnes et al., 1985). Thus, in contrast with man<br>other positive inotropic drugs, such as  $\beta$ -adrenocept<br>a Usuany, in normal adult hearts,  $\alpha_1$ -adrenoceptor<br>nists induce no chronotropic action (Wagner and Brc<br>1978; Osnes et al., 1985). Thus, in contrast with n<br>other positive inotropic drugs, such as  $\beta$ -adrenoce<br>agonists, t 1978; Osnes et al., 1985). Thus, in contrast with mare other positive inotropic drugs, such as  $\beta$ -adrenoceptiagonists, that produce cardiac acceleration,  $\alpha_1$ -adrenoceptiagonists, that produce cardiac acceleration,  $\$ 1976, Osnes et al., 1989). Thus, in contrast with many<br>other positive inotropic drugs, such as  $\beta$ -adrenoceptor<br>agonists, that produce cardiac acceleration,  $\alpha_1$ -adreno-<br>ceptor agonists produce a positive inotropic eff but positive inotropic urigs, such as p-adrenocepto<br>agonists, that produce cardiac acceleration,  $\alpha_1$ -adrenoceptor agonists produce a positive inotropic effect with<br>out concomitant tachycardia. This result is at first s out concomitant tachycardia. This result is at first surprising knowing that  $\alpha_1$ -adrenoceptor stimulation modulates several ionic currents present in cardiac cells.

of  $\alpha_1$ -adrenoceptor agonists.<br>
Unlike traditional "Ca<sup>2+</sup> sensitizers" which directly<br>
the transmembrane potential because, when Purkinje<br>
bind to contractile proteins,  $\alpha_1$ -adrenoceptor agonists fibers are depolariz Cardiac rhythm is driven by pacemaker cells localized<br>in specific areas of cardiac muscle, the sinoatrial and atrioventricular nodes. These cells are characterized by prising knowing that  $\alpha_1$ -adrenoceptor stimulation modulates several ionic currents present in cardiac cells.<br>Cardiac rhythm is driven by pacemaker cells localized<br>in specific areas of cardiac muscle, the sinoatrial and Cardiac rhythm is driven by pacemaker cells localized<br>in specific areas of cardiac muscle, the sinoatrial and<br>atrioventricular nodes. These cells are characterized by<br>spontaneous depolarizations. The lack of an effect of It specific areas of catual muscle, the sinoatrial and<br>atrioventricular nodes. These cells are characterized by<br>spontaneous depolarizations. The lack of an effect of  $\alpha_1$ -<br>adrenoceptor agonists do not alter the pacemake spontaneous depotarizations. The fact of an effect of  $\alpha_1$ -<br>adrenoceptor agonists on heart rate is probably due to<br>the fact that these agents do not alter the pacemaker<br>rate of the sinoatrial node (Hewett and Rosen, 198 the fact that these agents do not after the pacemaker<br>rate of the sinoatrial node (Hewett and Rosen, 1985).<br>Although  $\alpha_1$ -adrenoceptor agonists do not change the<br>nodal rhythm, they do modulate the automaticity of<br>latent Although  $\alpha_1$ -adrenoceptor agonists do not channodal rhythm, they do modulate the automatic latent pacemaker cells, such as isolated Purkinji (for review, see Rosen et al., 1989). The  $\alpha_1$ -adreno induced modulation of Athough  $\alpha_1$ -autenoceptor agomets do not enange the<br>nodal rhythm, they do modulate the automaticity of<br>latent pacemaker cells, such as isolated Purkinje fibers<br>(for review, see Rosen et al., 1989). The  $\alpha_1$ -adrenocept from the transmembrane potential because, when Purkinje fibers<br>(for review, see Rosen et al., 1989). The  $\alpha_1$ -adrenoceptor-<br>induced modulation of rhythm apparently depends on<br>the transmembrane potential because, when Pu facemeter centers, such as isolated Furking fibers (for review, see Rosen et al., 1989). The  $\alpha_1$ -adrenoceptor-<br>induced modulation of rhythm apparently depends on<br>the transmembrane potential because, when Purkinje<br>fiber (for review, see rosen et al., 1989). The  $\alpha_1$ -adrenoceptor-<br>induced modulation of rhythm apparently depends on<br>the transmembrane potential because, when Purkinje<br>fibers are depolarized to membrane potentials similar to induced modulation of rhythm apparently depends on<br>the transmembrane potential because, when Purkinje<br>fibers are depolarized to membrane potentials similar to<br>those normally found in cells of the sinoatrial node,  $\alpha_1$ -<br> the transmembrane potential because, when Purkinje<br>fibers are depolarized to membrane potentials similar to<br>those normally found in cells of the sinoatrial node,  $\alpha_1$ -<br>adrenergic stimulation loses its ability to modulat fibers are depolarized to mem<br>those normally found in cells<br>adrenergic stimulation loses is<br>automaticity of Purkinje fibers<br>Rosen and Robinson, 1990).<br> $\alpha_1$ -Adrenergic agonists incr be a formally found in cents of the sinoatrial hode, as<br>
irenergic stimulation loses its ability to modulate the<br>
tomaticity of Purkinje fibers (Hewett and Rosen, 198<br>
osen and Robinson, 1990).<br>  $\alpha_1$ -Adrenergic agonists

autemergic stimulation loses its ability to inotuate the<br>automaticity of Purkinje fibers (Hewett and Rosen, 1985;<br>Rosen and Robinson, 1990).<br> $\alpha_1$ -Adrenergic agonists increase or decrease the auto-<br>maticity of isolated ( depending on Turkinje inters (riewelt and rosen, 1966)<br>Rosen and Robinson, 1990).<br> $\alpha_1$ -Adrenergic agonists increase or decrease the auto-<br>maticity of isolated (normally polarized) Purkinje fibers<br>depending on the stage rosen and Robinson, 1990).<br>  $\alpha_1$ -Adrenergic agonists increase or decrease the auto-<br>
maticity of isolated (normally polarized) Purkinje fibers,<br>
depending on the stage of development and on the spe-<br>
cific subset of fib  $\alpha_1$ -Adrenergic agonists increase or decrease the auto-<br>maticity of isolated (normally polarized) Purkinje fibers,<br>depending on the stage of development and on the spe-<br>cific subset of fibers. The majority of adult Purk maticity of isolated (normally polarized) Purking fiber<br>depending on the stage of development and on the sp<br>cific subset of fibers. The majority of adult Purkin<br>fibers exposed to phenylephrine exhibit a decrease<br>spontaneo depending on the stage of development and on the specific subset of fibers. The majority of adult Purkinje fibers exposed to phenylephrine exhibit a decrease in spontaneous firing rate. By contrast,  $\alpha_1$ -adrenoceptor st fibers exposed to phenylephrine exhibit a decrease in spontaneous firing rate. By contrast,  $\alpha_1$ -adrenoceptor stimulation in immature Purkinje fibers usually produces an increase in automaticity. When neonatal rat cardi fibers exposed to phenylephrine exhibit a decrease in<br>spontaneous firing rate. By contrast,  $\alpha_1$ -adrenoceptor<br>stimulation in immature Purkinje fibers usually produces<br>an increase in automaticity. When neonatal rat cardi spontaneous firing rate. By contrast,  $\alpha_1$ -adrenoceptor<br>stimulation in immature Purkinje fibers usually produces<br>an increase in automaticity. When neonatal rat cardiac<br>myocytes were cocultured with sympathetic ganglioni stimulation in immature Purkinje fibers usually produce an increase in automaticity. When neonatal rat card myocytes were cocultured with sympathetic ganglion cells,  $\alpha_1$ -adrenoceptor agonists produced a negat chronotro an increase in automaticity. When heonatal rat cardiac myocytes were cocultured with sympathetic ganglionic cells,  $\alpha_1$ -adrenoceptor agonists produced a negative chronotropic effect rather than the usual positive chrono

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like chronotropic response to  $\alpha_1$ -adrenoceptor agonists<br>
(Malfatto et al., 1990; for review, see Rosen et al., 1989, 164<br>
like chronotropic response to  $\alpha_1$ -adrenoceptor agonists<br>
(Malfatto et al., 1990; for review, see Rosen et al., 1989,<br>
1991). 1991). In the chronotropic response to  $\alpha_1$ -adrenoceptor agonists falfatto et al., 1990; for review, see Rosen et al., 1989, 91).<br>In the adult postinnervated heart tissue, a pertussis xin-sensitive 41-kDa G-protein links the

like chronotropic response to  $\alpha_1$ -adrenoceptor ago (Malfatto et al., 1990; for review, see Rosen et al., 1991).<br>In the adult postinnervated heart tissue, a pert toxin-sensitive 41-kDa G-protein links the  $\alpha_1$ -adrenot (Malfatto et al., 1990; for review, see Rosen et al., 1989, 1991).<br>
In the adult postinnervated heart tissue, a pertussis<br>
toxin-sensitive 41-kDa G-protein links the  $\alpha_1$ -adrenoceptor<br>
to negative chronotropy through a 1991).<br>
In the adult postinnervated heart tissue, a pertussis<br>
toxin-sensitive 41-kDa G-protein links the  $\alpha_1$ -adrenocep-<br>
tor to negative chronotropy through a mechanism that<br>
involves activation of the Na<sup>+</sup>/K<sup>+</sup>-ATPa In the adult postinnervated heart tissue, a pertussis ad<br>toxin-sensitive 41-kDa G-protein links the  $\alpha_1$ -adrenocep-<br>tor to negative chronotropy through a mechanism that (C<br>involves activation of the Na<sup>+</sup>/K<sup>+</sup>-ATPase (S toxin-sensitive 41-kDa G-protein links the  $\alpha_1$ -adrenoceptor to negative chronotropy through a mechanism that (involves activation of the Na<sup>+</sup>/K<sup>+</sup>-ATPase (Steinberg et 1 al., 1985; Shah et al., 1988; Rosen et al., 198 tor to negative chronotropy through a mechanism that<br>involves activation of the Na<sup>+</sup>/K<sup>+</sup>-ATPase (Steinberg et<br>al., 1985; Shah et al., 1988; Rosen et al., 1989). In the<br>newborn heart, the  $\alpha_1$ -adrenoceptor is coupled t involves activation of the Na<sup>+</sup>/K<sup>+</sup>-ATPase (Steinberg al., 1985; Shah et al., 1988; Rosen et al., 1989). In the mewborn heart, the  $\alpha_1$ -adrenoceptor is coupled to positic chronotropy via a pertussis toxin-insensitive al., 1985; Shah et al., 1988; Rosen et al., 1989). In the no<br>newborn heart, the  $\alpha_1$ -adrenoceptor is coupled to positive my<br>chronotropy via a pertussis toxin-insensitive G-protein et<br>(Han et al., 1989). The acquisition newborn heart, the  $\alpha_1$ -adrenoceptor is coupled to positive<br>chronotropy via a pertussis toxin-insensitive G-protein<br>(Han et al., 1989). The acquisition of the pertussis toxin-<br>sensitive G-protein depends on the maturati chronotropy via a pertussis toxin-insensitive G-protein et a<br>(Han et al., 1989). The acquisition of the pertussis toxin-<br>sensitive G-protein depends on the maturation of the zati<br>sympathetic innervation. This provides an (Han et al., 1989). The acquisition of the pertussis toxin-<br>sensitive G-protein depends on the maturation of the<br>sympathetic innervation. This provides an explanation<br>for the ontogenic change in the  $\alpha_1$ -adrenergic effe sensitive G-protein depends on the maturation of the sympathetic innervation. This provides an explanation for the ontogenic change in the  $\alpha_1$ -adrenergic effects on the chronotropic response from excitation (in newborn sympathetic innervation. This provides an explanation fifter the ontogenic change in the  $\alpha_1$ -adrenergic effects on due the chronotropic response from excitation (in newborn) 1901). Neuropeptide Y, which is simultaneous for the ontogenic change in the  $\alpha_1$ -adrenergic effects on<br>the chronotropic response from excitation (in newborn)<br>to inhibition (in adult) (Drugge et al., 1985; Rosen et al.<br>1991). Neuropeptide Y, which is simultaneousl the emonotropic response from excitation (in newborn) is<br>to inhibition (in adult) (Drugge et al., 1985; Rosen et al., ki<br>1991). Neuropeptide Y, which is simultaneously released ei<br>with norepinephrine from the sympathetic n w initiation (in addit) (Drugge et al., 1980, Rosen et al., 1991). Neuropeptide Y, which is simultaneously released exith norepinephrine from the sympathetic nerve endings, is probably responsible for the expression of the 1991). Neuropeptide Y, which is simultaneously released eiverth norepinephrine from the sympathetic nerve end-<br>ings, is probably responsible for the expression of the the<br>pertussis toxin-sensitive G-protein (reviewed by Ro with norepinephrine from the sympathetic nerve end-<br>ings, is probably responsible for the expression of the<br>pertussis toxin-sensitive G-protein (reviewed by Rosen al.,<br>and Robinson, 1990) and, thus, could be the mediator o ings, is probably responsible for the expression<br>pertussis toxin-sensitive G-protein (reviewed by<br>and Robinson, 1990) and, thus, could be the media<br>the change in chronotropic response from posit<br>neonates to negative in ad rtussis toxin-sensitive G-protein (reviewed by Rosen<br>d Robinson, 1990) and, thus, could be the mediator of<br>e change in chronotropic response from positive in<br>onates to negative in adults (Sun et al., 1991).<br>Both types of

and Robinson, 1990) and, thus, could be the mediator of<br>the change in chronotropic response from positive in<br>neonates to negative in adults (Sun et al., 1991).<br>Both types of responses to  $\alpha_1$ -adrenoceptor agonists<br>are b the change in chronotropic response from positive in pect<br>neonates to negative in adults (Sun et al., 1991). In 1<br>Both types of responses to  $\alpha_1$ -adrenoceptor agonists  $Ca^2$ <br>are blocked by the  $\alpha_1$ -adrenoceptor antago meonates to negative in adults (Sun et al., 1991).<br>Both types of responses to  $\alpha_1$ -adrenoceptor agonists (are blocked by the  $\alpha_1$ -adrenoceptor antagonist, prazosin.<br>In addition, the decrease in automaticity is blocked Both types of responses to  $\alpha_1$ -adrenoceptor agonist<br>are blocked by the  $\alpha_1$ -adrenoceptor antagonist, prazosin<br>In addition, the decrease in automaticity is blocked by<br>CEC, an  $\alpha_{1B}$ -selective antagonist, whereas the are blocked by the  $\alpha_1$ -adrenoceptor antagonist, prazosin.<br>In addition, the decrease in automaticity is blocked by<br>CEC, an  $\alpha_{1B}$ -selective antagonist, whereas the increase<br>in automaticity is antagonized by the  $\alpha_{1A$ In addition, the decrease in automaticity is blocked by CEC, an  $\alpha_{1B}$ -selective antagonist, whereas the increase in automaticity is antagonized by the  $\alpha_{1A}$ -blocker, WB-4101 (del Balzo et al., 1990). These findings in automaticity is antagonist, whereas the increase during in automaticity is antagonized by the  $\alpha_{1A}$ -blocker, WB-<br>4101 (del Balzo et al., 1990). These findings suggest that (Za:<br>sponses (Rosen et al., 1991). after al

strimulation of the Na<sup>+</sup>/K<sup>+</sup> pump, generation of a net<br>specific receptor subtypes may modulate different re-<br>sponses (Rosen et al., 1991). af<br>stimulation of the Na<sup>+</sup>/K<sup>+</sup> pump, generation of a net<br>coutward current, and sponses (Rosen et al., 1991). af<br>
Evidence has been gathered to link the  $\alpha_{1B}$ -receptor to  $\alpha_1$ <br>
stimulation of the Na<sup>+</sup>/K<sup>+</sup> pump, generation of a net<br>
outward current, and suppression of automaticity (Rosen se<br>
et Evidence has been gathered to link the  $\alpha_{1B}$ -receptor to  $\alpha_1$ <br>stimulation of the Na<sup>+</sup>/K<sup>+</sup> pump, generation of a net tio<br>outward current, and suppression of automaticity (Rosen sel<br>et al., 1989; Shah et al., 1988; Z stimulation of the Na<sup>+</sup>/K<sup>+</sup> pump, generation of a net<br>outward current, and suppression of automaticity (Rosen<br>et al., 1989; Shah et al., 1988; Zaza et al., 1990). The<br>relationship between  $\alpha_{1A}$ -receptor stimulation w outward current, and suppression of automaticity (Rosen sele<br>et al., 1989; Shah et al., 1988; Zaza et al., 1990). The Mol<br>relationship between  $\alpha_{1A}$ -receptor stimulation which the<br>triggers the increase in automaticity et al., 1585, Shan et al., 1586, Zaza et al., 1590). The<br>relationship between  $\alpha_{1A}$ -receptor stimulation which<br>triggers the increase in automaticity and PI hydrolysis<br>also has been established. However, the role of the relationship between  $\alpha_{1A}$ -receptor stimulation which<br>triggers the increase in automaticity and PI hydrolysis<br>also has been established. However, the role of the PI<br>system in the increase of cardiac automaticity is sti triggers the increase in au<br>also has been established.<br>system in the increase of<br>unclear (del Balzo et al., 1<br>1990; Rosen et al., 1991). **Example 18 in the increase of cardiac automaticity is unclear (del Balzo et al., 1990; Molina-Viamonte et 1990; Rosen et al., 1991).**<br>*C. Arrhythmogenic and Other Detrimental Effects*<br> $\alpha_1$ -Adrenergic mechanisms not onl

1990; Rosen et al., 1991).<br>C. Arrhythmogenic and Other Detrimental Effects<br> $\alpha_1$ -Adrenergic mechanisms not only influence the au-<br>tomaticity of latent pacemakers but also play a role in 1990; Rosen et al., 1991). tive<br>
C. Arrhythmogenic and Other Detrimental Effects<br>  $\alpha_1$ -Adrenergic mechanisms not only influence the au-<br>
tomaticity of latent pacemakers but also play a role in fibe<br>
the genesis of speci C. Arrhythmogenic and Other Detrimental Effects<br>  $\alpha_1$ -Adrenergic mechanisms not only influence the automaticity of latent pacemakers but also play a role in<br>
the genesis of specific arrhythmias (Sheridan, 1986).<br>
Eviden C. Arrnythmogenic and Other Detrimental Effects<br>  $\alpha_1$ -Adrenergic mechanisms not only influence the<br>
tomaticity of latent pacemakers but also play a rc<br>
the genesis of specific arrhythmias (Sheridan, 1<br>
Evidence has been  $\alpha_1$ -Adrenergic mechanisms not only influence the automaticity of latent pacemakers but also play a role in the genesis of specific arrhythmias (Sheridan, 1986). Evidence has been obtained to implicate  $\alpha_1$ -adrenocept tomaticity of latent pacemakers but also play a role in<br>the genesis of specific arrhythmias (Sheridan, 1986).<br>Evidence has been obtained to implicate  $\alpha_1$ -adrenocep-<br>tors, at least in some species, in the arrhythmias th Evidence has been obtained to implicate  $\alpha_1$ -adrenoceptors, at least in some species, in the arrhythmias that occur during coronary artery occlusion and reperfusion (for review, see Benfey, 1987; Kurtz et al., 1991).  $\$ tors, at least in some species, in the arrhythmias that occur during coronary artery occlusion and reperfusion (for review, see Benfey, 1987; Kurtz et al., 1991).  $\alpha_1$ -Adrenoceptor blockade reduces the number of prematu occur during coronary artery occlusion and reperfusion (for review, see Benfey, 1987; Kurtz et al., 1991).<br>Adrenoceptor blockade reduces the number of premativentricular complexes during coronary reperfusion, duces or abol (for review, see Benfey, 1987; Kurtz et al., 1991).  $\alpha_1$ -<br>Adrenoceptor blockade reduces the number of premature the ventricular complexes during coronary reperfusion, re-<br>duces or abolishes ventricular tachycardia and f Adrenoceptor blockade reduces the number of premature<br>ventricular complexes during coronary reperfusion, re-<br>duces or abolishes ventricular tachycardia and fibrilla-<br>tion, and prevents the increase in idioventricular rate

FT AL.<br>adrenoceptor agonists increase idioventricular rate early<br>after reperfusion in animals depleted of myocardial cat-ET AL.<br>adrenoceptor agonists increase idioventricular rate early<br>after reperfusion in animals depleted of myocardial cat-<br>echolamines (Sheridan et al., 1980). The enhanced  $\alpha_1$ exhibitance of a setting adventuance of a setter reperfusion in animals depleted of myocardial catedral enhanced *a*<sub>1</sub>-echolamines (Sheridan et al., 1980). The enhanced  $\alpha_1$ -adrenergic responsiveness is associated with adrenoceptor agonists increase idioventricular rate early<br>after reperfusion in animals depleted of myocardial cat-<br>echolamines (Sheridan et al., 1980). The enhanced  $\alpha_1$ -<br>adrenergic responsiveness is associated with a r adrenoceptor agonists increase idioventricular rate early<br>after reperfusion in animals depleted of myocardial cat<br>echolamines (Sheridan et al., 1980). The enhanced  $\alpha_1$ <br>adrenergic responsiveness is associated with a rev after reperfusion in animals depleted of myocardial cat-<br>echolamines (Sheridan et al., 1980). The enhanced  $\alpha_1$ -<br>adrenergic responsiveness is associated with a reversible<br>increase in the number of myocardial  $\alpha_1$ -adre echolamines (Sheridan et al., 1980). The enhanced  $\alpha_1$ -<br>adrenergic responsiveness is associated with a reversible<br>increase in the number of myocardial  $\alpha_1$ -adrenoceptors<br>(Corr et al., 1981; Heathers et al., 1987; Dill adrenergic responsiveness is associated with a reversible<br>increase in the number of myocardial  $\alpha_1$ -adrenoceptors<br>(Corr et al., 1981; Heathers et al., 1987; Dillon et al.,<br>1988; Kurtz et al., 1991). However,  $\alpha_1$ -adre increase in the number of myocardial  $\alpha_1$ -adrenoceptors (Corr et al., 1981; Heathers et al., 1987; Dillon et al., 1988; Kurtz et al., 1991). However,  $\alpha_1$ -adrenoceptors are not consistently elevated in all experimenta 1988; Kurtz et al., 1991). However,  $\alpha_1$ -adrenoceptors are not consistently elevated in all experimental models of myocardial ischemia (Dillon et al., 1988; Chess-Williams et al., 1990; Steinberg and Alter, 1993).

The  $\alpha_1$ -adrenoceptor-triggered delayed afterdepolarinot consistently elevated in all experimental models of<br>myocardial ischemia (Dillon et al., 1988; Chess-Williams<br>et al., 1990; Steinberg and Alter, 1993).<br>The  $\alpha_1$ -adrenoceptor-triggered delayed afterdepolari-<br>zations w myocardial ischemia (Dillon et al., 1988; Chess-Williams<br>et al., 1990; Steinberg and Alter, 1993).<br>The  $\alpha_1$ -adrenoceptor-triggered delayed afterdepolari-<br>zations were often observed in Ca<sup>2+</sup>-overloaded Purkinje<br>fibers et al., 1990; Steinberg and Alter, 1993).<br>The  $\alpha_1$ -adrenoceptor-triggered delayed afterdepolarizations were often observed in Ca<sup>2+</sup>-overloaded Purking<br>fibers during ischemia when O<sub>2</sub> availability is severel<br>decreased The  $\alpha_1$ -adrenoceptor-triggered delayed afterdepolarizations were often observed in Ca<sup>2+</sup>-overloaded Purkinje<br>fibers during ischemia when  $O_2$  availability is severely<br>decreased (Kimura et al., 1984; Boutjdir and El-S fibers during ischemia when  $O_2$  availability is severely<br>decreased (Kimura et al., 1984; Boutjdir and El-Sheriff,<br>1991). In contrast, in normoxic cardiomyocytes or Pur-<br>kinje fibers,  $\alpha_1$ -adrenergic stimulation failed decreased (Kimura et al., 1984; Boutjdir and El-Sheriff;<br>
1991). In contrast, in normosic cartiomyocytes or Pur-<br>
kinje fibers,  $\alpha_1$ -adrenergic stimulation failed to induce<br>
either early or delayed afterdepolarizations decreased (Kimura et al., 1984; Boutjdir and El-Sheriff, 1991). In contrast, in normoxic cardiomyocytes or Purkinje fibers,  $\alpha_1$ -adrenergic stimulation failed to induce either early or delayed afterdepolarizations (Prio 1991). In contrast, in normoxic cardiomyocytes or Purkinje fibers,  $\alpha_1$ -adrenergic stimulation failed to induce either early or delayed afterdepolarizations (Priori and Corr, 1990; Marchi et al., 1991) even though it de kinje fibers,  $\alpha_1$ -adrenergic stimulation failed to ind<br>either early or delayed afterdepolarizations (Priori a<br>Corr, 1990; Marchi et al., 1991) even though it decrea<br>the threshold for ventricular fibrillation (Thandroye corr, 1990; Marchi et al., 1991) even though it decreased<br>the threshold for ventricular fibrillation (Thandroyen et<br>al., 1987). During reperfusion,  $\alpha_1$ -adrenoceptor stimula-<br>tion, by activating the Na<sup>+</sup>/H<sup>+</sup> antiport, the threshold for ventricular fibrillation (Thandroyen et al., 1987). During reperfusion,  $\alpha_1$ -adrenoceptor stimulation, by activating the Na<sup>+</sup>/H<sup>+</sup> antiport, could be expected to increase the intracellular Na<sup>+</sup> conce al., 1987). During reperfusion,  $\alpha_1$ -adrenoceptor stimulation, by activating the Na<sup>+</sup>/H<sup>+</sup> antiport, could be expected to increase the intracellular Na<sup>+</sup> concentration In turn, an increase in intracellular Na<sup>+</sup> could tion, by activating the Na<sup>+</sup>/H<sup>+</sup> antiport, could be ex-<br>pected to increase the intracellular Na<sup>+</sup> concentration.<br>In turn, an increase in intracellular Na<sup>+</sup> could lead to<br>Ca<sup>2+</sup> overload by a net uptake of Ca<sup>2+</sup> via t pected to increase the intracellular Na<sup>+</sup> concentration.<br>In turn, an increase in intracellular Na<sup>+</sup> could lead to<br>Ca<sup>2+</sup> overload by a net uptake of Ca<sup>2+</sup> via the Na<sup>+</sup>/Ca<sup>2+</sup><br>exchange. Although this cascade of events In turn, an increase in intracellular Na<sup>+</sup> could lead to Ca<sup>2+</sup> overload by a net uptake of Ca<sup>2+</sup> via the Na<sup>+</sup>/Ca<sup>2+</sup> exchange. Although this cascade of events might be responsible for arrhythmias (Dennis et al., 1990) Ca<sup>2+</sup> overload by a net uptake of Ca<sup>2+</sup> via the Na<sup>+</sup>/Ca<sup>2+</sup> exchange. Although this cascade of events might be responsible for arrhythmias (Dennis et al., 1990),  $\alpha_1$ -adrenoceptor agonists have not been shown to incr exchange. Although this cascade of responsible for arrhythmias (Dennis adrenoceptor agonists have not been s<br>intracellular Na<sup>+</sup> unless the Na<sup>+</sup>/K<sup>+</sup> p (Zaza et al., 1990; Terzic et al., 1991).<br>Automatic arrhythmias, as Automatic arrhythmias, (being et al., 1990),  $a_1$ -<br>adrenoceptor agonists have not been shown to increase<br>intracellular Na<sup>+</sup> unless the Na<sup>+</sup>/K<sup>+</sup> pump is inhibited<br>(Zaza et al., 1990); Terzic et al., 1991).<br>Automatic ar

(Zaza et al., 1990; Terzic et al., 1991).<br>Automatic arrhythmias, as well as induced delayed<br>afterdepolarizations and triggered activity, produced by<br> $\alpha_1$ -adrenoceptor agonists in simulated ischemic condi-<br>tions, are sig (*Laza* et al., 1990, 1erzic et al., 1991).<br>
Automatic arrhythmias, as well as induced delayed<br>
afterdepolarizations and triggered activity, produced by<br>  $\alpha_1$ -adrenoceptor agonists in simulated ischemic condi-<br>
tions, a afterdepolarizations and triggered activity, produced by  $\alpha_1$ -adrenoceptor agonists in simulated ischemic conditions, are significantly reduced by WB-4101, a rather selective  $\alpha_{1A}$ -antagonist (Anyukhovsky and Rosen,  $\alpha_1$ -adrenoceptor agonists in simulated ischemic condi-<br>tions, are significantly reduced by WB-4101, a rather<br>selective  $\alpha_{1A}$ -antagonist (Anyukhovsky and Rosen, 1991;<br>Molina-Viamonte et al., 1991). These results emph clons, are significantly reduced by WB-4101, a rathe<br>selective  $\alpha_{1A}$ -antagonist (Anyukhovsky and Rosen, 1991<br>Molina-Viamonte et al., 1991). These results emphasiz<br>the role of a WB-4101-sensitive receptor subtype is<br>isc Selective  $\alpha_{1A}$ -antagonist (Anyukhovsky and Rosen, 1991;<br>Molina-Viamonte et al., 1991). These results emphasize<br>the role of a WB-4101-sensitive receptor subtype in<br>ischemic arrhythmias and the potential antiarrhythmic<br> From all the role of a WB-4101-sensitive receptor subtype in<br>ischemic arrhythmias and the potential antiarrhythmic<br>ability for  $\alpha_1$ -receptor subtype-selective blockade (Rosen<br>et al., 1991). The increase in abnormal auto ischemic arrhythmias and the potential antiarrh<br>ischemic arrhythmias and the potential antiarrh<br>ability for  $\alpha_1$ -receptor subtype-selective blockade<br>et al., 1991). The increase in abnormal automati<br>ischemic Purkinje fib scheme arrhythmas and the potential antiarrhythmic<br>ability for  $\alpha_1$ -receptor subtype-selective blockade (Rosen<br>et al., 1991). The increase in abnormal automaticity in<br>ischemic Purkinje fibers depends on a WB-4101-sensiet al., 1991). The increase in abnormal automaticity<br>ischemic Purkinje fibers depends on a WB-4101-sen<br>tive  $\alpha_1$ -adrenoceptor subtype whose actions are tran<br>duced by a pertussis toxin-sensitive 41-kDa G-prot<br>and should ischemic Purkinje fibers depends on a WB-4101-sensitive  $\alpha_1$ -adrenoceptor subtype whose actions are trans-<br>duced by a pertussis toxin-sensitive 41-kDa G-protein<br>and should be distinguished from the mechanism under-<br>lyin duced by a pertussis toxin-sensitive 41-kDa G-protein<br>and should be distinguished from the mechanism under-<br>lying the increase in automaticity in normal Purkinje<br>fibers, which is independent of the pertussis toxin sub-<br>str and should be distinguished from the mechanism underlying the increase in automaticity in normal Purkinje fibers, which is independent of the pertussis toxin substrate (Anyukhovsky et al., 1992).<br>Stimulation of cardiac  $\$ In should be ustinguished from the mechanism under-<br>ing the increase in automaticity in normal Purkinje<br>bers, which is independent of the pertussis toxin sub-<br>rate (Anyukhovsky et al., 1992).<br>Stimulation of cardiac  $\alpha_1$ 

ventricular complexes during coronary reperfusion, re-<br>duces or abolishes ventricular tachycardia and fibrilla-<br>duces or abolishes ventricular tachycardia and fibrilla-<br>tion, and prevents the increase in idioventricular r potentiates the development of the pertussis toxin su<br>strate (Anyukhovsky et al., 1992).<br>Stimulation of cardiac  $\alpha_1$ -adrenoceptors hastens an<br>potentiates the development of digitalis glycoside card<br>otoxicity, as reporte fibers, which is independent of the pertussis toxin sub-<br>strate (Anyukhovsky et al., 1992).<br>Stimulation of cardiac  $\alpha_1$ -adrenoceptors hastens and<br>potentiates the development of digitalis glycoside cardi-<br>otoxicity, as r strate (Anyukhovsky et al., 1992).<br>
Stimulation of cardiac  $\alpha_1$ -adrenoceptors hastens and<br>
potentiates the development of digitalis glycoside cardi-<br>
otoxicity, as reported for isolated rat atria (Terzic and<br>
Vogel, 199 potentiates the development of digitalis glycoside cardiotoxicity, as reported for isolated rat atria (Terzic and Vogel, 1990; Terzic et al., 1991). It has been proposed that the enhancement of digitalis cardiotoxicity is potentiates the development of digitalis gives<br>identify discussed care of oxicity, as reported for isolated rat atria (Terzic at<br>Vogel, 1990; Terzic et al., 1991). It has been propose<br>that the enhancement of digitalis car bookiety, as reported for isolated rat atria (1 erzic and Vogel, 1990; Terzic et al., 1991). It has been proposed that the enhancement of digitalis cardiotoxicity is due to the stimulation of Na<sup>+</sup>/H<sup>+</sup> exchange by  $\alpha_1$ voger, 1990, 1erzic et al., 1991). It has been proposed<br>that the enhancement of digitalis cardiotoxicity is due to<br>the stimulation of Na<sup>+</sup>/H<sup>+</sup> exchange by  $\alpha_1$ -adrenoceptor<br>agonists. Indeed, the Na<sup>+</sup>/H<sup>+</sup> antiport pr the stimulation of  $\text{Na}^+/H^+$  exchange by  $\alpha_1$ -adrenoceptor agonists. Indeed, the  $\text{Na}^+/H^+$  antiport provides an important route of  $\text{Na}^+$  loading (and, subsequently,  $\text{Ca}^{2+}$ loading) in conditions in which t

CARDIAC  $\alpha_1$ -AD<br>1988; Kim and Smith, 1986; Kaila and Vaughan Jones,<br>1987). By stimulating the Na<sup>+</sup>/H<sup>+</sup> antiport,  $\alpha_1$ -agonists CARDIAC  $\alpha_1$ -AD<br>1988; Kim and Smith, 1986; Kaila and Vaughan Jones,<br>1987). By stimulating the Na<sup>+</sup>/H<sup>+</sup> antiport,  $\alpha_1$ -agonists<br>may aggravate digitalis-induced contractures by increas-CARDIAC  $\alpha$ <br>1988; Kim and Smith, 1986; Kaila and Vaughan Jor<br>1987). By stimulating the Na<sup>+</sup>/H<sup>+</sup> antiport,  $\alpha_1$ -agoni<br>may aggravate digitalis-induced contractures by incre<br>ing both intracellular Na<sup>+</sup> and pH. In this 1988; Kim and Smith, 1986; Kaila and Vaughan Jones, n<br>1987). By stimulating the Na<sup>+</sup>/H<sup>+</sup> antiport,  $\alpha_1$ -agonists timay aggravate digitalis-induced contractures by increas-<br>ing both intracellular Na<sup>+</sup> and pH. In this 1988; Kim and Smith, 1986; Kaila and Vaughan Jones, 1987). By stimulating the Na<sup>+</sup>/H<sup>+</sup> antiport,  $\alpha_1$ -agonists may aggravate digitalis-induced contractures by increasing both intracellular Na<sup>+</sup> and pH. In this regard may aggravate digitalis-induced contractures by increasing both intracellular Na<sup>+</sup> and pH. In this regard,  $\alpha_1$ -<br>adrenoceptor agonists exert an opposite modulatory ef-<br>fect on ouabain cardiotoxicity when compared to Na may aggravate digitalis-induced contractures by increas-<br>ing both intracellular Na<sup>+</sup> and pH. In this regard,  $\alpha_1$ - cy<br>adrenoceptor agonists exert an opposite modulatory ef-<br>fect on ouabain cardiotoxicity when compared adrenoceptor agonists exert an opposite modulatory effect on ouabain cardiotoxicity when compared to Na<sup>+</sup>/<br>H<sup>+</sup> exchange blockers (Terzic et al., 1991). The delayed<br>afterdepolarizations induced by ouabain in canine Pur-<br> adrenoceptor agonists exert an opposite modulatory ef-<br>fect on ouabain cardiotoxicity when compared to Na<sup>+</sup>/ tur<br>H<sup>+</sup> exchange blockers (Terzic et al., 1991). The delayed  $\alpha_1$ -<br>afterdepolarizations induced by ouabain i fect on ouabain<br>H<sup>+</sup> exchange b<br>afterdepolariza<br>kinje fibers are<br>Rosen, 1993). afterdepolarizations induced by ouabain in canine Pushinje fibers are also worsened by  $\alpha_1$ -stimulation (Lee an Rosen, 1993).<br>*D. Induction of Gene Expression and Stimulation of Hypertrophy* 

### *Hypertrophy*

Simpson, 1993).<br>*Induction of Gene Expression and Stimulation of*<br>ppertrophy<br>Simpson (1983, 1985; for review, see Simpson et al.,<br>91) demonstrated that, in cultured neonatal rat car-1991) D. Induction of Gene Expression and Stimulation of Hypertrophy<br>
1991) demonstrated that, in cultured neonatal rat car-<br>
1991) demonstrated that, in cultured neonatal rat car-<br>
1991) demonstrated that, in cultured ne divergence of the Expression and Stimulation of<br>Hypertrophy<br>Simpson (1983, 1985; for review, see Simpson et al.,<br>1991) demonstrated that, in cultured neonatal rat car-<br>diomyocytes, norepinephrine, via  $\alpha_1$ -adrenoceptors may<br>
duces cell hypertrophy.<br>
duces cell hypertrophy. Because cardiomyocytes which<br>
duces cell hypertrophy. Because cardiomyocytes which<br>
duces cell hypertrophy. Because cardiomyocytes which<br>
duces cell hypertrophy. Becau Simpson (1983, 1985; for review, see Simpson et al., 1991) demonstrated that, in cultured neonatal rat cardiomyocytes, norepinephrine, via  $\alpha_1$ -adrenoceptors, induces cell hypertrophy. Because cardiomyocytes which are h 1991) demonstrated that, in cultured neonatal rat car-<br>diomyocytes, norepinephrine, via  $\alpha_1$ -adrenoceptors, in-<br>duces cell hypertrophy. Because cardiomyocytes which<br>are highly differentiated are no longer able to divide diomyocytes, norepinephrine, via  $\alpha_1$ -adrenoceptors, duces cell hypertrophy. Because cardiomyocytes where highly differentiated are no longer able to div cardiac hypertrophy results primarily from an incre in protein co duces cell hypertrophy. Because cardiomyocytes which are highly differentiated are no longer able to divide, teardiac hypertrophy results primarily from an increase (in protein content and, hence, in cell size. The hypert are highly differentiated are no longer able to divident cardiac hypertrophy results primarily from an increase in protein content and, hence, in cell size. The hypertrophy produced by  $\alpha_1$ -adrenergic stimulation is ass cardiac hypertrophy results primarily from an increase<br>in protein content and, hence, in cell size. The hypertro-<br>phy produced by  $\alpha_1$ -adrenergic stimulation is associated<br>with an increase in myofibrillar protein synthe in protein content and, hence, in cell size. The hypertro-<br>phy produced by  $\alpha_1$ -adrenergic stimulation is associated<br>with an increase in myofibrillar protein synthesis with-<br>out an effect on protein degradation (Meidell phy produced by  $\alpha_1$ -adrenergic stimulation is associated<br>with an increase in myofibrillar protein synthesis with-<br>out an effect on protein degradation (Meidell et al., 1986).<br>Such an increase in protein content of cult with an increase in myofibrillar protein synthesis with-<br>out an effect on protein degradation (Meidell et al., 1986). and<br>Such an increase in protein content of cultured neonatal cor-<br>rat cardiac myocytes was inhibited by out an effect on protein degradation (Meidell et al., 19<br>Such an increase in protein content of cultured neon<br>rat cardiac myocytes was inhibited by WB-4101, an<br>antagonist, to nearly the same extent as by prazos<br>nonselecti Such an increase in protein content of cultured neonatal<br>rat cardiac myocytes was inhibited by WB-4101, an  $\alpha_{1A}$ -<br>antagonist, to nearly the same extent as by prazosin a<br>nonselective  $\alpha_1$ -adrenergic antagonist. The  $\$ rat cardiac myocytes was inhibited by WB-4101, an  $\alpha_{1A}$ -<br>antagonist, to nearly the same extent as by prazosin a<br>nonselective  $\alpha_1$ -adrenergic antagonist. The  $\alpha_{1A}$ -antago-<br>nist also inhibited the norepinephrine-ind antagonist, to nearly the same extent as by prazosi<br>nonselective  $\alpha_1$ -adrenergic antagonist. The  $\alpha_{1A}$ -anta<br>nist also inhibited the norepinephrine-induced incre<br>in [<sup>3</sup>H]inositol phosphates so that phosphoinosi<br>phosp nonselective  $\alpha_1$ -adrenergic antagonist. The  $\alpha_{1A}$ -antagonist also inhibited the norepinephrine-induced increase<br>in [<sup>3</sup>H]inositol phosphates so that phosphoinositide<br>phospholipase C seems to be involved in the " $\alpha_$ nist also inhibited the norepinephrine-induced increasing in  $[^3H]$  inositol phosphates so that phosphoinosi phospholipase C seems to be involved in the " $\alpha_1$ -hy trophic" response (Simpson et al., 1990). In contraction in [<sup>3</sup>H]inositol phosphates so that phosphoinositide ca<br>phospholipase C seems to be involved in the " $\alpha_1$ -hyper-<br>trophic" response (Simpson et al., 1990). In contrast, the<br>CEC, the  $\alpha_{1B}$ -antagonist, had no effect. T trophic" response (Simpson et al., 1990). In contrast, CEC, the  $\alpha_{1B}$ -antagonist, had no effect. The  $\alpha_{1}$ -adrenotrophic" response (Simpson et al., 1990). In contrast, the CEC, the  $\alpha_{1B}$ -antagonist, had no effect. The  $\alpha_1$ -adrenoceptor-mediated stimulation of protein synthesis is blocked by selective Na<sup>+</sup>/H<sup>+</sup> exchange inhibit CEC, the a<br>ceptor-med<br>blocked by<br>gesting the<br>al., 1992).<br>Following blocked by selective  $Na^+/H^+$  exchange inhibitors, suggesting the involvement of  $Na^+/H^+$  exchange (Kagiya et al., 1992).<br>Following neurohormonal stimulation, cardiac hyper-

gesting the involvement of Na<sup>+</sup>/H<sup>+</sup> exchange (Kagiya et sion of contractile protein genes.<br>al., 1992).<br>Following neurohormonal stimulation, cardiac hyper-<br>trophy proceeds through the following successive genetic The  $\alpha$ gesting the involvement of Na<sup>+</sup>/H<sup>+</sup> exchange (Kagiya et al., 1992).<br>
Following neurohormonal stimulation, cardiac hyper-<br>
trophy proceeds through the following successive genetic<br>
events: (a) an immediate early gene expr al., 1992). Following neurohormonal stimulation, cardiac hypertrophy proceeds through the following successive genetic events: (*a*) an immediate early gene expression of protooncogenes, such as *c-myc*, *c-fos*, *Egr1*, Following neurohormonal stimulation, cardiac hyper-<br>trophy proceeds through the following successive genetic T<br>events: (*a*) an immediate early gene expression of pro-<br>tooncogenes, such as c-*myc*, c-*fos*, *Egr1*, c-*jun* trophy proceeds through the following successive genevents: (*a*) an immediate early gene expression of p tooncogenes, such as  $c-myc$ ,  $c-fos$ ,  $Egr1$ ,  $c-jun$ , and  $j$  *B*. This genetic program occurs within 1 to 2 h and d not events: (*a*) an immediate early gene expression of pro-<br>tooncogenes, such as  $c\text{-}myc$ ,  $c\text{-}fos$ ,  $Egr1$ ,  $c\text{-}jun$ , and  $jun-B$ . This genetic program occurs within 1 to 2 h and does<br>not require any protein synthesis. Most of tooncogenes, such as c-myc, c-fos, Egr1, c-jun, and jun-<br>B. This genetic program occurs within 1 to 2 h and does Ca<br>not require any protein synthesis. Most of these protoon-<br>to cogenes encode transcriptional factors (or r B. This genetic program occurs within 1 to 2 h and does Ca<sup>2</sup> not require any protein synthesis. Most of these protoon-<br>cogenes encode transcriptional factors (or related pro-<br>teins that behave as transcriptional factors) not require any protein synthesis. Most of these protoon-<br>cogenes encode transcriptional factors (or related pro-<br>teins that behave as transcriptional factors) that bind<br>firm DNA and activate the transcription machinery; cogenes encode transcriptional factors (or related pro-<br>teins that behave as transcriptional factors) that bind<br>fDNA and activate the transcription machinery; (b) a<br>expression of embryonic genes such as ANP, skeletal  $\alpha$ DNA and activate the transcription machinery; (b) a *f* reactivation, within 24 h in neonatal cardiac cells, of the expression of embryonic genes such as ANP, skeletal  $\alpha$ - n actin, and  $\beta$ -myosin heavy-chain genes; (c) reactivation, within 24 h in neonatal cardiac cells, of the expression of embryonic genes such as ANP, skeletal  $\alpha$ -<br>actin, and  $\beta$ -myosin heavy-chain genes; (c) an up-regulation, within 24 and 48 h, of constitutively e expression of embryonic genes such as ANP, skeletal  $\alpha$ -<br>actin, and  $\beta$ -myosin heavy-chain genes; (c) an up-regu-<br>lation, within 24 and 48 h, of constitutively expressed 2<br>contractile protein genes (MLC-2, cardiac  $\alpha$ actin, and  $\beta$ -myosin heavy-chain genes; (c) an up-regulation, within 24 and 48 h, of constitutively expressed contractile protein genes (MLC-2, cardiac  $\alpha$ -actin). It should be pointed out that the time course of these lation, within<br>contractile pr<br>should be point<br>genetic events<br>of hypertrophy.<br> $\alpha_1$ -Adrenerg ntractile protein genes (MLC-2, cardiac  $\alpha$ -actin). It<br>ould be pointed out that the time course of these<br>netic events can vary between different in vivo models<br>hypertrophy.<br> $\alpha_1$ -Adrenergic stimulation triggers most of should be pointed out that the time course of these<br>genetic events can vary between different in vivo models<br>of hypertrophy.<br> $\alpha_1$ -Adrenergic stimulation triggers most of these ge-<br>netic events (table 2). More specifical

ENOCEPTORS<br>normally involved in cell proliferation and transfo<br>tion (Starksen et al., 1986; Ikeda et al., 1991). the income serve<br>
the produced in cell proliferation and transforma-<br>
tion (Starksen et al., 1986; Ikeda et al., 1991). The<br>
induction of c-myc expression in cultured cardiac myoinduction of the *c-myc* expression of the *c-myc* expression in cultured cardiac mycrotes is rapid (maximum reached within 1 to 2 h) and the *c*-myc expression in cultured cardiac mycrotes is rapid (maximum reached within normally involved in cell proliferation and transforma-<br>tion (Starksen et al., 1986; Ikeda et al., 1991). The<br>induction of c-myc expression in cultured cardiac myo-<br>cytes is rapid (maximum reached within 1 to 2 h) and<br>shor normally involved in cell proliferation and transformation (Starksen et al., 1986; Ikeda et al., 1991). The induction of c-myc expression in cultured cardiac myocytes is rapid (maximum reached within 1 to 2 h) and short-li tion (Starksen et al., 1986; Ikeda et al., 1991). The<br>induction of c-myc expression in cultured cardiac myo-<br>cytes is rapid (maximum reached within 1 to 2 h) and<br>short-lived (by 6 h after stimulation, c-myc mRNA re-<br>turns cytes is rapid (maximum reached within 1 to 2 h) and<br>short-lived (by 6 h after stimulation, c-myc mRNA re-<br>turns to control levels). The mechanism by which the<br> $\alpha_1$ -adrenoceptor enhances c-myc expression is not<br>known. T turns to control levels). The mechanism by which the short-lived (by 6 h after stimulation,  $c\text{-}myc$  mRNA returns to control levels). The mechanism by which the  $\alpha_1$ -adrenoceptor enhances  $c\text{-}myc$  expression is not known. The PKC activator, phorbol-12-myristate, also in turns to control levels). The mechanism by which the  $\alpha_1$ -adrenoceptor enhances c-*myc* expression is not known. The PKC activator, phorbol-12-myristate, also increases the levels of c-*myc* mRNA and produces hypertroph  $\alpha_1$ -adrenoceptor enhances c-*myc* expression is not<br>known. The PKC activator, phorbol-12-myristate, also<br>increases the levels of c-*myc* mRNA and produces hy-<br>pertrophy in cultured cardiac myocytes (Starksen et al.,<br>19 known. The PKC activator, phorbol-12-myristate, alincreases the levels of c-myc mRNA and produces hertrophy in cultured cardiac myocytes (Starksen et all 1986).  $\alpha_1$ -Adrenoceptor agonists rapidly activate (with 15 to 30 increases the levels of c-*myc* mRNA and produces hypertrophy in cultured cardiac myocytes (Starksen et al., 1986).  $\alpha_1$ -Adrenoceptor agonists rapidly activate (within 15 to 30 min) the expression of two other protoonco 1986).  $\alpha_1$ -Adrenoceptor agonists rapidly activate (within 15 to 30 min) the expression of two other protooncogenes, namely, c-*fos* and c-*jun*, and the inducible zinc finger gene, *Egr-1*. These genes are involved in 1986).  $\alpha_1$ -Adrenoceptor agonists rapidly activate (within 15 to 30 min) the expression of two other protooncogenes, namely, c-fos and c-jun, and the inducible zinc finger gene,  $Egr-1$ . These genes are involved in the d 15 to 30 min) the expression of two other protoon<br>namely, c-fos and c-jun, and the inducible zir<br>gene,  $Egr-1$ . These genes are involved in the deve<br>of cell hypertrophy through a pertussis toxin-in<br>mechanism (Iwaki et al., namely, c-*fos* and c-*jun*, and the inducible zinc finger<br>gene, *Egr*-1. These genes are involved in the development<br>of cell hypertrophy through a pertussis toxin-insensitive<br>mechanism (Iwaki et al., 1990). Phorbol-12-my gene, *Egr-1*. These genes are involved in the development<br>of cell hypertrophy through a pertussis toxin-insensitive<br>mechanism (Iwaki et al., 1990). Phorbol-12-myristate-<br>13-acetate is also capable of inducing the expressi mechanism (Iwaki et al., 1990). Phorbol-12-myristate-<br>13-acetate is also capable of inducing the expression of<br>the protooncogenes c-fos and c-jun and the Egr-1 gene<br>(Dunnmon et al., 1990).<br> $\alpha_1$ -Adrenergic stimulation pr echanism (Iwaki et al., 1990). Phorbol-12-myristate-<br>-acetate is also capable of inducing the expression of<br>e protooncogenes c-fos and c-jun and the Egr-1 gene<br>bunnmon et al., 1990).<br> $\alpha_1$ -Adrenergic stimulation produces

13-acetate is also capable of inducing the expression of<br>the protooncogenes c-fos and c-jun and the Egr-1 gene<br>(Dunnmon et al., 1990).<br> $\alpha_1$ -Adrenergic stimulation produces a several-fold in-<br>crease in the number of sarc the protooncogenes c-fos and c-jun and the *Egr*-1 gene<br>(Dunnmon et al., 1990).<br> $\alpha_1$ -Adrenergic stimulation produces a several-fold in-<br>crease in the number of sarcomere units in the cellular<br>content of cardiac myofibri (Dunnmon et al., 1990).<br>  $\alpha_1$ -Adrenergic stimulation produces a several-fold in-<br>
crease in the number of sarcomere units in the cellular<br>
content of cardiac myofibrillar genes (MLC-2, skeletal<br>
and cardiac  $\alpha$ -actin)  $\alpha_1$ -Adrenergic stimulation produces a several-fold in-<br>crease in the number of sarcomere units in the cellular<br>content of cardiac myofibrillar genes (MLC-2, skeletal<br>and cardiac  $\alpha$ -actin) and in the steady-state leve crease in the number of sarcomere units in the cellul<br>content of cardiac myofibrillar genes (MLC-2, skelet<br>and cardiac  $\alpha$ -actin) and in the steady-state levels of the<br>corresponding mRNA (Lee et al., 1988; Iwaki et al., content of cardiac myofibrillar genes (MLC-2, ske<br>and cardiac  $\alpha$ -actin) and in the steady-state levels o<br>corresponding mRNA (Lee et al., 1988; Iwaki et al., 1<br>Bishopric et al., 1987; Long et al., 1989). Because p<br>ylephr and cardiac  $\alpha$ -actin) and in the steady-state levels<br>corresponding mRNA (Lee et al., 1988; Iwaki et al.<br>Bishopric et al., 1987; Long et al., 1989). Because<br>ylephrine did not produce a similar effect in nonm<br>dial cells, corresponding mRNA (Lee et al., 1988; Iwaki et al., 1990;<br>Bishopric et al., 1987; Long et al., 1989). Because phen-<br>ylephrine did not produce a similar effect in nonmyocar-<br>dial cells, it was concluded that the  $\alpha_1$ -adr Bishopric et al., 1987; Long et al., 1989). Because phen-<br>ylephrine did not produce a similar effect in nonmyocar-<br>dial cells, it was concluded that the  $\alpha_1$ -adrenoceptor-<br>mediated increase in transcription activity is ylephrine did not produce a similar effect in nonmyocardial cells, it was concluded that the  $\alpha_1$ -adrenoceptor-<br>mediated increase in transcription activity is specific for<br>cardiac genes (Lee et al., 1988). The direct ac dial cells, it was concluded that the  $\alpha_1$ -adrenoceptor-<br>mediated increase in transcription activity is specific for<br>cardiac genes (Lee et al., 1988). The direct activation of<br>PKC by phorbol-12-myristate-13-acetate also mediated increase in transcription activity is specific for cardiac genes (Lee et al., 1988). The direct activation of PKC by phorbol-12-myristate-13-acetate also induces the expression of the MLC-2 gene and increases the cardiac genes (Lee et al., 1988). The direct activation of<br>
PKC by phorbol-12-myristate-13-acetate also induces<br>
the expression of the MLC-2 gene and increases the<br>
accumulation of the contractile protein in neonatal cell PKC by phorbol-12-myristate-13-acetate also inductive expression of the MLC-2 gene and increases accumulation of the contractile protein in neonatal contramination of the contractile protein in neonatal colular protein et the expression of the MLC-2 generative of the contractile proton (Dunnmon et al., 1990). These doculd participate in the  $\alpha_1$ -adrenometric sion of contractile protein genes.<br> $\alpha_1$ -Adrenoceptor agonists are also cumulation of the contractile protein in neonatal cells<br>bunnmon et al., 1990). These data suggest that PKC<br>uld participate in the  $\alpha_1$ -adrenoceptor-induced expres-<br>on of contractile protein genes.<br> $\alpha_1$ -Adrenoceptor ag could participate in the  $\alpha_1$ -adrenoceptor-induced expression of contractile protein genes.<br> $\alpha_1$ -Adrenoceptor agonists are also potent activators of

genetic events can vary between different in vivo models same approach, these authors reported that cotransfec-<br>of hypertrophy.<br> $\alpha_1$ -Adrenergic stimulation triggers most of these ge-<br> $\beta$ -isozymes of PKC also increased could participate in the  $\alpha_1$ -adrenoceptor-induced expression of contractile protein genes.<br>  $\alpha_1$ -Adrenoceptor agonists are also potent activators of<br>
the expression of the ANP gene (Knowlton et al., 1991).<br>
The  $\alpha_1$ sion of contractile protein genes.<br>  $\alpha_1$ -Adrenoceptor agonists are also potent activators of<br>
the expression of the ANP gene (Knowlton et al., 1991).<br>
The  $\alpha_1$ -adrenoceptor induced coexpression of the gene<br> *Egr-1* co  $\alpha_1$ -Adrenoceptor agonists are also potent activators of<br>the expression of the ANP gene (Knowlton et al., 1991).<br>The  $\alpha_1$ -adrenoceptor induced coexpression of the gene<br>Egr-1 could play a role in the expression of cont The  $\alpha_1$ -adrenoceptor induced coexpression of the gene *Egr-1* could play a role in the expression of contractile proteins and ANP genes (Iwaki et al., 1990). PKC and *Egr-1* could play a role in the expression of contractile proteins and ANP genes (Iwaki et al., 1990). PKC and  $Ca^{2+}$ -calmodulin-dependent kinases have been reported to be involved in the  $\alpha_1$ -adrenoceptor-induced ANP *Egr-1* could play a role in the expression of contractile proteins and ANP genes (Iwaki et al., 1990). PKC and  $Ca^{2+}$ -calmodulin-dependent kinases have been reported to be involved in the  $\alpha_1$ -adrenoceptor-induced ANP proteins and ANP genes (Iwaki et al., 1990). PKC and  $Ca^{2+}$ -calmodulin-dependent kinases have been reported to be involved in the  $\alpha_1$ -adrenoceptor-induced ANP gene expression (Sei et al., 1991). Shubeita et al. (1992) to be involved in the  $\alpha_1$ -adrenoceptor-induced ANP gene<br>expression (Sei et al., 1991). Shubeita et al. (1992) con-<br>firmed that phenylephrine induces the expression of<br>ANP and MLC-2 genes. The  $\alpha$ -agonist increased by to be involved in the  $\alpha_1$ -adrenoceptor-induced ANP gene<br>expression (Sei et al., 1991). Shubeita et al. (1992) con-<br>firmed that phenylephrine induces the expression of<br>ANP and MLC-2 genes. The  $\alpha$ -agonist increased by expression (Sei et al., 1991). Shubeita et al. (1992) confirmed that phenylephrine induces the expression of ANP and MLC-2 genes. The  $\alpha$ -agonist increased by 12-<br>and 5-fold the accumulation of the ANP and MLC-2<br>mRNA, re firmed that phenylephrine induces the expression ANP and MLC-2 genes. The  $\alpha$ -agonist increased by 1 and 5-fold the accumulation of the ANP and MLC mRNA, respectively. Moreover, using neonatal myocyt transfected with con ANP and MLC-2 genes. The  $\alpha$ -agonist increased by 12<br>and 5-fold the accumulation of the ANP and MLC-:<br>mRNA, respectively. Moreover, using neonatal myocyte<br>transfected with constructs containing the ANP or MLC<br>2 promoter and 5-fold the accumulation of the ANP and MLC-2 mRNA, respectively. Moreover, using neonatal myocytes transfected with constructs containing the ANP or MLC-2 promoter associated with the luciferase cDNA, Shubeita et al. ( mRNA, respectively. Moreover, using neonatal myocytes<br>transfected with constructs containing the ANP or MLC-<br>2 promoter associated with the luciferase cDNA, Shu-<br>beita et al. (1992) observed an increase in the luciferase<br>a 2 promoter associated with the luciferase cDNA, Shubeita et al. (1992) observed an increase in the luciferase activity in phenylephrine-stimulated cells. Using the 2 promoter associated with the luciferase cDNA, Shubeita et al. (1992) observed an increase in the luciferase activity in phenylephrine-stimulated cells. Using the same approach, these authors reported that cotransfection beita et al. (1992) observed an increase in the luciferase activity in phenylephrine-stimulated cells. Using the same approach, these authors reported that cotransfection of vectors encoding constitutively active  $\alpha$ - an activity in phenylephrine-stimulated cells. Using the<br>same approach, these authors reported that cotransfec-<br>tion of vectors encoding constitutively active  $\alpha$ - and/or<br> $\beta$ -isozymes of PKC also increased the luciferase a same approach, these authors reported that cotransfection of vectors encoding constitutively active  $\alpha$ - and/or  $\beta$ -isozymes of PKC also increased the luciferase activity.<br>This may suggest that the  $\alpha$ - and/or  $\beta$ -iso

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genes induced by  $\alpha$ -adrenoceptor agonists. The  $\alpha_{1A}$ -adre-noceptor-selective antagonist, (+)-niguldipine, inhibits Savetan d-actin: Esshophe<br>
Cardiac  $\alpha$ -actin: Long et al.<br>
genes induced by  $\alpha$ -adrenoceptor agonists. The  $\alpha_{1A}$ -adre-<br>
noceptor-selective antagonist, (+)-niguldipine, inhibits<br>
the transcriptional activation of the genes induced by  $\alpha$ -adrenoceptor agonists. The  $\alpha_{1A}$ -adrenoceptor-selective antagonist, (+)-niguldipine, inhibits<br>the transcriptional activation of the ANP-luciferase fu-<br>sion gene. This suggests that cardiac  $\alpha_{1A}$ genes induced by  $\alpha$ -adrenoceptor agonists. The  $\alpha_{1A}$ -adre-<br>noceptor-selective antagonist, (+)-niguldipine, inhibits we<br>the transcriptional activation of the ANP-luciferase fu-<br>sion gene. This suggests that cardiac  $\$ genes induced by  $\alpha$ -adrenoceptor agonists. The  $\alpha_{1A}$ -adrenoceptor-selective antagonist, (+)-niguldipine, inhibits<br>the transcriptional activation of the ANP-luciferase fu-<br>sion gene. This suggests that cardiac  $\alpha_{1A}$ noceptor-selective antagonist,  $(+)$ -niguldipine, inhibits<br>the transcriptional activation of the ANP-luciferase fu-<br>sion gene. This suggests that cardiac  $\alpha_{1A}$  may be involved<br>in the induction of embryonic gene expressi the transcriptional activation of the ANP-luciferase fusion gene. This suggests that cardiac  $\alpha_{1A}$  may be involved<br>in the induction of embryonic gene expression in neo-<br>natal cells (Michel et al., 1990), which is in ag sion gene. This suggests that cardiac  $\alpha_{1A}$  may be involved 19<br>in the induction of embryonic gene expression in neo-<br>natal cells (Michel et al., 1990), which is in agreement swith the finding that the  $\alpha_{1A}$ -adrenoce in the induction of embryonic gene expression in neo-<br>natal cells (Michel et al., 1990), which is in agreement<br>with the finding that the  $\alpha_{1A}$ -adrenoceptor mediates cell<br>hypertrophy (Simpson et al. 1990). The expressio natal cells (Michel et al., 1990), which is in agreement<br>with the finding that the  $\alpha_{1A}$ -adrenoceptor mediates cell<br>hypertrophy (Simpson et al. 1990). The expression of<br>these embryonic genes occurs following a 24- to 4 hypertrophy (Simpson et al. 1990). The expression of these embryonic genes occurs following a 24- to 48-h  $\alpha_1$ -<br>adrenergic stimulation of neonatal cardiomyocytes.  $\alpha_1$ -<br>Adrenoceptor stimulation was recently shown to u these embryonic genes occurs following a 24- to 48-h  $\alpha_1$ - mained higher than in control animals during the devel-<br>adrenergic stimulation of neonatal cardiomyocytes.  $\alpha_1$ - opment of the hypertrophic stage; the authors these embryonic genes occurs following a 24- to 48-h  $\alpha_1$ -<br>adrenergic stimulation of neonatal cardiomyocytes.  $\alpha_1$ -<br>Adrenoceptor stimulation was recently shown to up reg-<br>ulate  $\beta$ -myosin heavy chain iso-mRNA (Waspe adrenergic stimulation of neon<br>Adrenoceptor stimulation was<br>ulate  $\beta$ -myosin heavy chain i<br>1990), probably through the sti<br>of PKC (Kariya et al., 1991).<br>In adult ventricular cells,  $\alpha$ drenoceptor stimulation was recently shown to up reg-<br>ate  $\beta$ -myosin heavy chain iso-mRNA (Waspe et al.,<br>90), probably through the stimulation of the  $\beta$ -isozyme<br>PKC (Kariya et al., 1991).<br>In adult ventricular cells,  $\$ 

ulate  $\beta$ -myosin heavy chain iso-mRNA (Waspe et al., 1990), probably through the stimulation of the  $\beta$ -isozyme of PKC (Kariya et al., 1991).<br>In adult ventricular cells,  $\alpha$ -adrenoceptor agonists in-<br>duce the expressio 1990), probably through the stimulation of the  $\beta$ -isozyme<br>of PKC (Kariya et al., 1991).<br>In adult ventricular cells,  $\alpha$ -adrenoceptor agonists in-<br>duce the expression of the 15-kDa protein "Id" (for<br>"inhibitor of DNA bi of PKC (Kariya et al., 1991).<br>
In adult ventricular cells,  $\alpha$ -adrenoceptor agonists in-<br>
duce the expression of the 15-kDa protein "Id" (for<br>
"inhibitor of DNA binding") (Springhorn et al., 1992).<br>
This protein prevents In adult ventricular cells,  $\alpha$ -adrenoceptor agonists in-<br>duce the expression of the 15-kDa protein "Id" (for<br>"inhibitor of DNA binding") (Springhorn et al., 1992).<br>This protein prevents the binding to DNA of muscle<br>pote duce the expression of the 15-kDa protein "Id" (for<br>"inhibitor of DNA binding") (Springhorn et al., 1992).<br>This protein prevents the binding to DNA of muscle A<br>potentiators of differentiation, such as myoD, myogenin,<br>and "inhibitor of DNA binding") (Springhorn et al., 1992).<br>This protein prevents the binding to DNA of muscle A.<br>potentiators of differentiation, such as myoD, myogenin,<br>and Mif5 (Benezra et al., 1990). These molecules serve<br> This protein prevents the binding to DNA of muscle<br>potentiators of differentiation, such as myoD, myogenin,<br>and Mif5 (Benezra et al., 1990). These molecules serve<br>as tissue-specific transcriptional factors. It should be<br>p potentiators of differentiation, such as myoD, myogenin,<br>and Mif5 (Benezra et al., 1990). These molecules serve<br>as tissue-specific transcriptional factors. It should be<br>pointed out that, although these factors are not expr and Mif5 (Benezra et al., 1990). These molecules serve<br>as tissue-specific transcriptional factors. It should be<br>pointed out that, although these factors are not expressed<br>in the heart, it is likely that similar factors, n as tissue-specific transcriptional factors. It should be<br>pointed out that, although these factors are not expressed<br>in the heart, it is likely that similar factors, not yet<br>identified, are responsible for the cardiac phen pointed out that, although these factors are not expressed<br>in the heart, it is likely that similar factors, not yet<br>identified, are responsible for the cardiac phenotype (for<br>review, see Olson, 1993). The expression level in the heart, it is likely that similar factors, not yeldentified, are responsible for the cardiac phenotype (foreview, see Olson, 1993). The expression level is usuall high in undifferentiated proliferating cells but dim identified, are responsible for the cardiac phenotype (for<br>review, see Olson, 1993). The expression level is usually<br>high in undifferentiated proliferating cells but diminishes<br>with growth arrest and when cells begin to d review, see Olson, 1993). The expression level is usually<br>high in undifferentiated proliferating cells but diminishes<br>with growth arrest and when cells begin to differentiate.<br>Concomitantly with the induction of Id,  $\alpha$ high in undifferentiated proliferating cells but diminishes with growth arrest and when cells begin to differentiate. Concomitantly with the induction of Id,  $\alpha$ -agonists increased by 51% the rate of protein synthesis (S with growth arrest and when cells begin to differentiate.<br>Concomitantly with the induction of Id,  $\alpha$ -agonists in-<br>creased by 51% the rate of protein synthesis (Springhorn<br>et al., 1992). This study raises the possibility Concomitantly with the induction of Id,  $\alpha$ -agonists in<br>creased by 51% the rate of protein synthesis (Springhor<br>et al., 1992). This study raises the possibility that, in<br>response to physiological stimuli, including catec creased by 51% the rate of protein synthesis (Springhorn et al., 1992). This study raises the possibility that, in response to physiological stimuli, including catecholamines' action through  $\alpha$ -adrenoceptors, Id could m et al., 1992). This study raises the possibility that, in response to physiological stimuli, including catecholamines' action through  $\alpha$ -adrenoceptors, Id could modulate cell growth and regulate the cardiac phenotype's amines' action through  $\alpha$ -adrenoceptors, Id could modulate cell growth and regulate the cardiac phenotype's a m<br>plasticity both during cardiac ontogeny and in the adult. bett<br>Myocardial hypertrophy is an adaptive respon

ulate cell growth and regulate the cardiac phenotype's<br>plasticity both during cardiac ontogeny and in the adult.<br>Myocardial hypertrophy is an adaptive response of the<br>heart to hemodynamic overload and commonly occurs in<br>ga plasticity both during cardiac ontogeny and in the adult.<br>Myocardial hypertrophy is an adaptive response of the<br>heart to hemodynamic overload and commonly occurs in<br>patients with hypertension and valvular heart disease<br>(Sw Myocardial hypertrophy is an adaptive response of theart to hemodynamic overload and commonly occurs<br>patients with hypertension and valvular heart dises<br>(Swynghedauw and Delcayre, 1982). Zierhut and Zimn<br>(1989) reported th heart to hemodynamic overload and commonly occurs in<br>patients with hypertension and valvular heart disease<br>(Swynghedauw and Delcayre, 1982). Zierhut and Zimmer<br>(1989) reported that the intravenous infusion of norepi-<br>nephr patients with hypertension and valvular heart disease (Swynghedauw and Delcayre, 1982). Zierhut and Zimmer (1989) reported that the intravenous infusion of norepi-<br>nephrine for 3 days triggered the development of left<br>vent (Swynghedauw and Delcayre, 1982). Zierhut and Zimmer (1989) reported that the intravenous infusion of norepi-<br>nephrine for 3 days triggered the development of left<br>ventricular hypertrophy as indicated by changes in sev-<br>e (1989) reported that the intravenous infusion of norepi-<br>nephrine for 3 days triggered the development of left<br>ventricular hypertrophy as indicated by changes in sev-<br>eral functional parameters (e.g., increase in heart ra nephrine for 3 days triggered the development of left ventricular hypertrophy as indicated by changes in several functional parameters (e.g., increase in heart rate and left ventricular rate of change of pressure and incre ventricular hypertrophy as indicated by changes in several functional parameters (e.g., increase in heart rate the and left ventricular rate of change of pressure and increased total peripheral resistance), as well as inc eral functional parameters (e.g., increase in heart rate the and left ventricular rate of change of pressure and increased total peripheral resistance), as well as increases (Se in the RNA to DNA and left ventricle weight and left ventricular rate of change of pressure and in-<br>creased total peripheral resistance), as well as increases<br>in the RNA to DNA and left ventricle weight to body<br>weight ratios. The authors attributed this effect to b

(1989)<br>
(1989)<br>
diac overload, the density of cardiac  $\alpha_1$ -adrenoceptors<br>
was enhanced and preceded the development of cardiac<br>
hypertrophy in pressure-overloaded hearts (Tamai et al., diac overload, the density of cardiac  $\alpha_1$ -adrenoceptors<br>was enhanced and preceded the development of cardiac<br>hypertrophy in pressure-overloaded hearts (Tamai et al.,<br>1989). An enhanced  $\alpha_1$ -adrenoceptor activity and diac overload, the density of cardiac  $\alpha_1$ -adrenoceptors<br>was enhanced and preceded the development of cardiac<br>hypertrophy in pressure-overloaded hearts (Tamai et al.,<br>1989). An enhanced  $\alpha_1$ -adrenoceptor activity and diac overload, the density of cardiac  $\alpha_1$ -adrenoceptors<br>was enhanced and preceded the development of cardiac<br>hypertrophy in pressure-overloaded hearts (Tamai et al.,<br>1989). An enhanced  $\alpha_1$ -adrenoceptor activity and was enhanced and preceded the development of cardiac<br>hypertrophy in pressure-overloaded hearts (Tamai et al.,<br>1989). An enhanced  $\alpha_1$ -adrenoceptor activity and an<br>excessive  $\alpha_1$ -adrenoceptor-mediated growth may sub-<br>s 1989). An enhanced  $\alpha_1$ -adrenoceptor activity and an excessive  $\alpha_1$ -adrenoceptor-mediated growth may subserve protein synthesis in response to pressure overload. More recently, Kagiya et al. (1991a) showed that, in ca excessive  $\alpha_1$ -adrenoceptor-mediated growth may su<br>serve protein synthesis in response to pressure overloa<br>More recently, Kagiya et al. (1991a) showed that,<br>cardiomyopathic hamsters,  $\alpha_1$ -adrenoceptor density r<br>mained cardiomyopathic hamsters,  $\alpha_1$ -adrenoceptor density re-More recently, Kagiya et al. (1991a) showed that, cardiomyopathic hamsters,  $\alpha_1$ -adrenoceptor density mained higher than in control animals during the devopment of the hypertrophic stage; the authors also served an atte cardiomyopathic hamsters,  $\alpha_1$ -adrenoceptor density re-<br>mained higher than in control animals during the devel-<br>opment of the hypertrophic stage; the authors also ob-<br>served an attenuation of the hypertrophy when  $\alpha_1$ mained higher than in control animals during the devel-<br>opment of the hypertrophic stage; the authors also ob-<br>served an attenuation of the hypertrophy when  $\alpha_1$ -adre-<br>noceptors were blocked. They, thus, concluded that opment of the hypertrophic stage; the authors also<br>served an attenuation of the hypertrophy when  $\alpha_1$ -a<br>noceptors were blocked. They, thus, concluded that<br>adrenergic stimulation played an important role in<br>progression o adrenergic stimulation played an important role in the<br>progression of cardiac hypertrophy in cardiomyopathy.<br>VI. Existence of Functional  $\alpha_1$ -Adrenoceptors in<br>Human Cardiac Tissue

## progression of cardiac hypertrophy in cardiomyopathy.<br> **VI. Existence of Functional**  $\alpha_1$ **-Adrenoceptors in<br>
<b>Human Cardiac Tissue**<br> *A. In Vitro Studies Progression of cartiac*<br>**VI. Existence of Filtmen**<br>*A. In Vitro Studies*<br>Human cardiac cel

et al., 1992). This study raises the possibility that, in<br>
educator has been cloned (Ramarao et al., 1992).<br>
response to physiological stimuli, including catechol-<br>
The nucleotide sequence predicts a seven-transmem-<br>
amin 1989). An enhanced  $\alpha_1$ -adrenoceptor activity and an excessive  $\alpha_1$ -adrenoceptor-mediated growth may sub-<br>serve protein synthesis in response to pressure overload.<br>More recently, Kagiya et al. (1991a) showed that, in VI. Existence of Functional  $\alpha_1$ -Adrenoceptors in<br>Human Cardiac Tissue<br>In Vitro Studies<br>Human cardiac cells possess  $\alpha_1$ -adrenoceptors. This<br>is been demonstrated by binding studies using selective Human Cardiac Tissue<br>
A. In Vitro Studies<br>
Human cardiac cells possess  $\alpha_1$ -adrenoceptors. This<br>
has been demonstrated by binding studies using selective<br>  $\alpha_1$ -adrenoceptors ligands, [<sup>3</sup>H]prazosin or [<sup>125</sup>I]IBE 2254 A. In Vitro Studies<br>
Human cardiac cells possess  $\alpha_1$ -adrenoceptors. This<br>
has been demonstrated by binding studies using selective<br>  $\alpha_1$ -adrenoceptors ligands, [<sup>3</sup>H]prazosin or [<sup>125</sup>I]IBE 2254<br>
(Bevilacqua et al., Human cardiac cells possess  $\alpha_1$ -adrenoceptors. This<br>has been demonstrated by binding studies using selective<br> $\alpha_1$ -adrenoceptors ligands, [<sup>3</sup>H]prazosin or [<sup>125</sup>I]IBE 2254<br>(Bevilacqua et al., 1987; Böhm et al., 1988b Human cardiac cells possess  $\alpha_1$ -adrenoceptors. This<br>has been demonstrated by binding studies using selective<br> $\alpha_1$ -adrenoceptors ligands, [<sup>3</sup>H]prazosin or [<sup>125</sup>I]IBE 2254<br>(Bevilacqua et al., 1987; Böhm et al., 1988b has been demonstrated by binding studies using selective  $\alpha_1$ -adrenoceptors ligands, [<sup>3</sup>H]prazosin or [<sup>125</sup>I]IBE 2254 (Bevilacqua et al., 1987; Böhm et al., 1988b; Bristow et al., 1988; Steinfath et al., 1992a,b). In  $\alpha_1$ -adrenoceptors ligands, [<sup>3</sup>H]prazosin or [<sup>125</sup>I]IBE 2254 (Bevilacqua et al., 1987; Böhm et al., 1988b; Bristow et al., 1988; Steinfath et al., 1992a,b). In the presence of GTP, a rightward shift of the displacemen (Bevilacqua et al., 1987; Böhm et al., 1988b; Bristow et al., 1988; Steinfath et al., 1992a,b). In the presence of GTP, a rightward shift of the displacement curve for unlabeled  $\alpha_1$ -agonists occurred, suggesting that h al., 1988; Steinfath et al., 1992a,b). In the presence of GTP, a rightward shift of the displacement curve for unlabeled  $\alpha_1$ -agonists occurred, suggesting that human cardiac  $\alpha_1$ -adrenoceptors are linked to a GTP-bin GTP, a rightward shift of the displacement curve for<br>unlabeled  $\alpha_1$ -agonists occurred, suggesting that human<br>cardiac  $\alpha_1$ -adrenoceptors are linked to a GTP-binding<br>protein (Bevilacqua et al., 1987). It is not yet know unlabeled  $\alpha_1$ -agonists occurred, suggesting that human cardiac  $\alpha_1$ -adrenoceptors are linked to a GTP-binding protein (Bevilacqua et al., 1987). It is not yet known which  $\alpha_1$ -adrenoceptor subtypes are present in h cardiac  $\alpha_1$ -adrenoceptors are linked to a GTP-binding<br>protein (Bevilacqua et al., 1987). It is not yet known<br>which  $\alpha_1$ -adrenoceptor subtypes are present in human<br>myocardial cells. The gene encoding the human  $\alpha_{1B}$ protein (Bevilacqua et al., 1987). It is not yet<br>which  $\alpha_1$ -adrenoceptor subtypes are present in  $\alpha_1$ -adrenoceptor subtypes are present in  $\alpha_2$ <br>myocardial cells. The gene encoding the huma<br>adrenoceptor has been clon which  $\alpha_1$ -adrenoceptor subtypes are present in human<br>myocardial cells. The gene encoding the human  $\alpha_{1B}$ -<br>adrenoceptor has been cloned (Ramarao et al., 1992).<br>The nucleotide sequence predicts a seven-transmem-<br>brane myocardial cells. The gene encoding the human  $\alpha_{1B}$ -<br>adrenoceptor has been cloned (Ramarao et al., 1992).<br>The nucleotide sequence predicts a seven-transmem-<br>brane domain receptor made of 517 amino acids and with<br>a mole adrenoceptor has been cloned (Ramarao et al., 1992<br>The nucleotide sequence predicts a seven-transmen<br>brane domain receptor made of 517 amino acids and wit<br>a molecular mass of 57 kDa. A high homology exis<br>between this huma The nucleotide sequence predicts a seven-transmen<br>brane domain receptor made of 517 amino acids and wit<br>a molecular mass of 57 kDa. A high homology exis<br>between this human receptor and the  $\alpha_{1B}$ -adrenocepto<br>found in ra brane domain receptor made of 517 amino acids and with<br>a molecular mass of 57 kDa. A high homology exists<br>between this human receptor and the  $\alpha_{1B}$ -adrenoceptor<br>found in rat, hamster, and dog. The  $\alpha_{1B}$ -adrenoceptor a molecular mass of 57 kDa. A high homology exists between this human receptor and the  $\alpha_{1B}$ -adrenoceptor found in rat, hamster, and dog. The  $\alpha_{1B}$ -adrenoceptor gene is transcribed in human hearts as demonstrated by between this human receptor and the  $\alpha_{1B}$ -adrenoceptor<br>found in rat, hamster, and dog. The  $\alpha_{1B}$ -adrenoceptor<br>gene is transcribed in human hearts as demonstrated by<br>Northern blot analysis with the aid of a fragment found in rat, hamster, and dog. The  $\alpha_{1B}$ -adrenoceptor<br>gene is transcribed in human hearts as demonstrated by<br>Northern blot analysis with the aid of a fragment from<br>a heart CDNA library that corresponds to exon 1 of th

The stimulation of human atrial or ventricular  $\alpha_1$ -Northern blot analysis with the aid of a fragment from<br>a heart cDNA library that corresponds to exon 1 of the<br>gene (Ramarao et al., 1992).<br>The stimulation of human atrial or ventricular  $\alpha_1$ -<br>adrenoceptors by endogenous a heart cDNA library that corresponds to exon 1 of gene (Ramarao et al., 1992).<br>The stimulation of human atrial or ventricular adrenoceptors by endogenous catecholamines or s<br>thetic sympathomimetics, in the presence of  $\$ gene (Ramarao et al., 1992).<br>The stimulation of human atrial or ventricular  $\alpha_1$ -<br>adrenoceptors by endogenous catecholamines or syn-<br>thetic sympathomimetics, in the presence of  $\beta$ -adreno-<br>ceptor blockade, produces a p The stimulation of human atrial or ventricular  $\alpha_1$ -<br>adrenoceptors by endogenous catecholamines or syn-<br>thetic sympathomimetics, in the presence of  $\beta$ -adreno-<br>ceptor blockade, produces a positive inotropic effect<br>(Sch adrenoceptors by endogenous catecholamines or synthetic sympathomimetics, in the presence of  $\beta$ -adrenoceptor blockade, produces a positive inotropic effect (Schümann et al., 1978; Wagner et al., 1980; Brückner et al., 1 thetic sympathomimetics, in the presence of  $\beta$ -adreno-ceptor blockade, produces a positive inotropic effect (Schümann et al., 1978; Wagner et al., 1980; Brückner et al., 1984; Skomedal et al., 1985; Aass et al., 1986; A ceptor blockade, produces a positive inotropic effect<br>(Schümann et al., 1978; Wagner et al., 1980; Brückner<br>et al., 1984; Skomedal et al., 1985; Aass et al., 1986; Ask<br>et al., 1987; Böhm et al., 1988b; Kohl et al., 1989; J

CARDIAC  $\alpha_1$ -A<br>contractile force produced by  $\alpha_1$ -adrenergic agonists var-<br>ies among studies. Indeed, the responsiveness of the CARDIAC  $\alpha_1$ -ADREN<br>contractile force produced by  $\alpha_1$ -adrenergic agonists var-<br>ies among studies. Indeed, the responsiveness of the an<br>human cardiac tissue to  $\alpha_1$ -adrenoceptor stimulation can wi CARDIAC  $\alpha_1$ -ADREN<br>contractile force produced by  $\alpha_1$ -adrenergic agonists var-<br>ies among studies. Indeed, the responsiveness of the ant<br>human cardiac tissue to  $\alpha_1$ -adrenoceptor stimulation can wit<br>be affected by se contractile force produced by  $\alpha_1$ -adrenergic agonists varies among studies. Indeed, the responsiveness of the human cardiac tissue to  $\alpha_1$ -adrenoceptor stimulation can be affected by several factors. These include th contractile force produced by  $\alpha_1$ -adrenergic agonists var<br>ies among studies. Indeed, the responsiveness of the<br>human cardiac tissue to  $\alpha_1$ -adrenoceptor stimulation can<br>be affected by several factors. These include t ies among studies. Indeed, the responsiveness of the and human cardiac tissue to  $\alpha_1$ -adrenoceptor stimulation can wive affected by several factors. These include the prior fuscondition of the heart (e.g., failing versu human cardiac tissue to  $\alpha_1$ -adrenoceptor stimulation can<br>be affected by several factors. These include the prior<br>condition of the heart (e.g., failing versus nonfailing),<br>exposure of cardiac muscle to different drugs, be affected by several factors. These include the prior fucondition of the heart (e.g., failing versus nonfailing), resposure of cardiac muscle to different drugs, and the to procedure of tissue removal during surgery and condition of the heart (e.g., failing versus nonfailing), ragposure of cardiac muscle to different drugs, and the to procedure of tissue removal during surgery and further un manipulations of the specimens. In nonfailing exposure of cardiac muscle to different drugs, and the procedure of tissue removal during surgery and further manipulations of the specimens. In nonfailing human hearts  $\alpha_1$ -adrenoceptor stimulation can increase the for procedure of tissue removal during surgery and further<br>manipulations of the specimens. In nonfailing human<br>hearts  $\alpha_1$ -adrenoceptor stimulation can increase the force<br>of contraction more than 2-fold (Kohl et al., 1989; hearts  $\alpha_1$ -adrenoceptor stimulation can increase the force<br>of contraction more than 2-fold (Kohl et al., 1989; Terzic,<br>1990). In failing human hearts, the  $\alpha_1$ -mediated positive<br>inotropic effect is usually smaller (S hearts  $\alpha_1$ -adrenoceptor stimulation can increase the force<br>of contraction more than 2-fold (Kohl et al., 1989; Terzic,<br>1990). In failing human hearts, the  $\alpha_1$ -mediated positive<br>inotropic effect is usually smaller (S of contraction more than 2-fold (Kohl et al., 1989; Terzic, thou<br>1990). In failing human hearts, the  $\alpha_1$ -mediated positive tilit<br>inotropic effect is usually smaller (Schmitz et al., 1987a; anta<br>Böhm et al., 1988b; Jako 1990). In failing human hearts, the  $\alpha_1$ -mediated positive tili inotropic effect is usually smaller (Schmitz et al., 1987a; ant Böhm et al., 1988b; Jakob et al., 1988; Steinfath et al., per 1992b). The mechanism respons Böhm et al., 1988b; Jakob et al., 1988; Steinfath et al., 1992b). The mechanism responsible for the decrease in inotropic responsiveness to  $\alpha_1$ -adrenergic agonists with the progression of heart failure is not known.<br>Th bhm et al., 1988b; Jakob et al., 1988; Steinfath et al., 92b). The mechanism responsible for the decrease in otropic responsiveness to  $\alpha_1$ -adrenergic agonists with e progression of heart failure is not known.<br>The absol

inotropic responsiveness to  $\alpha_1$ -adrenergic agonists with<br>the progression of heart failure is not known.<br>The absolute number of  $\alpha_1$ -adrenoceptors does not<br>change or even increase during the development of car-<br>diac f inotropic responsiveness to  $\alpha_1$ -adrenergic agonists with<br>the progression of heart failure is not known.<br>The absolute number of  $\alpha_1$ -adrenoceptors does not<br>change or even increase during the development of car-<br>diac f the progression of heart failure is not known.<br>The absolute number of  $\alpha_1$ -adrenoceptors does not<br>change or even increase during the development of car-<br>diac failure (Bristow et al., 1988; Steinfath et al., 1992b)<br>In ca The absolute number of  $\alpha_1$ -adrenoceptors does not when the approximate of cartian chainer (Bristow et al., 1988; Steinfath et al., 1992b).<br>In cardiac membranes obtained from patients with end-<br>stage heart failure (New change or even increase during the development of car-<br>diac failure (Bristow et al., 1988; Steinfath et al., 1992b).<br>In cardiac membranes obtained from patients with end-<br>stage heart failure (New York Heart Association IV In cardiac membranes obtained from patients with end-<br>stage heart failure (New York Heart Association IV, due<br>to an idiopathic dilated cardiomyopathy), the density of In cardiac membranes obtained from patients with end-<br>stage heart failure (New York Heart Association IV, due<br>to an idiopathic dilated cardiomyopathy), the density of<br>ventricular  $\alpha_1$ -adrenoceptors, assessed using [<sup>3</sup>H stage heart failure (New York Heart Association IV, due<br>to an idiopathic dilated cardiomyopathy), the density of<br>ventricular  $\alpha_1$ -adrenoceptors, assessed using [<sup>3</sup>H]prazo-<br>sin, was found to be 11 fmol/mg protein (nonfa ventricular  $\alpha_1$ -adrenoceptors, assessed using [<sup>3</sup>H]prazo-<br>sin, was found to be 11 fmol/mg protein (nonfailing<br>hearts, 4 fmol/mg protein) (Steinfath et al., 1992a,b).<br>Because there is no reduction of cardiac  $\alpha$ -adren ventricular  $\alpha_1$ -adrenoceptors, assessed using [<sup>3</sup>H]pra<br>sin, was found to be 11 fmol/mg protein (nonfail<br>hearts, 4 fmol/mg protein) (Steinfath et al., 1992a,<br>Because there is no reduction of cardiac  $\alpha$ -adrenocept<br>but sin, was found to be 11 fmol/mg protein (nonfailing n<br>hearts, 4 fmol/mg protein) (Steinfath et al., 1992a,b). p<br>Because there is no reduction of cardiac  $\alpha$ -adrenoceptors a<br>but an increased ratio of  $\alpha$  to  $\beta$  adrenoce hearts, 4 fmol/mg protein) (Steinfath et al., 1993 Because there is no reduction of cardiac  $\alpha$ -adrenoceptors,  $\alpha$  noceptors might contribute to the maintenance of contractility in heart failure, in which  $\beta$ -adrenoce Because there is no reduction of cardiac  $\alpha$ -adrenoceptors adrespot to the maintenance of cardiac are f<br>noceptors might contribute to the maintenance of cardiac are f<br>contractility in heart failure, in which  $\beta$ -adrenoc but an increased ratio of  $\alpha$  to  $\beta$  and increased rootribute to the contractility in heart failure, in we mediated responses are severely  $\alpha$  et al., 1982; Böhm et al., 1988b). The mechanism of the positive ceptors might contribute to the maintenance of cardiac<br>ntractility in heart failure, in which  $\beta$ -adrenoceptors-<br>ediated responses are severely compromised (Bristow<br>al., 1982; Böhm et al., 1988b).<br>The mechanism of the po

contractility in heart failure, in which  $\beta$ -adrenoceptors-<br>mediated responses are severely compromised (Bristow<br>et al., 1982; Böhm et al., 1988b).<br>The mechanism of the positive inotropic effect of  $\alpha_1$ -<br>adrenergic ago mediated responses are severely compromised (Bristow<br>et al., 1982; Böhm et al., 1988b).<br>The mechanism of the positive inotropic effect of  $\alpha_1$ -<br>adrenergic agonists in human tissue is a matter of current<br>investigation. I et al., 1982; Böhm et al., 1988b).<br>The mechanism of the positive inotropic effect of  $\alpha_1$ -<br>adrenergic agonists in human tissue is a matter of current<br>investigation. In atrial tissue, the positive inotropic effect<br>is not The mechanism of the positive inotropic effect of  $\alpha_1$ -<br>adrenergic agonists in human tissue is a matter of current<br>investigation. In atrial tissue, the positive inotropic effect<br>is not accompanied by an increase in the adrenergic agonists in human tissue is a matter of current<br>investigation. In atrial tissue, the positive inotropic effect<br>is not accompanied by an increase in the action potential<br>duration but rather by a decrease (Jahnel is not accompanied by an increase in the action potential<br>duration but rather by a decrease (Jahnel et al., 1992a). In this overview, we have attempted to summarize the<br>On the other hand, in a preliminary study performed duration but rather by a decrease (Jahnel et al., 1992a).<br>On the other hand, in a preliminary study performed<br>using the whole cell patch clamp technique in single<br>atrial cells isolated from nonfailing hearts, methoxamine,<br> duration but rather by a decrease (Jahnel et al., 1992a).<br>On the other hand, in a preliminary study performed<br>using the whole cell patch clamp technique in single<br>atrial cells isolated from nonfailing hearts, methoxamine,<br> On the other hand, in a preliminary study performed<br>using the whole cell patch clamp technique in single<br>atrial cells isolated from nonfailing hearts, methoxamine,<br>in the presence of propranolol, reduced the transient<br>out using the whole cell patch clamp technique in single atrial cells isolated from nonfailing hearts, methoxamine, in the presence of propranolol, reduced the transient outward current independent of  $Ca^{2+}$ , an effect that atrial cells isolated from nonfailing hearts, methoxation the presence of propranolol, reduced the transout outward current independent of  $Ca^{2+}$ , an effect might favor a prolongation of the action potential Legrand and the presence of propranolol, reduced the transient<br>tward current independent of  $Ca^{2+}$ , an effect that<br>ight favor a prolongation of the action potential (B.<br>grand and E. Coraboeuf, personal communication).<br>In human ventr

might favor a prolongation of the action potential (B. Legrand and E. Coraboeuf, personal communication).<br>In human ventricular trabeculae, phenylephrine produces an enhanced breakdown of  $\text{PIP}_2$  and phosphati-dylinosito duces an enhanced breakdown of  $\text{PIP}_2$  and phosphati-Legrand and E. Coraboeuf, personal communio<br>In human ventricular trabeculae, phenylepl<br>duces an enhanced breakdown of  $\text{PIP}_2$  and p<br>dylinositol phosphate. Accordingly, IP<sub>3</sub> and its<br>IP<sub>2</sub> and IP<sub>1</sub> are increased (Kohl e **B. In Vivo Studies**<br>*B. In Vivo Studies*<br>*B. In Vivo Studies*<br>**Attempts to demon** 

linositol phosphate. Accordingly, IP<sub>3</sub> and its cong<br>
<sup>2</sup>/<sub>2</sub> and IP<sub>1</sub> are increased (Kohl et al., 1989).<br> *In Vivo Studies*<br>
Attempts to demonstrate the effects of  $\alpha_1$ -adrenor<br>
r agonists and antagonists on myocardia IP<sub>2</sub> and IP<sub>1</sub> are increased (Kohl et al., 1989).<br>
B. In Vivo Studies<br>
Attempts to demonstrate the effects of  $\alpha_1$ -adrenoceptor agonists and antagonists on myocardial contractility<br>
in vivo in humans are hampered by th B. In Vivo Studies<br>Attempts to demonstrate the effects of  $\alpha_1$ -adrenoceptor agonists and antagonists on myocardial contractility<br>in vivo in humans are hampered by the confounding<br>effects of stimulation and inhibition of B. In vivolus studies<br>Attempts to demonstrate the effects of  $\alpha_1$ -adrenoctor<br>tor agonists and antagonists on myocardial contractii<br>in vivo in humans are hampered by the confound<br>effects of stimulation and inhibition of Attempts to demonstrate the effects of  $\alpha_1$ -adrenoceptor agonists and antagonists on myocardial contractility tice in vivo in humans are hampered by the confounding creflects of stimulation and inhibition of vascular  $\$ tor agonists and antagonists on myocardial contractility<br>in vivo in humans are hampered by the confounding<br>effects of stimulation and inhibition of vascular  $\alpha_1$ -adre-<br>moceptors on ventricular loading conditions and ref in vivo in humans are hampered by the confounding<br>effects of stimulation and inhibition of vascular  $\alpha_1$ -adre-<br>noceptors on ventricular loading conditions and reflex<br>mechanisms (Curiel et al., 1989). To avoid the system

ENOCEPTORS<br>ndzberg et al. (1991) infused  $\alpha_1$ -adrenoceptor agonists or<br>antagonists into the left main coronary artery of subjects ENOCEPTORS 167<br>
ndzberg et al. (1991) infused  $\alpha_1$ -adrenoceptor agonists or<br>
antagonists into the left main coronary artery of subjects<br>
with normal left ventricular function. Intracoronary in-ENOCEPTORS 167<br>
ndzberg et al. (1991) infused  $\alpha_1$ -adrenoceptor agonists or<br>
antagonists into the left main coronary artery of subjects<br>
with normal left ventricular function. Intracoronary in-<br>
fusion of phenylephrine mdzberg et al. (1991) infused  $\alpha_1$ -adrenoceptor agonists or antagonists into the left main coronary artery of subjects with normal left ventricular function. Intracoronary infusion of phenylephrine caused an increase in ndzberg et al. (1991) infused  $\alpha_1$ -adrenoceptor agonists or antagonists into the left main coronary artery of subjects with normal left ventricular function. Intracoronary infusion of phenylephrine caused an increase in antagonists into the left main coronary artery of subjects<br>with normal left ventricular function. Intracoronary in-<br>fusion of phenylephrine caused an increase in the peak<br>rate of left ventricular pressure increase, which i fusion of phenylephrine caused an increase in the peak<br>rate of left ventricular pressure increase, which is known<br>to provide a reliable index of changes in inotropic state<br>under these conditions (Colucci, 1990). The concur rate of left ventricular pressure increase, which is known rate of left ventricular pressure increase, which is known<br>to provide a reliable index of changes in inotropic state<br>under these conditions (Colucci, 1990). The concurrent<br>infusion of phentolamine significantly reduced th to provide a reliable index of changes in inotropic st<br>under these conditions (Colucci, 1990). The concurr<br>infusion of phentolamine significantly reduced the<br>sponse to phenylephrine (Landzberg et al., 1991).<br>though  $\alpha_1$ under these conditions (Colucci, 1990). The concurrentifiusion of phentolamine significantly reduced the response to phenylephrine (Landzberg et al., 1991). Although  $\alpha_1$ -adrenoceptor stimulation increased contractility infusion of phentolamine significantly reduced the re-<br>sponse to phenylephrine (Landzberg et al., 1991). Al-<br>though  $\alpha_1$ -adrenoceptor stimulation increased contrac-<br>tility, the intracoronary infusion of the  $\alpha_1$ -adren though  $\alpha_1$ -adrenoceptor stimulation increased contractility, the intracoronary infusion of the  $\alpha_1$ -adrenoceptor antagonist, phentolamine, did not affect the baseline peak rate of left ventricular pressure increase. though  $\alpha_1$ -adrenoceptor stimulation increased contility, the intracoronary infusion of the  $\alpha_1$ -adrenoce antagonist, phentolamine, did not affect the base peak rate of left ventricular pressure increase. The thors co tility, the intracoronary infusion of the  $\alpha_1$ -adrenoceptor<br>antagonist, phentolamine, did not affect the baseline<br>peak rate of left ventricular pressure increase. The au-<br>thors concluded that endogenous myocardial  $\alpha_1$ antagonist, phentolamine, did not affect the baseline<br>peak rate of left ventricular pressure increase. The au-<br>thors concluded that endogenous myocardial  $\alpha_1$ -adrener-<br>gic tone may not play a role in maintaining the bas peak rate of left ventricular pressure increase. The authors concluded that endogenous myocardial  $\alpha_1$ -adrenergic tone may not play a role in maintaining the basal state of left ventricular contractility in humans, at l thors conclu<br>gic tone ma<br>state of left<br>when subje<br>al., 1991).<br>Consister state of left ventricular contractility in humans, at least<br>when subjects rest in the supine position (Landzberg et<br>al., 1991).<br>Consistent with the in vitro studies, the  $\alpha_1$ -adrenocep-

state of left ventricular contractility in humans, at least<br>when subjects rest in the supine position (Landzberg et<br>al., 1991).<br>Consistent with the in vitro studies, the  $\alpha_1$ -adrenocep-<br>tor-mediated positive inotropic e when subjects rest in the supine position (Landzberg et al., 1991).<br>Consistent with the in vitro studies, the  $\alpha_1$ -adrenoceptor-mediated positive inotropic effect is reduced in congestive heart failure (Landzberg et al. al., 1991).<br>Consistent with the in vitro studies, the  $\alpha_1$ -adrenector-mediated positive inotropic effect is reduced<br>congestive heart failure (Landzberg et al., 1991). A reduction of  $\alpha_1$ -adrenergic responsiveness with Consistent with the in vitro studies, the  $\alpha_1$ -adrenoceptor-mediated positive inotropic effect is reduced in congestive heart failure (Landzberg et al., 1991). A reduction of  $\alpha_1$ -adrenergic responsiveness without a r tor-mediated positive inotropic effect is reduced in<br>congestive heart failure (Landzberg et al., 1991). A re-<br>duction of  $\alpha_1$ -adrenergic responsiveness without a reduc-<br>tion in  $\alpha_1$ -adrenoceptor density (Bristow et al congestive heart failure (Landzberg et al., 1991). A reduction of  $\alpha_1$ -adrenergic responsiveness without a reduction in  $\alpha_1$ -adrenoceptor density (Bristow et al., 1988) might either reflect reduced efficiency of recep adrenoceptors. might either reflect reduced efficiency of receptor coupling or be due to a cause not specifically related to  $\alpha_1$ -<br>adrenoceptors.<br>The demonstration that myocardial  $\alpha_1$ -adrenoceptor<br>are functional and capable of incr

might either reflect reduced efficiency of receptor coupling or be due to a cause not specifically related to  $\alpha_1$ -adrenoceptors.<br>The demonstration that myocardial  $\alpha_1$ -adrenoceptors are functional and capable of incr pling or be due to a cause not specifically related to  $\alpha_1$ -<br>adrenoceptors.<br>The demonstration that myocardial  $\alpha_1$ -adrenoceptor<br>are functional and capable of increasing myocardial con-<br>tractility in humans may also ha adrenoceptors.<br>The demonstration that myocardial  $\alpha_1$ -adrenoceptor are functional and capable of increasing myocardial contractility in humans may also have implications for other actions related to the myocardial  $\alpha_1$ The demonstration that myocardial  $\alpha_1$ -adrenoceptor<br>are functional and capable of increasing myocardial con-<br>tractility in humans may also have implications for other<br>actions related to the myocardial  $\alpha_1$ -adrenocepto are functional and capable of increasing myocardial con-<br>tractility in humans may also have implications for other<br>actions related to the myocardial  $\alpha_1$ -adrenoceptor,<br>namely, the modulation of gene expression, myocardi tractility in humans may a<br>actions related to the<br>namely, the modulation of<br>hypertrophy, recovery fro<br>ischemia, and arrhythmia **VII. Concluding Remarks**<br>**VII. Concluding Remarks**<br>view. we have attempted to sure hypertrophy, recovery from intracellular acidosis during<br>ischemia, and arrhythmias.<br>VII. Concluding Remarks<br>In this overview, we have attempted to summarize the

ischemia, and arrhythmias.<br>
VII. Concluding Remarks<br>
In this overview, we have attempted to summarize the<br>
remarkable progress that has been made in recent years<br>
toward understanding the function of cardiac  $\alpha_1$ -adre-**VII. Concluding Remarks**<br>In this overview, we have attempted to summarize the remarkable progress that has been made in recent ye<br>toward understanding the function of cardiac  $\alpha_1$ -adre-<br>noceptors. However, many unresol In this overview, we have attempted to summarize the<br>remarkable progress that has been made in recent years<br>toward understanding the function of cardiac  $\alpha_1$ -adre-<br>noceptors. However, many unresolved issues regarding<br>th In this overview, we have attempted to summarize the<br>remarkable progress that has been made in recent years<br>toward understanding the function of cardiac  $\alpha_1$ -adre-<br>noceptors. However, many unresolved issues regarding<br>th remarkable progress that has been made in recent ye<br>toward understanding the function of cardiac  $\alpha_1$ -ad<br>noceptors. However, many unresolved issues regard<br>the  $\alpha_1$ -adrenoceptor-mediated regulation of myocare<br>function toward understanding the function of cardiac  $\alpha_1$ -adre-noceptors. However, many unresolved issues regarding the  $\alpha_1$ -adrenoceptor-mediated regulation of myocardial function remain to be addressed. Although the stimula noceptors. However, many unresolved issues regard<br>the  $\alpha_1$ -adrenoceptor-mediated regulation of myocare<br>function remain to be addressed. Although the stime<br>tion of cardiac  $\alpha_1$ -adrenoceptors produces a variety<br>cellular the  $\alpha_1$ -adrenoceptor-mediated regulation of myocard<br>function remain to be addressed. Although the stimul<br>tion of cardiac  $\alpha_1$ -adrenoceptors produces a variety<br>cellular effects, especially during concomitant  $\beta$ -adre tion of cardiac  $\alpha_1$ -adrenoceptors produces a variety of<br>cellular effects, especially during concomitant  $\beta$ -adreno-<br>ceptor blockade, it is still unknown under which condi-<br>tions  $\alpha_1$ -adrenoceptors play a major role tion of cardiac  $\alpha_1$ -adreno<br>cellular effects, especially<br>ceptor blockade, it is still<br>tions  $\alpha_1$ -adrenoceptors pla<br>modulation of the heart.<br>The most studied acute Illular effects, especially during concomitant  $\beta$ -adreno-<br>ptor blockade, it is still unknown under which condi-<br>ons  $\alpha_1$ -adrenoceptors play a major role in the adrenergic<br>odulation of the heart.<br>The most studied acute ceptor blockade, it is still unknown under which conditions  $\alpha_1$ -adrenoceptors play a major role in the adrenergic modulation of the heart.<br>The most studied acute  $\alpha_1$ -adrenergic effect in cardiac preparations is the

tions  $\alpha_1$ -adrenoceptors play a major role in the adrenergic<br>modulation of the heart.<br>The most studied acute  $\alpha_1$ -adrenergic effect in cardiac<br>preparations is the increase in twitch contractile force.<br>Further investig modulation of the heart.<br>The most studied acute  $\alpha_1$ -adrenergic effect in cardiac<br>preparations is the increase in twitch contractile force.<br>Further investigation is required to quantify the extent<br>to which different pro The most studied acute  $\alpha_1$ -adrenergic effect in cardiac<br>preparations is the increase in twitch contractile force.<br>Further investigation is required to quantify the extent<br>to which different proposed inotropic mechanism preparations is the increase in twitch contractile force.<br>Further investigation is required to quantify the extent<br>to which different proposed inotropic mechanisms par-<br>ticipate in the overall positive inotropic effect. A Further investigation is required to quantify the extent<br>to which different proposed inotropic mechanisms par-<br>ticipate in the overall positive inotropic effect. An in-<br>crease in the responsiveness of myofibrils to  $Ca^{2+}$ to which different proposed inotropic mechanisms par-<br>ticipate in the overall positive inotropic effect. An in-<br>crease in the responsiveness of myofibrils to  $Ca^{2+}$ , sub-<br>sequent to phosphorylation of contractile protein ticipate in the overall positive inotropic effect. An in-<br>crease in the responsiveness of myofibrils to  $Ca^{2+}$ , sub-<br>sequent to phosphorylation of contractile proteins and<br>cytosolic alkalinization, appears to be importan sequent to phosphorylation of contractile proteins and<br>cytosolic alkalinization, appears to be important because,<br>contrary to  $\beta$ -adrenoceptors,  $\alpha_1$ -adrenoceptors mediate a<br>positive inotropic effect without a marked c

168 TERZ<br>intracellular  $Ca^{2+}$  concentration. In addition, the inhi-<br>bition of the  $I_{to}$ , as well as the modulation of othe 168 TERZIC I<br>intracellular  $Ca^{2+}$  concentration. In addition, the inhi-<br>bition of the I<sub>to</sub>, as well as the modulation of other<br>conductances that lead to an action potential prolonga-168 TE<br>intracellular Ca<sup>2+</sup> concentration. In addition, the in<br>bition of the  $I_{\text{to}}$ , as well as the modulation of ot<br>conductances that lead to an action potential prolor<br>tion, could also contribute to the positive inot intracellular  $Ca^{2+}$  concentration. In addition, the inhibition of the  $I_{\text{to}}$ , as well as the modulation of oth conductances that lead to an action potential prolong tion, could also contribute to the positive inotrop anism. conductances that lead to an action potential prolongation, could also contribute to the positive inotropic mechanism.<br>The nature of  $\alpha_1$ -adrenoceptor subtypes and the sub-<br>cellular pathways that transduce their signal

conductances that lead to an action potential prolonga-<br>tion, could also contribute to the positive inotropic mech-<br>ger<br>anism.<br>The nature of  $\alpha_1$ -adrenoceptor subtypes and the sub-<br>tarellular pathways that transduce the tion, could also contribute to the positive inotropic mech<br>anism.<br>The nature of  $\alpha_1$ -adrenoceptor subtypes and the sub<br>cellular pathways that transduce their signal need to b<br>further elucidated. Although several  $\alpha_1$ anism.<br>The nature of  $\alpha_1$ -adrenoceptor subtypes and the sucellular pathways that transduce their signal need to further elucidated. Although several  $\alpha_1$ -adrenocept subtypes have been identified, their physiological s The nature of  $\alpha_1$ -adrenoceptor subtypes and the sub-<br>cellular pathways that transduce their signal need to be<br>further elucidated. Although several  $\alpha_1$ -adrenoceptor<br>subtypes have been identified, their physiological cellular pathways that transduce their signal need to be<br>further elucidated. Although several  $\alpha_1$ -adrenoceptor<br>subtypes have been identified, their physiological signif-<br>icance and their exact relationship to specific further elucidated. Although several  $\alpha_1$ -adrenoceptor<br>subtypes have been identified, their physiological signif-<br>icance and their exact relationship to specific cellular<br>effects is still to be uncovered. Moreover, alth subtypes have been identified, their physiological significance and their exact relationship to specific cellular effects is still to be uncovered. Moreover, although it is established that the stimulation of  $\alpha_1$ -adren icance and their exact relationship to specific cellular<br>
effects is still to be uncovered. Moreover, although it is<br>
established that the stimulation of  $\alpha_1$ -adrenoceptors ac-<br>
civates the turnover of PI through a G-pr effects is still to be uncovered. Moreover, although established that the stimulation of  $\alpha_1$ -adrenoceptors tivates the turnover of PI through a G-protein, the narof this regulatory protein is unknown. Furthermore, phos established that the stimulation of  $\alpha_1$ -adrenoceptors activates the turnover of PI through a G-protein, the nature of this regulatory protein is unknown. Furthermore, the  $\frac{1}{3}$ .<br>phospholipase C isoenzyme(s) involve tivates the turnover of PI through a G-protein, the nature<br>of this regulatory protein is unknown. Furthermore, the<br>phospholipase C isoenzyme(s) involved in the transduc-<br>tion cascade remain(s) to be elucidated. In additio of this regulatory protein is unknown. Furthermore, the phospholipase C isoenzyme(s) involved in the transduction cascade remain(s) to be elucidated. In addition the PI metabolism,  $\alpha_1$ -adrenergic stimulation could stiv phospholipase C isoenzyme(s) involved in the transduction cascade remain(s) to be elucidated. In addition to the PI metabolism,  $\alpha_1$ -adrenergic stimulation could activate, at least under some circumstances, a CAMP-phosp the PI metabolism,  $\alpha_1$ -adrenergic stimulation could ac-<br>
tivate, at least under some circumstances, a cAMP-<br>
phosphodiesterase, a Ca<sup>2+</sup>-calmodulin-dependent kinase,<br>
and phospholipases A<sub>2</sub> and/or phospholipase D. The the PI metabolism,  $\alpha_1$ -adrenergic stimulation could activate, at least under some circumstances, a CAMP-<br>phosphodiesterase, a Ca<sup>2+</sup>-calmodulin-dependent kinase,<br>and phospholipases A<sub>2</sub> and/or phospholipase D. These<br>tw tivate, at least under some circumstances, a cAMP-<br>phosphodiesterase, a Ca<sup>2+</sup>-calmodulin-dependent kinase,<br>and phospholipases A<sub>2</sub> and/or phospholipase D. These<br>isources, which in turn could either activate specific PKC<br> and phospholipases  $A_2$  and/or phospholipase D. These<br>two last enzymes could produce DAG from several<br>sources, which in turn could either activate specific PKC<br>isozymes or give rise to additional second messengers<br>such a two last enzymes could produce DAG from several<br>sources, which in turn could either activate specific PKC<br>isozymes or give rise to additional second messengers<br>such as leukotrienes, prostaglandins, or cyclic guanosine<br>mon two last enzymes could produce DAG from seve<br>sources, which in turn could either activate specific Pl<br>isozymes or give rise to additional second messeng<br>such as leukotrienes, prostaglandins, or cyclic guanos<br>monophosphate sources, which in turn could either activate specific PKC<br>isozymes or give rise to additional second messengers<br>such as leukotrienes, prostaglandins, or cyclic guanosine<br>monophosphate. A plethora of putative second messen isozymes or give rise to additional second messen;<br>such as leukotrienes, prostaglandins, or cyclic guano;<br>monophosphate. A plethora of putative second mess<br>gers could be involved in mediating  $\alpha_1$ -effects<br>thereby permit ch as leukotrienes, prostaglandins, or cyclic guanosine<br>onophosphate. A plethora of putative second messen<br>rs could be involved in mediating  $\alpha_1$ -effects and<br>ereby permit a fine regulation of cardiac function.<br>Most of t

monophosphate. A plethora of putative second messen-<br>gers could be involved in mediating  $\alpha_1$ -effects and<br>thereby permit a fine regulation of cardiac function.<br>Most of the investigations related to  $\alpha_1$ -adrenoceptors<br> gers could be involved in mediating  $\alpha_1$ -effects and<br>thereby permit a fine regulation of cardiac function.<br>Most of the investigations related to  $\alpha_1$ -adrenoceptors<br>have been performed on single cardiomyocytes, isolate thereby permit a fine regulation of cardiac function.<br>
Most of the investigations related to  $\alpha_1$ -adrenoceptors<br>
have been performed on single cardiomyocytes, isolated<br>
atria, ventricles, or perfused hearts. In some pre Most of the investigations related to  $\alpha_1$ -adrenoceptors<br>have been performed on single cardiomyocytes, isolated<br>atria, ventricles, or perfused hearts. In some preparations<br>the lack of consistent reproducibility has been have been performed on single cardiomyocytes, isolate<br>atria, ventricles, or perfused hearts. In some preparation<br>the lack of consistent reproducibility has been reporte<br>with regard to  $\alpha_1$ -adrenergic effects on  $I_{C_a}$  atria, ventricles, or perfused hearts. In some preparations<br>the lack of consistent reproducibility has been reported<br>with regard to  $\alpha_1$ -adrenergic effects on  $I_{Ca}$  (Alvarez et al.,<br>1987), Na<sup>+</sup>/K<sup>+</sup> pump activation (E the lack of consistent reproducibility has been reported<br>with regard to  $\alpha_1$ -adrenergic effects on  $I_{C_a}$  (Alvarez et al., BEI<br>1987), Na<sup>+</sup>/K<sup>+</sup> pump activation (Ertl et al., 1991), intra-<br>cellular Ca<sup>2+</sup> (Failli et al with regard to  $\alpha_1$ -adrenergic effects on  $I_{CA}$  (Alvarez et al., BENEZRA, R., DAVIS, R. L., LOCKSHON, D., TURNER, D. L., AND WEINTRAUB,<br>1987), Na<sup>+</sup>/K<sup>+</sup> pump activation (Ertl et al., 1991), intra-<br>cellular Ca<sup>2+</sup> (Fai 1987), Na<sup>+</sup>/K<sup>+</sup> pump activation (Ertl et al., 1991), intracellular Ca<sup>2+</sup> (Failli et al., 1992; Gambassi et al., 1992), <sup>BEI</sup><br>or contraction (Niedergerke and Page, 1981). The origin BEI<br>of this variability is unknown, b cellular Ca<sup>2+</sup> (Failli et al., 1992; Gambassi et al., 1992), <sup>BE</sup><br>or contraction (Niedergerke and Page, 1981). The origin<br>of this variability is unknown, but it might be compared<br>to the weakening of  $\alpha_1$ -adrenergic eff or contraction (Niedergerke and Page, 1981). The origin<br>of this variability is unknown, but it might be compared<br>to the weakening of  $\alpha_1$ -adrenergic effects in the failing<br>heart (Schmitz et al., 1987a), their variations of this variability is unknown, but it might be compared<br>to the weakening of  $\alpha_1$ -adrenergic effects in the failing<br>heart (Schmitz et al., 1987a), their variations during<br>development (Rosen et al., 1989), or the presenc to the weakening of  $\alpha_1$ -adrenergic effects in the failing BER<br>heart (Schmitz et al., 1987a), their variations during BER<br>development (Rosen et al., 1989), or the presence of the c<br>endocardial endothelium (Meulemans et heart (Schmitz et al., 1987a), their variations durindevelopment (Rosen et al., 1989), or the presence of the<br>endocardial endothelium (Meulemans et al., 1990). I<br>addition, synthetic  $\alpha_1$ -sympathomimetics have been use<br>i development (Rosen et al., 1989), or the presence of the<br>endocardial endothelium (Meulemans et al., 1990). In<br>addition, synthetic  $\alpha_1$ -sympathomimetics have been used<br>in these investigations more commonly than the physendocardial endothelium (Meulemans et al., 1990). In<br>addition, synthetic  $\alpha_1$ -sympathomimetics have been used<br>in these investigations more commonly than the phys-<br>iological neurotransmitter norepinephrine. Although<br>mark addition, synthetic  $\alpha_1$ -sympathomimetics have been used<br>in these investigations more commonly than the physiological neurotransmitter norepinephrine. Although<br>markedly contributing to the understanding of  $\alpha_1$ -effect in these investigations more commonly than the phys-<br>iological neurotransmitter norepinephrine. Although<br>markedly contributing to the understanding of  $\alpha_1$ -effects<br>in vitro, these studies have not uncovered the role of iological neurotransmitter norepinephrine. Although<br>markedly contributing to the understanding of  $\alpha_1$ -effects<br>in vitro, these studies have not uncovered the role of the<br> $\alpha_1$ -adrenoceptor in vivo, because the cardiac markedly contributing to the understanding of  $\alpha_1$ -effect<br>in vitro, these studies have not uncovered the role of th<br> $\alpha_1$ -adrencceptor in vivo, because the cardiac preparation<br>used were devoid of systemic regulatory me in vitro, these studies have not uncovered the role of the<br>  $\alpha_1$ -adrenoceptor in vivo, because the cardiac preparations<br>
used were devoid of systemic regulatory mechanisms<br>
(e.g., concomitant  $\beta$ -adrenergic and other n  $\alpha_1$ -adrenoceptor in vivo, because the cardiac preparation<br>used were devoid of systemic regulatory mechanism<br>(e.g., concomitant  $\beta$ -adrenergic and other neurohormone<br>stimulations, cardiovascular reflexes) which interfe used were devoid of systemic regulatory mechanisms (e.g., concomitant  $\beta$ -adrenergic and other neurohormonal<br>stimulations, cardiovascular reflexes) which interfere<br>with the response of cardiac muscle to  $\alpha_1$ -adrenocept (e.g., concomitant  $\beta$ -adrenergic and other neurohormonal<br>stimulations, cardiovascular reflexes) which interfere<br>with the response of cardiac muscle to  $\alpha_1$ -adrenoceptor<br>stimulation. In this regard, Guse et al. (1991) stimulations, cardiovascular reflexes) which interfere<br>with the response of cardiac muscle to  $\alpha_1$ -adrenoceptor<br>stimulation. In this regard, Guse et al. (1991) recently<br>reported that a simultaneous  $\beta$ -adrenergic stimu with the response of cardiac muscle to  $\alpha_1$ -adrenoceptor stimulation. In this regard, Guse et al. (1991) recently reported that a simultaneous  $\beta$ -adrenergic stimulation strongly decreases the  $\alpha_1$ -adrenoceptor-induc stimulation. In this regreported that a simult strongly decreases the *c* in inositol phosphates mains to be determined Finally, most of these reported that a simultaneous  $\beta$ -adrenergic stimulation<br>strongly decreases the  $\alpha_1$ -adrenoceptor-induced increase<br>in inositol phosphates through a mechanism that re-<br>mains to be determined.<br>Finally, most of these studi

ET AL.<br>the information provided by molecular biology studies.<br>Indeed, chronic stimulation of cardiac muscle with  $\alpha_1$ -IT AL.<br>the information provided by molecular biology studies.<br>Indeed, chronic stimulation of cardiac muscle with  $\alpha_1$ -<br>adrenoceptor agonists modifies the expression of specific ET AL.<br>the information provided by molecular biology studies.<br>Indeed, chronic stimulation of cardiac muscle with  $\alpha_1$ -<br>adrenoceptor agonists modifies the expression of specific<br>genes and could alter in a quantitative or The information provided by molecular biology studies.<br>Indeed, chronic stimulation of cardiac muscle with  $\alpha_1$ -<br>adrenoceptor agonists modifies the expression of specific<br>genes and could alter in a quantitative or qualit Indeed, chronic stimulation of cardiac muscle with  $\alpha_1$ -<br>adrenoceptor agonists modifies the expression of specific<br>genes and could alter in a quantitative or qualitative<br>manner several of the same cellular proteins that adrenoceptor agonists modifies the expression of specific<br>genes and could alter in a quantitative or qualitative<br>manner several of the same cellular proteins that are<br>targets of  $\alpha_1$ -adrenergic action also on a short ti

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