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Pharmacological Reviews<br>
Copyright © 1988 by The American Society for Pharmacology and Experimental Therapeutics<br> **Calcium Mobilization and Cardiac Inotropic Mechanisms**<br>
MELCHIOR REITER<br>
MELCHIOR REITER **ICIUM MObilization and Cardiac Inotropic Mechanism**<br>MELCHIOR REITER<br>Institut für Pharmakologie und Toxikologie der Technischen Universität München, 8000 München 40, Federal Republic of Germany

# MELCHIOR REITER



# **I. Introduction**

I. Introduction<br>THIS REVIEW is based on a contribution to a sympon-<br>non the role of calcium in cardiac function\* whi I. Introduction has a real of calcium in cardiac function\* which<br>sium on the role of calcium in cardiac function\* which<br>was held in honor of Otto Krayer, Pharmacologist at **I.** Introduction<br>THIS REVIEW is based on a contribution to a symposium on the role of calcium in cardiac function\* which<br>was held in honor of Otto Krayer, Pharmacologist at<br>Harvard from 1939 to 1966 (144). Krayer had dev 1. Introduction<br>THIS REVIEW is based on a contribution to a sympo-<br>sium on the role of calcium in cardiac function\* which<br>was held in honor of Otto Krayer, Pharmacologist at<br>Harvard from 1939 to 1966 (144). Krayer had deve THIS REVIEW is based on a contribution to a sym<br>sium on the role of calcium in cardiac function\* wh<br>was held in honor of Otto Krayer, Pharmacologist<br>Harvard from 1939 to 1966 (144). Krayer had develop<br>in 1931, a method whi

nation, in the heart-lung preparation, of the ability of<br>the heart to function as a pump (224). He thereby pronation, in the heart-lung preparation, of the ability of<br>the heart to function as a pump (224). He thereby pro-<br>vided a new and greatly improved means for the experi-<br>mental evaluation of inotropic drugs which he used most e heart to function as a pump (224). He thereby pro-<br>ded a new and greatly improved means for the experi-<br>ental evaluation of inotropic drugs which he used most<br>fectively for most of the rest of a distinguished career.<br>The vided a new and greatly improved means for the experimental evaluation of inotropic drugs which he used most effectively for most of the rest of a distinguished career.

was held in honor of Otto Krayer, Pharmacologist at Harvard from 1939 to 1966 (144). Krayer had developed,<br>
in 1931, a method which allowed quantitative determi-<br>
<sup>the</sup> elucidation of the cellular mode of action of ino-<br>
<sup></sup> effectively for most of the rest of a distinguished career.<br>The elucidation of the cellular mode of action of ino-<br>tropic drugs became possible only after the intracellular<br>messenger function of calcium in muscle became re The elucidation of the cellular mode of action of ino-<br>tropic drugs became possible only after the intracellular<br>messenger function of calcium in muscle became recog-<br>nized in the late forties and fifties (for reviews, see tropic drugs became possible only after the intracellular messenger function of calcium in muscle became recognized in the late forties and fifties (for reviews, see refs. 337 and 405). The first evidence that calcium migh messenger function of calcium in muscle became recognized in the late forties and fifties (for reviews, see refs.<br>337 and 405). The first evidence that calcium might<br>transmit the signal given by the action potential on the nized in the late forties and fifties (for reviews, see refs.<br>337 and 405). The first evidence that calcium might<br>transmit the signal given by the action potential on the<br>membrane surface to the contractile material in the 337 and 405). The first evidence that calcium might transmit the signal given by the action potential on the membrane surface to the contractile material in the center of the fiber came from the injection of calcium into l transmit the signal given by the action potential on the membrane surface to the contractile material in the center of the fiber came from the injection of calcium into living muscle by Heilbrunn and Wiercinski (156). They

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in 1931, a method which allowed quantitative determi-<br>\* This article is the first of a series of articles arising from a program<br>on Vistas in Pharmacology presented at a joint meeting of the American<br>Society for Pharmacolo Society for Pharmacology presented at a joint meeting of the American<br>
Society for Pharmacology presented at a joint meeting of the American<br>
Society for Pharmacology and Experimental Therapeutics and the<br>
American Chemica on Vistas in Pharmacology presented at a joint meeting of the American<br>Society for Pharmacology and Experimental Therapeutics and the<br>3. American Chemical Society Division of Medicinal Chemistry, August<br>18-22, 1985, in Bos assex. The program entitled "The Role of Calcium<br>Cardiac Function" was dedicated to Otto Krayer. The material<br>been updated by the authors and prepared for publication with<br>assistance of John R. Blinks whose participation i edged.

RETT<br>cause an immediate and pronounced shortening, an effect<br>which is not shared by any other cation in a concentra-190<br>cause an immediate and pronounced shortening, an et<br>which is not shared by any other cation in a concention normally present in muscle. Later, a relaxing fa REIT<br>cause an immediate and pronounced shortening, an effect<br>which is not shared by any other cation in a concentra-<br>tion normally present in muscle. Later, a relaxing factor<br>was identified and found to consist of calciumcause an immediate and pronounced shortening, an which is not shared by any other cation in a conction normally present in muscle. Later, a relaxing was identified and found to consist of calcium-aclating vesicles formed f cause an immediate and pronounced shortening, an effect The if which is not shared by any other cation in a concentra-<br>tion normally present in muscle. Later, a relaxing factor of the was identified and found to consist of which is not shared by any other cation in a concentration normally present in muscle. Later, a relaxing factor was identified and found to consist of calcium-accumulating vesicles formed from the sarcoplasmic reticulum wh tion normally present in muscle. Later, a relaxing factor<br>was identified and found to consist of calcium-accumu-<br>lating vesicles formed from the sarcoplasmic reticulum<br>which contains much of the cellular calcium content<br>du In a identified and found to consist of calcium-accumu-<br>
ing vesicles formed from the sarcoplasmic reticulum<br>
inich contains much of the cellular calcium content<br>
other<br>
ing rest (154, 95).<br>
In asking why cardiac muscle is

lating vesicles formed from the sarcoplasmic reticulum<br>which contains much of the cellular calcium content<br>during rest (154, 95).<br>In asking why cardiac muscle is more susceptible to<br>inotropic interventions than skeletal mu which contains much of the cellular calcium content of<br>during rest (154, 95).<br>In asking why cardiac muscle is more susceptible to<br>cinotropic interventions than skeletal muscle, it was rea-<br>sonable to look for differences i during rest (154, 95).<br>In asking why cardiac muscle is more susceptible to<br>inotropic interventions than skeletal muscle, it was rea-<br>sonable to look for differences in the ultrastructure of<br>the two types of striated muscle In asking why cardiac muscle is more susceptible to<br>inotropic interventions than skeletal muscle, it was rea-<br>sonable to look for differences in the ultrastructure of<br>the two types of striated muscle (123). In cardiac musc inotropic interventions than skeletal muscle, it was reasonable to look for differences in the ultrastructure of the two types of striated muscle (123). In cardiac muscle, likely which is much more dependent on extracellul sonable to look for differences in the ultrastructure of calculate that of striated muscle (123). In cardiac muscle, by which is much more dependent on extracellular calcium, lose than that of skeletal muscle. The differe the two types of striated muscle  $(123)$ . In cardiac muscle, by the which is much more dependent on extracellular calcium, loads the sarcoplasmic reticulum was found to be less extensive later than that of skeletal muscle which is much more dependent on extracellular calcium,<br>the sarcoplasmic reticulum was found to be less extensive<br>than that of skeletal muscle. The difference between the<br>two kinds of muscle with respect to calcium metaboli the sarcoplasmic reticulum was found<br>than that of skeletal muscle. The diff<br>two kinds of muscle with respect to  $\alpha$ <br>was therefore assumed to reside prin<br>ence in their sarcoplasmic reticulum.<br>The lower capacity of cardiac an that of skeletal muscle. The difference between the o kinds of muscle with respect to calcium metabolism<br>as therefore assumed to reside primarily in the differ-<br>ce in their sarcoplasmic reticulum.<br>The lower capacity of

two kinds of muscle with respect to calcium metabolis was therefore assumed to reside primarily in the difference in their sarcoplasmic reticulum.<br>The lower capacity of cardiac muscle for calcium stage may be indirectly co was therefore assumed to reside primarily in the difference in their sarcoplasmic reticulum. The lower capacity of cardiac muscle for calcium stor-<br>age may be indirectly connected with a special electro-<br>physiological feat ence in their sarcoplasmic reticulum. The lower capacity of cardiac muscle for calcium stor-<br>age may be indirectly connected with a special electro-<br>physiological feature of the cardiac cell: the long duration<br>of its actio The lower capacity of cardiac muscle for calcium stor-<br>age may be indirectly connected with a special electro-<br>physiological feature of the cardiac cell: the long duration<br>of its action potential (408). Its long-lasting pl age may be indirectly connected with a special electro-<br>physiological feature of the cardiac cell: the long duration<br>of its action potential (408). Its long-lasting plateau<br>allows voltage-dependent passive movements of ion physiological feature of the cardiac cell: the long duration<br>of its action potential (408). Its long-lasting plateau the<br>allows voltage-dependent passive movements of ions to<br>altake place which might be relevant for contra of its action potential (408). Its long-lasting plateau than<br>allows voltage-dependent passive movements of ions to appe<br>take place which might be relevant for contraction. In-<br>fluences on passive or active transport of ion allows voltage-dependent passive movements of id<br>take place which might be relevant for contraction<br>fluences on passive or active transport of ions the<br>the sarcolemma may affect cellular calcium metab<br>and thereby the inotr

# and thereby the inotropic state of cardiac muscle.<br> **II.** Control Sites of Contraction-related Cal<br>
in the Cardiac Ventricular Cell<br> *A.* Calcium Influx **II. Control Sites of Contraction-related Calcium**

I. Control Sites of Contraction-related Calcium ne<br>in the Cardiac Ventricular Cell and<br>minute cytoplasmic concentration of Ca ions is<br>when the cytoplasmic concentration of Ca ions is<br>ised above a threshold concentration of in the Cardiac Ventricular Cell a remember and the cytoplasmic concentration of Ca ions is of C<br>When the cytoplasmic concentration of Ca ions is Traised above a threshold concentration of about 200 regard nmol/liter, the c A. Calcium Influx<br>
When the cytoplasmic concentration of Ca ions is<br>
raised above a threshold concentration of about 200<br>
nmol/liter, the contraction of cardiac muscle is activated (361). In order to relax, the muscle has (361). In order to relax, the muscle has to relax, the muscle is activated concentration of about 200 reduce its muscle is activated (361). In order to relax, the muscle has to reduce its to sarcoplasmic Ca concentration a When the cytoplasmic concentration of Ca ions is<br>raised above a threshold concentration of about 200 reg<br>nmol/liter, the contraction of cardiac muscle is activated Ca<br>(361). In order to relax, the muscle has to reduce its raised above a threshold concentration of about 2<br>nmol/liter, the contraction of cardiac muscle is activat<br>(361). In order to relax, the muscle has to reduce<br>sarcoplasmic Ca concentration again to values below t<br>threshold nmol/liter, the contraction of cardiac muscle is activated (361). In order to relax, the muscle has to reduce its sarcoplasmic Ca concentration again to values below the threshold concentration which is four orders of magn (361). In order to relax, the muscle has to reduce its to sarcoplasmic Ca concentration again to values below the my threshold concentration which is four orders of magnitude lower than the Ca concentration of the extrace sarcoplasmic Ca concentration again to values below th<br>threshold concentration which is four orders of magnitude<br>lower than the Ca concentration of the extracellula<br>fluid. The contraction, therefore, is governed by rapic<br>c threshold concentration which is four orders of magni-<br>tude lower than the Ca concentration of the extracellular vol<br>fluid. The contraction, therefore, is governed by rapid tin<br>changes in intracellular Ca concentration (ca tude lower than the Ca concentration of the extracellular<br>fluid. The contraction, therefore, is governed by rapid<br>changes in intracellular Ca concentration (calcium tran-<br>sients) as can be convincingly shown by means of th fluid. The contraction, therefore, is governed by rapid tinchanges in intracellular Ca concentration (calcium transients) as can be convincingly shown by means of the pocalcium-sensitive bioluminescent protein aequorin (39 sients) as can be convincingly shown by means of the calcium-sensitive bioluminescent protein aequorin (39, 41). In principle, there are two ways of modifying the strength of contraction: either by influencing the concentr sients) as can be convincingly shown by means of the position-sensitive bioluminescent protein aequorin (39, ti 41). In principle, there are two ways of modifying the strength of contraction: either by influencing the conc calcium-sensitive bioluminescent protein aequorin (39, tio.<br>41). In principle, there are two ways of modifying the sare<br>strength of contraction: either by influencing the concen-<br>tration (more precisely, the activity) of f 41). In principle, there are tv<br>strength of contraction: either<br>tration (more precisely, the<br>which is obtained after excitat<br>sensitivity of the myofilament<br>One way to increase the sarce rength of contraction: either by influencing the concention (more precisely, the activity) of free Ca ions hich is obtained after excitation, or by changing the Ca ositivity of the myofilaments.<br>One way to increase the sar tration (more precisely, the activity) of free Ca ions gravition is obtained after excitation, or by changing the Ca presentivity of the myofilaments. The sarcolemma during of the sarcolemma during SH the action potential,

which is obtained after excitation, or by changing the Ca<br>sensitivity of the myofilaments. of<br>One way to increase the sarcoplasmic Ca concentration<br>jured would be to open a channel in the sarcolemma during SR<br>the action p sensitivity of the myofilaments. The same of the way to increase the sarcoplasmic Ca concentration ium<br>would be to open a channel in the sarcolemma during SR<br>the action potential, thus allowing Ca ions to flow down (13<br>th One way to increase the sarcoplasmic Ca concentration<br>would be to open a channel in the sarcolemma during<br>the action potential, thus allowing Ca ions to flow down<br>their electrochemical gradient. This is probably the way<br>in would be to open a channel in the sarcolemma during SF<br>the action potential, thus allowing Ca ions to flow down (13)<br>their electrochemical gradient. This is probably the way<br>in which contraction is activated in the amphib the action potential, thus allowing Ca ions to flow down (1)<br>their electrochemical gradient. This is probably the way<br>in which contraction is activated in the amphibian heart<br>(407, 287, 204). However, in the mammalian hea their electrochemical gradient. This is probably the way<br>in which contraction is activated in the amphibian heart<br>(407, 287, 204). However, in the mammalian heart the<br>mechanism is more complicated. This can be deduced con in which contraction is activated in the amphibian heart  $(407, 287, 204)$ . However, in the mammalian heart the mechanism is more complicated. This can be deduced from experiments in which the influence on contraction of (407, 287, 204). However, in the mammalian heart the mechanism is more complicated. This can be deduced from experiments in which the influence on contraction of a prolongation of the action potential by current injection

ER<br>The frog's ventricle responded to each lengthening of the<br>action potential duration with an increase of the strength ER<br>The frog's ventricle responded to each lengthening of the<br>action potential duration with an increase of the strength<br>of the accompanying beat, whereas in the mammalian ER<br>The frog's ventricle responded to each lengthening of the<br>action potential duration with an increase of the strength<br>of the accompanying beat, whereas in the mammalian<br>ventricle the change was observed not in the accomp The frog's ventricle responded to each lengthening of action potential duration with an increase of the stren of the accompanying beat, whereas in the mammal ventricle the change was observed not in the accompaigned but in The frog's ventricle responded to each lengthening of the action potential duration with an increase of the strength<br>of the accompanying beat, whereas in the mammalian<br>ventricle the change was observed not in the accompa-<br> action potential duration with an increase of the strength<br>of the accompanying beat, whereas in the mammalian<br>ventricle the change was observed not in the accompa-<br>nying beat but in the next following one. From these and<br>o of the accompanying beat, whereas in the mammalian<br>ventricle the change was observed not in the accompa-<br>nying beat but in the next following one. From these and<br>other comparable experiments (421) we must conclude<br>that, in ventricle the change was observed not in the accompa-<br>nying beat but in the next following one. From these and<br>other comparable experiments (421) we must conclude<br>that, in the mammalian heart cell, most of the activator<br>ca nying beat but in the next following one. From these and<br>other comparable experiments (421) we must conclude<br>that, in the mammalian heart cell, most of the activator<br>calcium does not come directly from the extracellular<br>sp other comparable experiments (421) we must conclude<br>that, in the mammalian heart cell, most of the activator<br>calcium does not come directly from the extracellular<br>space but from an intracellular compartment that stores<br>cal that, in the mammalian heart cell, most of the activator calcium does not come directly from the extracellular space but from an intracellular compartment that stores calcium in such a way that its release can be triggered calcium does not come directly from the extracellular space but from an intracellular compartment that stores calcium in such a way that its release can be triggered by the action potential. Simultaneously, calcium influx space but from<br>calcium in su<br>by the action<br>loads this container release.<br>B. Introcallul by the action potential. Simultaneously, calcium influx<br>loads this compartment from which it is available for<br>later release.<br>*B. Intracellular Calcium Stores* Noticellular compartment from which it is available for<br>
inter release.<br>
B. Intracellular Calcium Stores<br>
Two intracellular compartments are known to accu-<br>
mulate calcium, the mitochondria and the sarcoplasmic

take place which might be relevant for contraction. In-<br>fluences on passive or active transport of ions through<br>tochondria occurs only if the free  $Ca^{2+}$  concentration is<br>the sarcolemma may affect cellular calcium metabo later release.<br>
B. Intracellular Calcium Stores<br>
Two intracellular compartments are known to accu-<br>
mulate calcium, the mitochondria and the sarcoplasmic<br>
reticulum. In terms of total capacity the mitochondria B. Intracellular Calcium Stores<br>Two intracellular compartments are known to accu-<br>mulate calcium, the mitochondria and the sarcoplasmic<br>reticulum. In terms of total capacity the mitochondria<br>represent the largest calcium r B. Intracellular Calcium Stores<br>Two intracellular compartments are known to accumulate calcium, the mitochondria and the sarcoplasmi<br>reticulum. In terms of total capacity the mitochondri<br>represent the largest calcium reser Two intracellular compartments are known to accumulate calcium, the mitochondria and the sarcoplasmic reticulum. In terms of total capacity the mitochondria represent the largest calcium reservoir in the cell. However, the mulate calcium, the mitochondria and the sarcoplasmic<br>reticulum. In terms of total capacity the mitochondria<br>represent the largest calcium reservoir in the cell. How-<br>ever, their maximal velocity of Ca uptake is much less<br> reticulum. In terms of total capacity the mitochond<br>represent the largest calcium reservoir in the cell. Ho<br>ever, their maximal velocity of Ca uptake is much le<br>than that of the sarcoplasmic reticulum (69), and th<br>appear n represent the largest calcium reservoir in the cell. However, their maximal velocity of Ca uptake is much less than that of the sarcoplasmic reticulum (69), and they appear not to accumulate much calcium under physiologic ever, their maximal velocity of Ca uptake is much less<br>than that of the sarcoplasmic reticulum (69), and they<br>appear not to accumulate much calcium under physio-<br>logical conditions (83). Considerable Ca uptake by mi-<br>toch than that of the sarcoplasmic reticulum (69), and they<br>appear not to accumulate much calcium under physio-<br>logical conditions (83). Considerable Ca uptake by mi-<br>tochondria occurs only if the free Ca<sup>2+</sup> concentration is<br> appear not to accumulate much calcium under physio-<br>logical conditions (83). Considerable Ca uptake by mi-<br>tochondria occurs only if the free Ca<sup>2+</sup> concentration is<br>raised to levels that cause contractures (83). At 1  $\mu$ logical conditions (83). Considerable Ca uptake by mitochondria occurs only if the free Ca<sup>2+</sup> concentration is raised to levels that cause contractures (83). At 1  $\mu$ M sarcoplasmic concentration, Ca uptake was calculate B. Intracellular Calcium Stores<br>
Two intracellular compartments are known to accu-<br>
mulate calcium, the mitochondria and the sarcoplasmic<br>
reticulum. In terms of total capacity the mitochondria<br>
represent the largest calc raised to levels that cause contractures (83). At 1  $\mu$ M<br>sarcoplasmic concentration, Ca uptake was calculated to<br>amount to only 6% of total uptake as compared with<br>nearly 90% by the sarcoplasmic reticulum (69). This and<br> sarcoplasmic concentration, Ca uptake was calculated to amount to only 6% of total uptake as compared with nearly 90% by the sarcoplasmic reticulum (69). This and a relatively low rate of Na-induced Ca release make the mit amount to only<br>nearly 90% by the<br>a relatively low re<br>mitochondria not<br>of Ca movements<br>The sarcoplasn

of Ca movements.<br>The sarcoplasmic reticulum (SR) (see table 1) must be regarded as the chief regulator of the contraction-related Ca in the mammalian heart. The SR is suitably located relatively low rate of Na-induced Ca release make the mitochondria not adequate for the beat-to-beat control<br>of Ca movements.<br>The sarcoplasmic reticulum (SR) (see table 1) must be<br>regarded as the chief regulator of the con mitochondria not adequate for the beat-to-beat control<br>of Ca movements.<br>The sarcoplasmic reticulum (SR) (see table 1) must be<br>regarded as the chief regulator of the contraction-related<br>Ca in the mammalian heart. The SR is of Ca movements.<br>The sarcoplasmic reticulum (SR) (see table 1) must be<br>regarded as the chief regulator of the contraction-related<br>Ca in the mammalian heart. The SR is suitably located<br>to serve its purpose. Its dense networ I ne sarcopiasmic reticulum (SK) (see table 1) must be regarded as the chief regulator of the contraction-related Ca in the mammalian heart. The SR is suitably located to serve its purpose. Its dense network surrounds the Ca in the mammalian heart. The SR is suitably located<br>to serve its purpose. Its dense network surrounds the<br>myofibrils, and it is abundant in the space directly sub-<br>jacent to the sarcolemma (123, 365, 282, 364, 338). The to serve its purpose. Its dense network surrounds the<br>myofibrils, and it is abundant in the space directly sub-<br>jacent to the sarcolemma (123, 365, 282, 364, 338). The<br>volume of SR associated with each myofibril is up to 1 pacent to the sarcolemma (123, 363, 262, 364, 356). The<br>volume of SR associated with each myofibril is up to 15<br>times greater in the mammalian heart than in the frog<br>ventricle (300). The SR consists essentially of two comtimes greater in the mammalian heart than in the frog<br>ventricle (300). The SR consists essentially of two com-<br>ponents, the free SR (or longitudinal SR) and the junc-<br>tional SR, a synonym for the terminal cisterna or sub-<br> ventricle (300). The SR consists essentially of two components, the free SR (or longitudinal SR) and the junctional SR, a synonym for the terminal cisterna or subsarcolemmal cisterna. In contrast to the tubules of the free ponents, the free SR (or longitudinal SR) and the junctional SR, a synonym for the terminal cisterna or subsarcolemmal cisterna. In contrast to the tubules of the free SR, the junctional SR contains an electron-dense granu tional SR, a synonym for the terminal cisterna or sub-<br>sarcolemmal cisterna. In contrast to the tubules of the<br>free SR, the junctional SR contains an electron-dense<br>granular material which consists of a calcium binding<br>pro sarcolemmal cisterna. In contrast to the tubules of the free SR, the junctional SR contains an electron-dense granular material which consists of a calcium binding protein referred to as calsequestrin (258). The structure free SR, the junctional SR contains an electron-dense<br>granular material which consists of a calcium binding<br>protein referred to as calsequestrin (258). The structure<br>of the junctional SR is characterized by the presence of granular material which consists of a calcium binding<br>protein referred to as calsequestrin (258). The structure<br>of the junctional SR is characterized by the presence of<br>junctional processes (feet) bridging the gap between protein referred to as calsequestrin (2<br>of the junctional SR is characterized l<br>junctional processes (feet) bridging th<br>SR membrane and the inner surface (<br>137, 261, 364, 131, 100, 336).<br>C. Excitation-Contraction Coupling *C. Excitation-Contraction-Contraction-Contraction-Contraction-Contraction-Coupling*<br>C. Excitation-Contraction Coupling<br>The regulation of intracellular Ca as represent R membrane and the inner surface of the sarcolemma<br>37, 261, 364, 131, 100, 336).<br>Excitation-Contraction Coupling<br>The regulation of intracellular Ca as related to cardiac<br>ntraction is connected with the excitation of the ce

(137, 261, 364, 131, 100, 336).<br>
C. Excitation-Contraction Coupling<br>
The regulation of intracellular Ca as related to cardiac<br>
contraction is connected with the excitation of the cell<br>
in a complex way (52). The depolariz C. Excitation-Contraction Coupling<br>The regulation of intracellular Ca as related to cardia<br>contraction is connected with the excitation of the ce<br>in a complex way (52). The depolarization of the mem-<br>brane triggers the rel C. *Excitation-Contraction Couping*<br>The regulation of intracellular Ca as related to card<br>contraction is connected with the excitation of the me<br>in a complex way (52). The depolarization of the me<br>brane triggers the relea lemmal cisternae of the sarcoplasmic reticulum (see sec-

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T-system Transverse tubular system<br>
UD-CG-115 Finobendane<br>
tion III A), which leads to a rise of the sarcoplasmic C<br>
concentration. The calcium release is apparently influ-<br>
enced by muscle length (189, 84, 10). Increase i UD-CG-115 Pimobendane<br>
tion III A), which leads to a rise of the sarcoplasmic Ca<br>
concentration. The calcium release is apparently influ-<br>
enced by muscle length (189, 84, 10). Increase in muscle<br>
length causes an immedia length causes an immediate increase is apparently influ-<br>enced by muscle length (189, 84, 10). Increase in muscle<br>length causes an immediate increase in contractility and<br>a gradual subsequent rise. Whereas the former is mo tion III A), which leads to a rise of the sarcoplasmic Ca<br>concentration. The calcium release is apparently influ-<br>enced by muscle length (189, 84, 10). Increase in muscle<br>length causes an immediate increase in contractilit concentration. The calcium release is apparently influenced by muscle length (189, 84, 10). Increase in muscle<br>length causes an immediate increase in contractility and<br>a gradual subsequent rise. Whereas the former is most enced by muscle length (189, 84, 10). Increase in muscle<br>length causes an immediate increase in contractility and<br>a gradual subsequent rise. Whereas the former is most<br>likely the result of an increase in the affinity of t length causes an immediate increase in contractility and<br>a gradual subsequent rise. Whereas the former is most<br>likely the result of an increase in the affinity of troponin<br>C for calcium (159, 10), the slowly developing inc a gradual subsequent rise. Whereas the former is most<br>
likely the result of an increase in the affinity of troponin<br>
C for calcium (159, 10), the slowly developing increase<br>
in during which the muscle is not stimulated. T likely the result of an increase in the affinity of troponin C for calcium (159, 10), the slowly developing increase<br>in force is probably the result of a change in the amount<br>of calcium released by the SR (189, 84, 10). Th U for calcium (159, 10), the slowly developing increase<br>in force is probably the result of a change in the amount<br>of calcium released by the SR (189, 84, 10). The binding<br>of calcium by troponin C activates the sliding fila of calcium released by the SR (189, 84, 10). The binding<br>of calcium by troponin C activates the sliding filament<br>system, and the muscle contracts. Relaxation results<br>from the active uptake of calcium by the longitudinal<br>p of calcium by troponin C activates the sliding filament system, and the muscle contracts. Relaxation results from the active uptake of calcium by the longitudinal parts of the sarcoplasmic reticulum, from where it is retur SR). om the active uptake of calcium by the longitudinal calciunts of the sarcoplasmic reticulum, from where it is contriumed with some delay to the release sites (junctional pender).<br>
(3). During the plateau of the action pote

parts of the sarcoplasmic reticulum, from where it is constrained with some delay to the release sites (junctional perception of the action potential, calcium site flows from the extracellular space into the cell with the returned with some delay to the release sites (junctional ISR).<br>
SR).<br>
During the plateau of the action potential, calcium<br>
flows from the extracellular space into the cell with the<br>
second (slow) inward current  $(I_{ai})$ . T SR).<br>
During the plateau of the action potential, calcium<br>
flows from the extracellular space into the cell with the<br>
second (slow) inward current  $(I_{xi})$ . This current differs<br>
from the (fast) sodium current in having slo During the plateau of the action potential, calcium<br>flows from the extracellular space into the cell with the<br>second (slow) inward current  $(I_{xi})$ . This current differs<br>from the (fast) sodium current in having slower kinet flows from the extracellular space into the cell with second (slow) inward current  $(I_{xi})$ . This current different (fast) sodium current in having slower kine and different voltage dependence (for review, see 329). The slo second (slow) inward current  $(I_{xi})$ . This current differs<br>from the (fast) sodium current in having slower kinetics<br>and different voltage dependence (for review, see ref.<br>329). The slow inward current is increased by catec from the (fast) sodium current in having slower kinetics<br>and different voltage dependence (for review, see ref.<br>329). The slow inward current is increased by catechol-<br>amines and produces a "slow action potential" if the and different voltage dependence (for review, see ref. 329). The slow inward current is increased by catechol-<br>amines and produces a "slow action potential" if the fast<br>sodium current is prevented by partial depolarizatio 329). The slow inward current is increased by catecholamines and produces a "slow action potential" if the fast calcordium current is prevented by partial depolarization ideal (302). The second inward current  $(I_{ci})$  may c amines and produces a "slow action potential" if the fast capable<br>sodium current is prevented by partial depolarization ident tl<br>(302). The second inward current  $(I_{ci})$  may consist not be rega<br>of calcium current  $(I_{Cs})$  al

and V A).  $I_{C_a}$  flows through special channels with a relatively long-lasting activity. These channels have been relatively long-lasting activity. These channels with a relatively long-lasting activity. These channels have been<br>designated as L-type channels, in contrast to newly and V A).  $I_{Ca}$  flows through special channels with a relatively long-lasting activity. These channels have been designated as L-type channels, in contrast to newly observed channels  $(20, 289, 269)$  with a short activit and V A).  $I_{C_a}$  flows through special channels with a relatively long-lasting activity. These channels have been designated as L-type channels, in contrast to newly observed channels (20, 289, 269) with a short activity relatively long-lasting activity. These channels have been<br>designated as L-type channels, in contrast to newly<br>observed channels (20, 289, 269) with a short activity of<br>a markedly transient time course (T-type Ca channels) relatively long-lasting activity. These channels have been<br>designated as L-type channels, in contrast to newly<br>observed channels (20, 289, 269) with a short activity of<br>a markedly transient time course (T-type Ca channels) designated as L-type channels, in contrast to new observed channels (20, 289, 269) with a short activity a markedly transient time course (T-type Ca channel T-channel current is much smaller and decays mumore quickly than observed channels (20, 289, 269) with a short activity of<br>a markedly transient time course (T-type Ca channels).<br>T-channel current is much smaller and decays much<br>more quickly than L-type channel current, so it contri-<br>but a markedly transient time course (T-type Ca channels).<br>T-channel current is much smaller and decays much<br>more quickly than L-type channel current, so it contri-<br>butes relatively little to Ca influx during the action<br>potent T-channel current is much smaller and decays much<br>more quickly than L-type channel current, so it contri-<br>butes relatively little to Ca influx during the action<br>potential plateau. Since T-type channels are activated at<br>rel more quickly than L-type channel current, so it concludes relatively little to Ca influx during the activate potential plateau. Since T-type channels are activate relatively negative potentials, they are thought to h funct butes relatively little to Ca influx during the action potential plateau. Since T-type channels are activated at relatively negative potentials, they are thought to have functional significance mainly for pacemaker depolar potential plateau. Since T-type c<br>relatively negative potentials, th<br>functional significance mainly f<br>zation and action potential initia<br>spontaneous activity (20, 289).<br>Most of the inflowing calciu latively negative potentials, they are thought to have<br>nctional significance mainly for pacemaker depolari-<br>tion and action potential initiation in cells capable of<br>ontaneous activity (20, 289).<br>Most of the inflowing calci functional significance mainly for pacemaker depolarization and action potential initiation in cells capable of spontaneous activity (20, 289).<br>Most of the inflowing calcium is taken up by the sarcoplasmic reticulum and s

zation and action potential initiation in cells capable of<br>spontaneous activity (20, 289).<br>Most of the inflowing calcium is taken up by the<br>sarcoplasmic reticulum and stored, after some delay, in<br>its release compartments ( spontaneous activity (20, 289).<br>
Most of the inflowing calcium is taken up by the<br>
sarcoplasmic reticulum and stored, after some delay, in<br>
its release compartments (324; see section III A). The<br>
loading effect of each act Most of the inflowing calcium is taken up by sarcoplasmic reticulum and stored, after some delay, its release compartments  $(324)$ ; see section III A). To loading effect of each action potential is opposed by net extrusio sarcoplasmic reticulum and stored, after some delay, in<br>its release compartments (324; see section III A). The<br>loading effect of each action potential is opposed by a<br>net extrusion of calcium from the cell through sodiumits release compartments (324; see section III A).<br>loading effect of each action potential is opposed<br>net extrusion of calcium from the cell through sod<br>calcium exchange (see section V A) and partly b<br>ATP-dependent Ca pump loading effect of each action potential is opposed by a<br>net extrusion of calcium from the cell through sodium-<br>calcium exchange (see section V A) and partly by an<br>ATP-dependent Ca pump (see section VI). Sodium-cal-<br>cium ex net extrusion of calcium from the cell through sodium-<br>calcium exchange (see section V A) and partly by an<br>ATP-dependent Ca pump (see section VI). Sodium-cal-<br>cium exchange plays a special role in the regulation of<br>Ca move calcium exchange (see section V A) and partly by an ATP-dependent Ca pump (see section VI). Sodium-calcium exchange plays a special role in the regulation of Ca movements through the sarcolemma (for review, see ref. 32). ATP-dependent Ca pump (see section VI). Sodium-calcium exchange plays a special role in the regulation of Ca movements through the sarcolemma (for review, see ref. 32). Since this exchange is electrogenic, Ca transport eit cium exchange plays a special role in the regulation of Ca movements through the sarcolemma (for review, see ref. 32). Since this exchange is electrogenic, Ca transport either to the outside or the inside depends on membra Ca movements throu<br>ref. 32). Since this ex-<br>either to the outside of<br>potential and the intra<br>Ca (see section V).<br>Calcium leaks during f. 32). Since this exchange is electrogenic, Ca transpointer to the outside or the inside depends on membran tential and the intracellular concentrations of Na an  $($ see section V $)$ . Calcium leaks during rest from the sa

etther to the outside or the inside depends on memorane<br>potential and the intracellular concentrations of Na and<br>Ca (see section V).<br>Calcium leaks during rest from the sarcoplasmic retic-<br>ulum of cardiac muscle (108, 210), potential and the intracentuar concentrations of Na and<br>Ca (see section V).<br>Calcium leaks during rest from the sarcoplasmic retic-<br>ulum of cardiac muscle (108, 210), at a rate which is<br>influenced by the resting membrane po Calcium leaks during rest from the sarcoplasmic retic-<br>ulum of cardiac muscle (108, 210), at a rate which is<br>influenced by the resting membrane potential (399; sec-<br>tion IV C). The calcium content of the store (release<br>com ulum of cardiac muscle (108, 210), at a rate which is<br>influenced by the resting membrane potential (399; sec-<br>tion IV C). The calcium content of the store (release<br>compartment) therefore depends, at a given resting po-<br>te influenced by the resting membrane potential (399; section IV C). The calcium content of the store (release compartment) therefore depends, at a given resting potential, on the frequency and pattern of stimulation. In vent tion IV C). The calcium content of the store (release compartment) therefore depends, at a given resting potential, on the frequency and pattern of stimulation. In ventricular muscle from most mammalian species (there are sarcoplasmic reticulum and stored, after some delay, in<br>its release compartments (324; see section III A). The<br>loading effect of each action potential is opposed by a<br>net extrusion of calcium from the cell through sodiumtential, on the frequency and pattern of stimulation. In ventricular muscle from most mammalian species (there are some exceptions like that of the rat, but see section VI B), the store will be empty after a period of 5 to ventricular muscle from most mammalian species (there are some exceptions like that of the rat, but see section VI B), the store will be empty after a period of 5 to 10 min during which the muscle is not stimulated. Then, are some exceptions like that of the rat, but see section VI B), the store will be empty after a period of 5 to 10 min during which the muscle is not stimulated. Then, total calcium content of the cardiac muscle has droppe v1 B), the store will be empty after a period of 5 to 10<br>
min during which the muscle is not stimulated. Then,<br>
total calcium content of the cardiac muscle has dropped<br>
to one-fourth of its steady-state value (241), and m (6) to one-fourth of its steady-state value (241), and most of the regions corresponding presumably to junctional SR are found "empty" of calcium by X-ray microanalysis (413, 412). As the muscle is continuously stimulated, the regions corresponding presumably to junctions<br>are found "empty" of calcium by X-ray microans<br>(413, 412). As the muscle is continuously stimulated<br>calcium release from the store and consequently<br>contractile force will i are found "empty" of calcium by X-ray microanalysis  $(413, 412)$ . As the muscle is continuously stimulated, the calcium release from the store and consequently the contractile force will increase until the frequency-depen  $(413, 412)$ . As the muscle is continuously stimulated, t calcium release from the store and consequently t contractile force will increase until the frequency-d pendent steady state is reached. As more of it is release c calcium release from the store and consequently the contractile force will increase until the frequency-dependent steady state is reached. As more of it is released, calcium becomes more effective in increasing the potassi contractile force will increase until the frequency-de-<br>pendent steady state is reached. As more of it is released<br>calcium becomes more effective in increasing the potas-<br>sium conductance of the cellular membrane (185, 351 pendent steady state is reached. As more of it is released,<br>calcium becomes more effective in increasing the potas-<br>sium conductance of the cellular membrane (185, 351,<br>65); this leads to an abbreviation of the action pote calcium becomes more effective in increasing the pot<br>sium conductance of the cellular membrane (185, 3<br>65); this leads to an abbreviation of the action potent<br>(184, 18) and thereby to a negative feedback in regard<br>calcium tial. (i); this leads to an abbreviation of the action potential  $84$ , 18) and thereby to a negative feedback in regard to lcium loading during the plateau of the action poten-<br>al.<br>The fact that so many regulatory mechanisms ar

(184, 18) and thereby to a negative feedback in regard to calcium loading during the plateau of the action potential.<br>The fact that so many regulatory mechanisms are capable of influencing cardiac contractility makes it e calcium loading during the plateau of the action potential.<br>
The fact that so many regulatory mechanisms are<br>
capable of influencing cardiac contractility makes it ev-<br>
ident that a number of different cellular structures tial.<br>The fact that so many regulatory mechanisms are<br>capable of influencing cardiac contractility makes it ev-<br>ident that a number of different cellular structures may<br>be regarded as sites of contractile control and there The fact that so many regulatory mechanisms are<br>capable of influencing cardiac contractility makes it ev-<br>ident that a number of different cellular structures may<br>be regarded as sites of contractile control and therefore<br> ident that a number of different cellular structures may<br>be regarded as sites of contractile control and therefore<br>as likely sites of pharmacological interaction. These are<br>mainly: (a) the sarcolemma because of its role i

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**a**spet

# 192<br>Ca uptake and elimination [sodium- and potential-de-<br>pendent Na-Ca exchange, potential-dependent Ca cur- the sur RE<br>Ca uptake and elimination [sodium- and potential-de-<br>pendent Na-Ca exchange, potential-dependent Ca cur-<br>rent, calcium release, and the Ca pump (Ca<sup>2+</sup>-transport 192<br>Ca uptake and elimination [sodium- and potential-d<br>pendent Na-Ca exchange, potential-dependent Ca cu<br>rent, calcium release, and the Ca pump  $(Ca^{2+}$ -transport<br>ATPase)]; (b) the intracellular compartments—the sa Ca uptake and elimination [sodium- and potential-de-<br>pendent Na-Ca exchange, potential-dependent Ca cur-<br>rent, calcium release, and the Ca pump (Ca<sup>2+</sup>-transport (<br>ATPase)]; (b) the intracellular compartments—the sar-<br>copl pendent Na-Ca exchange, potential-dependent Ca current, calcium release, and the Ca pump (Ca<sup>2+</sup>-transport (ATPase)]; (*b*) the intracellular compartments—the sarcoplasmic reticulum (with Ca uptake and release mechanisms) rent, calcium release, and the Ca pump (Ca<sup>2+</sup>-transport ATPase)]; (b) the intracellular compartments—the sar-<br>coplasmic reticulum (with Ca uptake and release mech-<br>anisms) and the mitochondria (Ca buffer); (c) Ca-binding<br> ATPase)]; (b) the intracellular compartments—the sar-<br>coplasmic reticulum (with Ca uptake and release mech-<br>anisms) and the mitochondria (Ca buffer); (c) Ca-binding<br>"modulator" proteins (e.g., calmodulin); and (d) the mycoplasmic remisms) and<br>
"modulator"<br>
ofilaments v<br>
to calcium.<br>
III Incre Incolution and the Indian Calcium,  $\langle e, g, e \rangle$  (d) the my<br>filaments with possible changes of their responsiveness<br>co calcium.<br>III. Increase of Calcium Influx through Voltage-<br>dependent Channels by Catecholamines of ilaments with possible changes of their responsiveness<br>to calcium.<br>III. Increase of Calcium Influx through Voltage-<br>dependent Channels by Catecholamines

**III.** Increase of Calcium Influx through Voltage-<br>dependent Channels by Catecholamines<br>Calcium uptake in electrically stimulated heart muscle<br>is increased under the influence of epinephrine (326).<br>This effect is exerted dependent Channels by Catecholamines<br>
calcium uptake in electrically stimulated heart muscle<br>
is increased under the influence of epinephrine (326).<br>
This effect is exerted through a  $\beta$ -adrenoceptor-induced<br>
increase in Calcium uptake in electrically stimulated heart muscle<br>is increased under the influence of epinephrine (326).<br>This effect is exerted through a  $\beta$ -adrenoceptor-induced<br>increase in  $I_{Ca}$  (327, 328, 393) which results fro is increased under the influence of epinephrine (326). relations of the sarcted through a  $\beta$ -adrenoceptor-induced responces in  $I_{Ca}$  (327, 328, 393) which results from a from lengthening of the mean open time of activa This effect is exerted through a  $\beta$ -adrenoceptor-induced reincrease in  $I_{Ca}$  (327, 328, 393) which results from a frequenchening of the mean open time of activated (L-type) sincalcium channels in the sarcolemma (331). increase in  $I_{Ca}$  (327, 328, 393) which results from a from<br>lengthening of the mean open time of activated (L-type) sim<br>calcium channels in the sarcolemma (331).  $I_{Ca}$  can be at inhibited by various calcium channel bloc lengthening of the mean open time of activated  $(L$ -type) sincalcium channels in the sarcolemma  $(331)$ .  $L_{ca}$  can be at inhibited by various calcium channel blockers  $(129)$ . The poinfluence of the increase in Ca influx calcium channels in the sarcolemma  $(331)$ .  $L_{ca}$  can be at<br>inhibited by various calcium channel blockers  $(129)$ . The po<br>influence of the increase in Ca influx on contraction can<br>be demonstrated very clearly when the Ca inhibited by various calcium channel blockers  $(129)$ . The pointleance of the increase in Ca influx on contraction can<br>be demonstrated very clearly when the Ca store of the restroplasmic reticulum is empty and, accordingl influence of the increase in Ca influx on contraction can<br>be demonstrated very clearly when the Ca store of the<br>sarcoplasmic reticulum is empty and, accordingly, the<br>force of contraction is negligibly small as in rested st be demonstrated very clearly when the Ca store of the relations in the exceptions, the force of contraction is negligibly small as in rested state a scontractions of cardiac ventricular muscle from most sloman malian spec sarcopiasmic reforce of contract<br>contractions of<br>mammalian spe<br>section VI B). contractions of cardiac ventricular muscle from most<br>mammalian species (213; regarding the exceptions, see<br>section VI B).<br>*A. Late and Early Rested State Contractions* 

Rested state contractions are defined as contractions<br>preceded by intervals of rest long enough that the section VI B). Frequency intervals of restead State Contractions contractions contractions contractions fills of rest long enough that the contraction of previous beats the strength of contraction is independent of previou A. Late and Early Rested State Contractions<br>
Rested state contractions are defined as contractions<br>
preceded by intervals of rest long enough that the<br>
strength of contraction is independent of previous beats<br>
(38). It is (38). It is characteristic for the small rested state con-<br>
strength of contraction is independent of previous beats<br>
(38). It is characteristic for the small rested state con-<br>
tractions of mammalian ventricular muscle th preceded by intervals of rest long enough that the strength of contraction is independent of previous beats (38). It is characteristic for the small rested state contractions of mammalian ventricular muscle that peak force strength of contraction is independent of previous beats<br>
(38). It is characteristic for the small rested state con-<br>
tractions of mammalian ventricular muscle that peak<br>
force is achieved relatively late after stimulation (38). It is characteristic for the small rested state con-<br>tractions of mammalian ventricular muscle that peak<br>force is achieved relatively late after stimulation  $(7, 8)$ .<br>Catecholamines increase the late peak of rested tractions of mammalian ventricular muscle that peak<br>force is achieved relatively late after stimulation  $(7, 8)$ .<br>Catecholamines increase the late peak of rested state<br>contractions  $(344, 345, 24)$ . This is also true of t Catecholamines increase the late peak of rested state<br>contractions (344, 345, 24). This is also true of the<br>dibutyryl derivative of cyclic adenosine monophosphate<br>(cyclic AMP) (379, 344, 345), 8-substituted cyclic AMF<br>anal contractions (344, 345, 24). This is also true of<br>dibutyryl derivative of cyclic adenosine monophosph<br>(cyclic AMP) (379, 344, 345), 8-substituted cyclic A<br>analogues (220), and phosphodiesterase inhibitors (<br>feine, 40, 240; dibutyryl derivative of cyclic adenosine monophosphate<br>
(cyclic AMP) (379, 344, 345), 8-substituted cyclic AMP<br>
analogues (220), and phosphodiesterase inhibitors (caf-<br>
feine, 40, 240; theophylline, 24; amrinone, 173; pimo (cyclic AMP) (379, 344, 345), 8-substituted cyclic AMP no<br>analogues (220), and phosphodiesterase inhibitors (caf-<br>feine, 40, 240; theophylline, 24; amrinone, 173; pimoben-<br>dane, UD-CG-115, 168; OPC-8212, 380). As is illus analogues (220), and phosphodiesterase inhibitors (caf-<br>feine, 40, 240; theophylline, 24; amrinone, 173; pimoben-<br>dane, UD-CG-115, 168; OPC-8212, 380). As is illustrated<br>in figs. 1a, 2, and 3, the rested state contraction feine, 40, 240; theophylline, 24; amrinone, 173; pimoben-<br>dane, UD-CG-115, 168; OPC-8212, 380). As is illustrated<br>in figs. 1a, 2, and 3, the rested state contraction of the<br>guinear pig papillary muscle under the influence dane, UD-CG-115, 168; OPC-8212, 380). As is illustrated cific in figs. 1*a*, 2, and 3, the rested state contraction of the contraction at physiological frequencies. Force starts to rise soon after stimulation and the upst in figs. 1a, 2, and 3, the rested state contraction of the compute pig papillary muscle under the influence of a excate cholamine has a time course quite unlike that of the IV contractions at physiological frequencies. Fo guinea pig papillary muscle under the influence of cate cholamine has a time course quite unlike that of contractions at physiological frequencies. Force start rise soon after stimulation and the upstroke of the act potent catecholamine has a time course quite unlike that of the contractions at physiological frequencies. Force starts to rise soon after stimulation and the upstroke of the action potential in both cases, but in the rested stat contractions at physiological frequencies. Force starts to<br>rise soon after stimulation and the upstroke of the action<br>potential in both cases, but in the rested state contrac-<br>tion, it rises very slowly at first. Then, som rise soon after stimulation and the upstroke of the acceptotential in both cases, but in the rested state cont<br>tion, it rises very slowly at first. Then, some 100 ms at<br>the stimulus, there is an inflection point, after whi potential in both cases, but in the rested state contraction, it rises very slowly at first. Then, some 100 ms after the stimulus, there is an inflection point, after which the force rises much more rapidly to the late pea tion, it rises very slowly at first. Then, some 100 ms after the stimulus, there is an inflection point, after which the force rises much more rapidly to the late peak characteristic of the rested state contraction. In wha the stimulus, there is an inflection point, after which the<br>force rises much more rapidly to the late peak character-<br>istic of the rested state contraction. In what follows I<br>shall refer to the time to the inflection point force rises much more rapidly to the late peak characteristic of the rested state contraction. In what follows I<br>shall refer to the time to the inflection point as the *latent*<br>period of the rested state contraction. There istic of the rested state contraction. In what follow<br>shall refer to the time to the inflection point as the *lat*<br>period of the rested state contraction. There has be<br>some debate about the mechanisms underlying the lat<br>pe shall refer to the time to the inflection point as the *latent*<br>period of the rested state contraction. There has been<br>some debate about the mechanisms underlying the latent<br>period and the peculiar shape of the rested stat period of the rested state contraction. There has been<br>some debate about the mechanisms underlying the latent<br>period and the peculiar shape of the rested state contraction.<br>Some have suggested that the slow rise and delay

to calcium.<br>
III. Increase of Calcium Influx through Voltage-<br>
dependent Channels by Catecholamines<br>
Calcium uptake in electrically stimulated heart muscle<br>
is increased under the influence of epinephrine (326).<br>
The same the basis of the time required for the diffusion of Ca from the surface membrane to the myofibrils. However, others ER<br>the basis of the time required for the diffusion of Ca fi<br>the surface membrane to the myofibrils. However, oth<br>(ref. 8), including the author, believe that this interpretation<br>is not sufficient to explain either the exi Intertual to the time required for the diffusion of Ca from<br>the surface membrane to the myofibrils. However, others<br>(ref. 8), including the author, believe that this interpre-<br>tation is not sufficient to explain either the the surface membrane to the myofibrils. However, others<br>(ref. 8), including the author, believe that this interpre-<br>tation is not sufficient to explain either the existence of<br>the inflection point, or the virtual constancy the surface membrane to the myofibrils. However, others<br>(ref. 8), including the author, believe that this interpre-<br>tation is not sufficient to explain either the existence of<br>the inflection point, or the virtual constancy (ref. 8), including the author, believe that this interpre-<br>tation is not sufficient to explain either the existence of<br>the inflection point, or the virtual constancy of the latent<br>period (regardless of the amplitude of th tation is not sufficient to explain either the existence of<br>the inflection point, or the virtual constancy of the latent<br>period (regardless of the amplitude of the delayed peak)<br>illustrated in fig. 2. We feel that these fe the inflection point, or the virtual constancy of the laten<br>period (regardless of the amplitude of the delayed peak<br>illustrated in fig. 2. We feel that these features of th<br>rested state contraction (and a number of others illustrated in fig. 2. We feel that these features of the rested state contraction (and a number of others that will be discussed in the pages to follow) are most plausibly explained by assuming that most of the calcium en illustrated in fig. 2. We feel that these features of the rested state contraction (and a number of others that will be discussed in the pages to follow) are most plausibly explained by assuming that most of the calcium en rested state contraction (and a number of others that<br>will be discussed in the pages to follow) are most plau-<br>sibly explained by assuming that most of the calcium<br>entering the cell during the action potential is first<br>seq will be discussed in the pages to follow) are most plausibly explained by assuming that most of the calcium<br>entering the cell during the action potential is first<br>sequestered by some intracellular store (presumably a<br>compo sibly explained by assuming that most of the calcium<br>entering the cell during the action potential is first<br>sequestered by some intracellular store (presumably a<br>component of the sarcoplasmic reticulum), and then<br>released entering the cell during the action potential is first sequestered by some intracellular store (presumably a component of the sarcoplasmic reticulum), and then released again after a mandatory delay which may represent th sequestered by some intracellular store (presumably a<br>equestered by some intracellular store (presumably and then<br>component of the sarcoplasmic reticulum), and then<br>released again after a mandatory delay which may rep-<br>re component or the sarcoplasmic reticulum), and then<br>released again after a mandatory delay which may rep-<br>resent the time required for translocation of calcium<br>from uptake sites to release sites within the SR. (A<br>similar de resent the time required for translocation of calcium<br>from uptake sites to release sites within the SR. (A<br>similar delay is manifest in the restitution curve observed<br>at higher frequencies of contraction, when the action<br>p from uptake sites to release sites within the SR. (A<br>similar delay is manifest in the restitution curve observed<br>at higher frequencies of contraction, when the action<br>potential is considerably briefer: very little force is similar delay is manifest in the restitution curve observed thigher frequencies of contraction, when the action<br>potential is considerably briefer: very little force is deloped during closely coupled extrasystoles, even tho at higher frequencies of contraction, when the action<br>potential is considerably briefer: very little force is de-<br>veloped during closely coupled extrasystoles, even though<br>relaxation from the preceding beat is complete and potential is considerably briefer: very little force is developed during closely coupled extrasystoles, even though<br>relaxation from the preceding beat is complete and there-<br>fore the SR must contain the calcium required to veloped during closely coupled extrasystoles, even though<br>relaxation from the preceding beat is complete and there-<br>fore the SR must contain the calcium required to activate<br>a strong contraction.) In rested state contracti relaxation from the preceding beat is complete and there-<br>fore the SR must contain the calcium required to activate<br>a strong contraction.) In rested state contractions the<br>slow phase of force development before the inflec a strong contraction.) In rested state contractions the<br>slow phase of force development before the inflection<br>point may represent the effect of  $Ca^{2+}$  entering the cell<br>from the extracellular space and acting directly on slow phase of force development before the inflection<br>point may represent the effect of  $Ca^{2+}$  entering the cel<br>from the extracellular space and acting directly on th<br>myofilaments. During this phase of the contraction th from the extracellular space and acting directly on the myofilaments. During this phase of the contraction the sarcoplasmic reticulum will be competing with the myofilaments for the entering  $Ca^{2+}$ . The late peak of the from the extracentuar space and acting urectly on the<br>myofilaments. During this phase of the contraction the<br>sarcoplasmic reticulum will be competing with the myo-<br>filaments for the entering  $Ca^{2+}$ . The late peak of the<br> sarcopiasmic reticulum will be competing with the myo-<br>filaments for the entering  $Ca^{2+}$ . The late peak of the<br>contraction occurs only if the action potential outlasts<br>the mandatory delay period and causes the release of filaments for the entering  $Ca^{2+}$ . The late peak of the contraction occurs only if the action potential outlasts the mandatory delay period and causes the release of some of the  $Ca^{2+}$  sequestered by the SR during the l contraction occurs only if the action potential outlasts<br>the mandatory delay period and causes the release of<br>some of the Ca<sup>2+</sup> sequestered by the SR during the latent<br>period. It seems likely, therefore, that the delayed me of the Ca<sup>2+</sup> sequestered by the SR during the latent riod. It seems likely, therefore, that the delayed release calcium must be under the control of the membrane tential, as is the initial release.<br>That the calcium re

period. It seems likely, therefore, that the delayed release<br>of calcium must be under the control of the membrane<br>potential, as is the initial release.<br>That the calcium responsible for the rested state con-<br>traction in fig of calcium must be under the control of the membrane<br>potential, as is the initial release.<br>That the calcium responsible for the rested state con-<br>traction in fig. 1a came from the extracellular space and<br>not from an intrac potential, as is the initial release.<br>
That the calcium responsible for the rested state con-<br>
traction in fig. 1*a* came from the extracellular space and<br>
not from an intracellular store can be deduced from the<br>
fact tha I hat the calcium responsible for the rested state con-<br>traction in fig. 1a came from the extracellular space and<br>not from an intracellular store can be deduced from the<br>fact that the contraction was completely abolished b not from an intracellular store can be deduced from the<br>fact that the contraction was completely abolished by<br>the 1,4-dihydropyridine derivative nifedipine, which spe-<br>cifically blocks L-type calcium channels (214, 20, 289 fact that the contraction was completely abolished by<br>the 1,4-dihydropyridine derivative nifedipine, which spe-<br>cifically blocks L-type calcium channels (214, 20, 289) at<br>concentrations more than 100-fold higher (237a) th the 1,4-dihydropyridine derivative nifedipine, which specifically blocks L-type calcium channels (214, 20, 289) at concentrations more than 100-fold higher (237a) than expected from radioligand binding (23a, 165a; see sect



FIG. 1. Different effects of the calcium channel blocker nifedipine (1 Mm)<br>
(1 Mmol/liter) on rested state contractions of the same guinea pig<br>
(1  $\mu$ mol/liter) on rested state contractions of the same guinea pig<br>
papillary muscle under the influence of either norepinephrine (30  $\mu$ mol/ 100 ms<br>
FIG. 1. Different effects of the calcium channel blocker nifedipine<br>
(1  $\mu$ mol/liter) on rested state contractions of the same guinea pig<br>
papillary muscle under the influence of either norepinephrine (30  $\mu$ mol FIG. 1. Different effects of the calcium channel blocker nifedipine (1  $\mu$ mol/liter) on rested state contractions of the same guinea pig papillary muscle under the influence of either norepinephrine (30  $\mu$ mol/liter) (a



CALCIUM MOBILIZATION AND CARDIAC INOTROPIC MECHANISMS <sup>193</sup>

the case with a distinctly use-dependent Ca channel CALCIUM MOBILIZATION AND C.<br>the drug at the applied concentration was fully effective<br>even after a long rest period (which might not have been<br>the case with a distinctly use-dependent Ca channel<br>blocker, such as verapamil, the drug at the applied concentration was fully effective even after a long rest period (which might not have been the case with a distinctly use-dependent Ca channel blocker, such as verapamil, as shown in fig. 5 of ref. the drug at the applied concentration was fully effective up<br>even after a long rest period (which might not have been<br>the case with a distinctly use-dependent Ca channel co<br>blocker, such as verapamil, as shown in fig. 5 of even after a long rest period (which might not have been<br>the case with a distinctly use-dependent Ca channel<br>blocker, such as verapamil, as shown in fig. 5 of ref. 46).<br>Fig. 1b shows a rested state contraction of the same<br> the case with a distinctly use-dependent Ca chand blocker, such as verapamil, as shown in fig. 5 of ref. 4 Fig. 1b shows a rested state contraction of the samuscle in low sodium solution. Studies with radioact tracers had blocker, such as verapamil, as shown in fig. 5 of ref. 46). <br>Fig. 1b shows a rested state contraction of the same consider in low sodium solution. Studies with radioactive stracers had shown that, at low external sodium co Fig. 1b shows a rested state contraction of the same dimuscle in low sodium solution. Studies with radioactive shared tracers had shown that, at low external sodium concentrations, the calcium influx increases (286, 287, 2 muscle in low sodium solution. Studies with radioactive tracers had shown that, at low external sodium concentrations, the calcium influx increases (286, 287, 233) while the calcium efflux diminishes (330), thus leading to tracers had shown that, at low external sodium concentrations, the calcium influx increases (286, 287, 233) while the calcium efflux diminishes (330), thus leading to a net increase of intracellular Ca (see section V) and, trations, the calcium influx increases  $(286, 287, 233)$  tions while the calcium efflux diminishes  $(330)$ , thus leading contraction and the rest period and accordingly, to a filled Ca store of the sarcoplasmic of reticul while the calcium efflux diminishes (330), thus leading<br>to a net increase of intracellular Ca (see section V) and,<br>accordingly, to a filled Ca store of the sarcoplasmic<br>reticulum. The first contraction after the rest perio we a net increase of intracemuar Ca (see section v) and,<br>accordingly, to a filled Ca store of the sarcoplasmic<br>reticulum. The first contraction after the rest period<br>started without any delay after stimulation (see also re reticulum. The first contraction after the rest period the started without any delay after stimulation (see also ref. no 3) and reached its peak at a time when the contraction sp in normal Na was just beginning. In low Na started without any delay after stimulation (see also ref. normal 3) and reached its peak at a time when the contraction speed in normal Na was just beginning. In low Na solution, that infedipine had no influence on the as 3) and reached its peak at a time when the contraction sp<br>in normal Na was just beginning. In low Na solution, the<br>nifedipine had no influence on the ascending slope of the<br>contraction curve; it only shortened the contrac in normal Na was just beginning. In low Na solution, that the infedipine had no influence on the ascending slope of the contraction curve; it only shortened the contraction in fects of accordance with a shortening of the d nifedipine had no influence on the ascending slope of the contraction curve; it only shortened the contraction is accordance with a shortening of the duration of the action potential. The lack of influence of the calcium c in a concentration which completed the contraction in the accordance with a shortening of the duration of the leadium channel blocker on the velocity of the early contraction, see contraction in the presence of norepinephr action potential. The lack of influence of the calcium<br>channel blocker on the velocity of the early contraction,<br>in a concentration which completely inhibited the late<br>contraction in the presence of norepinephrine, shows<br>t channel blocker on the velocity of the early contraction, seeing in a concentration which completely inhibited the late montraction in the presence of norepinephrine, shows that the dihydropyridine-sensitive Ca current was in a concentration which completely inhibited the late<br>contraction in the presence of norepinephrine, shows the<br>that the dihydropyridine-sensitive Ca current was not<br>involved in this contraction. A comparable finding was<br> contraction in the presence of norephrephrine, shows<br>that the dihydropyridine-sensitive Ca current was not<br>involved in this contraction. A comparable finding was<br>made by Mascher (fig. 3 of ref. 252) using partially<br>depolar involved in this contraction. A comparable finding was<br>made by Mascher (fig. 3 of ref. 252) using partially<br>depolarized (18.9 mmol/liter of KCl) field-stimulated cat<br>papillary muscles. These responded to threshold stimu-<br>l made by Mascher (fig. 3 of ref. 252) using partially the depolarized (18.9 mmol/liter of KCl) field-stimulated cat per papillary muscles. These responded to threshold stimulation with either regenerative or nonregenerativ depolarized (18.9 mmol/liter of KCl) field-stimulated of papillary muscles. These responded to threshold stimulation with either regenerative or nonregenerative (locelectrical responses which were accompanied by a we late papillary muscles. These responded to threshold stinution with either regenerative or nonregenerative (look electrical responses which were accompanied by a whate contraction. In low-sodium solution even nor generative ele relation with either regenerative of homegenerative (focal<br>electrical responses which were accompanied by a weal<br>late contraction. In low-sodium solution even nonre<br>generative electrical responses elicited strong contracti electrical responses which were accompanied by a weak<br>late contraction. In low-sodium solution even nonre-<br>generative electrical responses elicited strong contrac-<br>tions which appeared early after stimulation. The acti-<br>va late contraction. In low-sodium solution even nonre-<br>generative electrical responses elicited strong contrac-<br>tions which appeared early after stimulation. The acti-<br>vation of slow (calcium-dependent) potentials, therefore generative electrical responses elicited strong contrac-<br>tions which appeared early after stimulation. The activation of slow (calcium-dependent) potentials, therefore, pig<br>was not necessary as a trigger for calcium relea tions which appeared early after stimulation. The a<br>vation of slow (calcium-dependent) potentials, therefore was not necessary as a trigger for calcium release. Un<br>the influence of ouabain which causes an increase<br>intracel vation of slow (calcium-dependent) potentials, therefore, was not necessary as a trigger for calcium release. Under the influence of ouabain which causes an increase in blocke intracellular calcium (see section V B), stro was not necessary as a trigger for calcium release. Under<br>the influence of ouabain which causes an increase in<br>intracellular calcium (see section  $V$  B), strong contrac-<br>tions could be induced in spite of an inhibition of the infrace of ouaballit which causes an increase in<br>intracellular calcium (see section V B), strong contrac-<br>potentials by the calcium channel blocker verapamil<br>(382). With skeletal muscle, a comparable observation<br>was ma tions could be induced in spite of an inhibition of slow<br>potentials by the calcium channel blocker verapamil<br>(382). With skeletal muscle, a comparable observation<br>was made by Ildefonse et al. (181), who found that frog<br>sem potentials by the calcium channel blocker verapamil (382). With skeletal muscle, a comparable observation was made by Ildefonse et al. (181), who found that from a holding semitendinosus fibers developed biphasic contract (382). With skeletal muscle, a comparable observation<br>was made by Ildefonse et al. (181), who found that from<br>semitendinosus fibers developed biphasic contractions<br>during long-lasting clamp depolarizations from a holding<br> was made by Ildefonse et al.  $(181)$ , who found that frog<br>semitendinosus fibers developed biphasic contractions<br>during long-lasting clamp depolarizations from a holding<br>potential of  $-90$  mV. The first, rapid, phase reach semitendinosus fibers developed biphasic contractions<br>during long-lasting clamp depolarizations from a holding<br>potential of -90 mV. The first, rapid, phase reached its<br>maximum before the activation of an inward calcium<br>cu during long-lasting clamp depolarizations from a holding potential of  $-90$  mV. The first, rapid, phase reached its maximum before the activation of an inward calcium current. A slow second phase correlated in time with t potential of  $-90$  mV. The first, rapid, phase reached its maximum before the activation of an inward calcium current. A slow second phase correlated in time with the inward current. Nifedipine  $(10 \ \mu \text{mol/liter})$  inhibited maximum before the activation of an inward calcium<br>current. A slow second phase correlated in time with the<br>inward current. Nifedipine (10  $\mu$ mol/liter) inhibited I<sub>Ca</sub><br>and the second contraction component, but not the i current. A slow second phase correlated in time with the iniward current. Nifedipine  $(10 \mu \text{mol/liter})$  inhibited  $I_{Ca}$  and the second contraction component, but not the initial rapid one. The lack of effect of nifedipine on inward current. Nifedipine (10  $\mu$ mol/liter) inhibited I<sub>Ca</sub><br>and the second contraction component, but not the ini-<br>tial rapid one. The lack of effect of nifedipine on the<br>initial contraction was confirmed by Neuhaus (28 and the second contraction component, but not the initial rapid one. The lack of effect of nifedipine on the initial contraction was confirmed by Neuhaus (284a), but the author observed that the plateau phase was prolonge tial rapid one. The lack of effect of nifedipine on the initial contraction was confirmed by Neuhaus (284a), but the author observed that the plateau phase was prolonged which led him to suggest that the calcium inward cu itial contraction was confirmed by Neuhaus (284a), be author observed that the plateau phase was prolong<br>nich led him to suggest that the calcium inward curre<br>celerates the inactivation of  $Ca^{2+}$  release from the S<br>The q the author observed that the plateau phase was prolonged<br>which led him to suggest that the calcium inward current<br>accelerates the inactivation of  $Ca^{2+}$  release from the SR.<br>The question of whether the latent period of t

which led him to suggest that the calcium inward current<br>accelerates the inactivation of  $Ca^{2+}$  release from the SR.<br>The question of whether the latent period of the rested-<br>state contraction under the influence of catec accelerates the inactivation of  $Ca^{2+}$  release from the SR.<br>The question of whether the latent period of the rested-<br>state contraction under the influence of catecholamines<br>is the consequence of a slow diffusion of Ca to

the drug at the applied concentration was fully effective uptake into and release from the sarcoplasmic reticulum<br>even after a long rest period (which might not have been can be answered from the relation of the catecholam UPIAC INOTROPIC MECHANISMS 193<br>uptake into and release from the sarcoplasmic reticulum<br>can be answered from the relation of the catecholamine can be answered from the sarcoplasmic reticulum<br>uptake into and release from the sarcoplasmic reticulum<br>can be answered from the relation of the catecholamine<br>concentration to both height and time of appearance of concentration to both height and transfer as increased to and release from the sarcoplasmic reticulum<br>can be answered from the relation of the cate cholamine<br>concentration to both height and time of appearance of<br>the late the late into and release from the sarcoplasmic reticulum<br>can be answered from the relation of the catecholamine<br>concentration to both height and time of appearance of<br>the late peak. If the late peak were the result of a s uptake into and release from the sarcoplasmic reticulum<br>can be answered from the relation of the catecholamine<br>concentration to both height and time of appearance of<br>the late peak. If the late peak were the result of a sim can be answered from the relation of the catecholamine<br>concentration to both height and time of appearance of<br>the late peak. If the late peak were the result of a simple<br>diffusion lag, one would expect the latent period to diffusion lag, one would expect the latent period to shorten with increasing Ca fluxes (assuming linear kinetics of diffusion), since then the threshold concentration of Ca which triggers contraction should be reached cons diffusion lag, one would expect the latent period<br>shorten with increasing Ca fluxes (assuming linear<br>netics of diffusion), since then the threshold concent<br>tion of Ca which triggers contraction should be reac<br>considerably shorten with increasing Ca fluxes (assuming linear kinetics of diffusion), since then the threshold concentration of Ca which triggers contraction should be reached considerably faster if Ca entry is enhanced by catecholam netics of diffusion), since then the threshold concentra-<br>tion of Ca which triggers contraction should be reached<br>considerably faster if Ca entry is enhanced by catechol-<br>amines. The tracings of fig. 2 show that the latent tion of Ca which triggers contraction should be reached<br>considerably faster if Ca entry is enhanced by catechol-<br>amines. The tracings of fig. 2 show that the latent period<br>of the rested state contraction was not shortened considerably faster if Ca entry is enhanced by catecholamines. The tracings of fig. 2 show that the latent period of the rested state contraction was not shortened when the Ca uptake was more than quadrupled with increasin amines. The tracings of fig. 2 show that the latent period<br>of the rested state contraction was not shortened when<br>the Ca uptake was more than quadrupled with increasing<br>norepinephrine concentrations, as evidenced by the re of the resteal state contraction was not shortened when<br>the Ca uptake was more than quadrupled with increasing<br>norepinephrine concentrations, as evidenced by the re-<br>spective increased Ca inflow was compensated for in its<br> norepinephrine concentrations, as evidenced by the respective increase in force of contraction. One could argue<br>that the increased Ca inflow was compensated for in its<br>contraction-activating effect by various intracellular spective increase in force of contraction. One could argue<br>that the increased Ca inflow was compensated for in its<br>contraction-activating effect by various intracellular ef-<br>fects of a catecholamine-induced elevation in c that the increased Ca inflow was compensated for in its contraction-activating effect by various intracellular effects of a catecholamine-induced elevation in cyclic AMP levels which occurs in contracting (334) as well as contraction-activating effect by various intracellular effects of a catecholamine-induced elevation in cyclic AMP<br>levels which occurs in contracting (334) as well as in<br>resting muscle (92). In particular, a reduction in th fects of a catecholamine-induced elevation in cyclic AM<br>levels which occurs in contracting (334) as well as i<br>resting muscle (92). In particular, a reduction in the C<br>sensitivity of the contractile apparatus (359, 250, 333 levels which occurs in contracting (334) as well as in<br>resting muscle (92). In particular, a reduction in the Ca<br>sensitivity of the contractile apparatus (359, 250, 333)<br>might be supposed to counteract, at least temporaril resting muscle (92). In particular, a reduction in the Ca sensitivity of the contractile apparatus (359, 250, 333) might be supposed to counteract, at least temporarily, the contraction-activating effect of the inflowing C sensitivity of the contractile apparatus (359, 250, 333)<br>might be supposed to counteract, at least temporarily,<br>the contraction-activating effect of the inflowing Ca and<br>thus be responsible for the constancy of the latent might be supposed to counteract, at least temporarily,<br>the contraction-activating effect of the inflowing Ca and<br>thus be responsible for the constancy of the latent period.<br>However, such an interference seems improbable, s the contraction-activating effect of the inflowing Ca and<br>thus be responsible for the constancy of the latent period.<br>However, such an interference seems improbable, since<br>the late peak appears in addition to an early con thus be responsible for the constancy of the latent period.<br>However, such an interference seems improbable, since<br>the late peak appears in addition to an early contraction<br>peak in rested state contractions at low external However, such an interference seems improbable, since<br>the late peak appears in addition to an early contraction<br>peak in rested state contractions at low external sodium<br>concentration. In this situation the contractile syst peak in rested state contractions at low external sodium<br>concentration. In this situation the contractile system is<br>already highly activated as a result of calcium release<br>from a filled storage compartment of the SR; furth peak in rested state contractions at low external sodium<br>concentration. In this situation the contractile system is<br>already highly activated as a result of calcium release<br>from a filled storage compartment of the SR; furth concentration. In this situation the contractile system is<br>already highly activated as a result of calcium release<br>from a filled storage compartment of the SR; further-<br>more, in this case the late, and not the early, peak aready mgmy activated as a result of calcium release<br>from a filled storage compartment of the SR; further-<br>more, in this case the late, and not the early, peak is<br>sensitive to calcium channel blockade by nifedipine (fig.<br>6 more, in this case the late, and not the early, peak is<br>sensitive to calcium channel blockade by nifedipine (fig.<br>6 in Ref. 323). In two-component contractions of a guinea<br>pig papillary muscle in the presence of norepineph sensitive to calcium channel blockade by nifedipine (fig. 6 in Ref. 323). In two-component contractions of a guinea pig papillary muscle in the presence of norepinephrine at a stimulation frequency of 0.3 Hz, the calcium c 6 in Ref. 323). In two-component contractions of a guinea<br>pig papillary muscle in the presence of norepinephrine<br>at a stimulation frequency of  $0.3$  Hz, the calcium channel<br>blocker verapamil diminished only the late contr pig papillary muscle in the presence of norepinephrine<br>at a stimulation frequency of 0.3 Hz, the calcium channel<br>blocker verapamil diminished only the late contraction<br>peak (46). Obviously, the development of the late peak at a stimulation frequency of 0.3 Hz, the calcium channel<br>blocker verapamil diminished only the late contraction<br>peak (46). Obviously, the development of the late peak<br>of the rested state contraction is independent of an e blocker verapamil diminished only the late contraction<br>peak (46). Obviously, the development of the late peak<br>of the rested state contraction is independent of an early<br>force generation after stimulation. Furthermore, the that the increased Ca inflow was compensated for in its<br>contraction-activating effect by various intractellular effects of a catecholamine-induced elevation in cyclic AMP<br>levels which occurs in contracting (334) as well a of the rested state contraction is independent of an each<br>force generation after stimulation. Furthermore, the<br>layed appearance of the late peak did not change i<br>was increased by the dihydropyridine derivative BAY<br>8644 ins force generation after stimulation. Furthermore, the de-<br>layed appearance of the late peak did not change if it<br>was increased by the dihydropyridine derivative BAY K<br>8644 instead of a catecholamine (unpublished observa-<br>ti rent by a direct action on calcium channels without by a direct action on calcium channels without by a direct action on calcium channels without



FIG. 2. Unchanged late appearance of rested state contractions<br>under the influence of increasing concentrations of norepinephrine (1<br>to 100  $\mu$ mol/liter). The electrical stimuli are marked by the *arrow*. to 100 km 100 fm 100 mS<br>The electrical stimuli are marked by the *arrow*.<br>Adapted from Seibel et al. (345).<br>Adapted from Seibel et al. (345).

194<br>increasing the intracellular cyclic AMP level (215, 60,<br>381). 381).

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The constancy of the latent period of the rested state the<br>
ntraction points to the functional involvement of the is increasing the intracellular cyclic AMP level (215, 60, com<br>381). the constancy of the latent period of the rested state via<br>contraction points to the functional involvement of the is<br>sarcoplasmic reticulum. Its dense peri 381).<br>The constancy of the latent period of the rested state contraction points to the functional involvement of the<br>sarcoplasmic reticulum. Its dense peripheral networ<br>which is located immediately subjacent to the cell me The constancy of the latent period of the rested state ventraction points to the functional involvement of the isoarcoplasmic reticulum. Its dense peripheral network function, seems which is located immediately subjacent t contraction points to the functional involvement of the is<br>sarcoplasmic reticulum. Its dense peripheral network fro<br>which is located immediately subjacent to the cell mem-<br>brane, instead of only retarding calcium diffusion sarcoplasmic reticulum. Its dense peripheral network from the cell mem-<br>which is located immediately subjacent to the cell mem-<br>brane, instead of only retarding calcium diffusion, seems lii<br>to act as a diffusion barrier by which is located immediately subjacent to the cell mem-<br>brane, instead of only retarding calcium diffusion, seems<br>likely the act as a diffusion barrier by taking up most of the<br>inflowing Ca, especially under the facilitati brane, instead of only retarding calcium diffusion, seems<br>to act as a diffusion barrier by taking up most of the<br>inflowing Ca, especially under the facilitating effect of<br>cyclic AMP (for reviews, see refs. 385, 342, and 37 to act as a diffusion barrier by taking up most of the inflowing Ca, especially under the facilitating effect expectively cyclic AMP (for reviews, see refs. 385, 342, and 378). corresponding observation regarding extracell inflowing Ca, especially under the facilitating effect of cyclic AMP (for reviews, see refs. 385, 342, and 378). A corresponding observation regarding extracellular calcium transients as measured with tetramethylmurexide w cyclic AMP (for reviews, see refs. 385, 342, and 378). A like corresponding observation regarding extracellular calcium transients as measured with tetramethylmurexide the was made by Hilgemann (161). He found that premat corresponding observation regarding extracellular calcum transients as measured with tetramethylmurexide the was made by Hilgemann (161). He found that premature 202 excitations (i.e., when the calcium release stores are v cium transients as measured with tetramethylmurexide<br>was made by Hilgemann (161). He found that premature<br>excitations (i.e., when the calcium release stores are<br>depleted and the elicited contraction is weak) result in a<br>pr was made by Hilgemann (161). He found that premature excitations (i.e., when the calcium release stores are depleted and the elicited contraction is weak) result in a prolonged depletion of extracellular calcium due to pro excitations (i.e., when the calcium release stores are voldepleted and the elicited contraction is weak) result in a formula prolonged depletion of extracellular calcium due to prolonged calcium influx. This can be explai depleted and the elicited contraction is weak) result in a<br>prolonged depletion of extracellular calcium due to pro-<br>longed calcium influx. This can be explained by internal d<br>calcium sequestration sufficiently fast to pre prolonged depletion of extracellular calcium due to prolonged calcium influx. This can be explained by interna<br>calcium sequestration sufficiently fast to prevent the<br>cytosolic calcium accumulation that would be necessar-<br>n longed calcium influx. This can be explained by internal divergentiation sequestration sufficiently fast to prevent the correction of calcium accumulation that would be necessary With would of calcium channel inactivation calcium sequestration sufficiently fast to prevent the cytosolic calcium accumulation that would be necessary<br>not only for activation of contraction but also for initi-<br>ation of calcium channel inactivation (237), which wo cytosolic calcium accumulation that would be necessary<br>not only for activation of contraction but also for initi-<br>ation of calcium channel inactivation (237), which would<br>obterminate the influx of extracellular calcium. C not only for activation of contraction but also for initiation of calcium channel inactivation (237), which would terminate the influx of extracellular calcium. Consistent with this view is the finding that, in skinned ca ation of calcium channel inactivation (237), which would<br>terminate the influx of extracellular calcium. Consistent<br>with this view is the finding that, in skinned cardiac<br>cells, the SR that is wrapped around individual myo with this view is the finding that, in skinned cardiac cells, the SR that is wrapped around individual myofibrils accumulated calcium rapidly enough to prevent high  $Ca^{2+}$  concentrations of externally applied solutions f cells, the SR that is wrapped around individual myofibriac<br>cumulated calcium rapidly enough to prevent high Ca<br>concentrations of externally applied solutions from a<br>tivating the myofilaments (fig. 10 in ref. 120; fig. 7 in accumulated calcium rapidly enough to prevent high to<br>concentrations of externally applied solutions from<br>tivating the myofilaments (fig. 10 in ref. 120; fig. 7 in<br>115). This is analogous to the reaccumulation and m<br>ment b concentrations of externally applied solutions from activating the myofilaments (fig. 10 in ref. 120; fig. 7 in ref. 115). This is analogous to the reaccumulation and movement back to release sites of Ca during an activat civating the inyomalities (i.g. 10 in fer. 120, i.g.  $\cdot$  in 115). This is analogous to the reaccumulation and moment back to release sites of Ca during an activative relaxation cycle in skeletal (312) as well as in mamma 115). This is analogous to the reaccumulation and move-<br>ment back to release sites of Ca during an activation-<br>relaxation cycle in skeletal (312) as well as in mammalian<br>cardiac muscle (275). In the latter, mechanical res ment back to release sites of Ca during an activation-<br>relaxation cycle in skeletal (312) as well as in mammalian<br>cardiac muscle (275). In the latter, mechanical restitu-<br>tion, indicating the transfer of calcium from the u relaxation cycle in skeletal (312) as well as in mammalian cardiac muscle (275). In the latter, mechanical restitution, indicating the transfer of calcium from the uptake sites of the sarcoplasmic reticulum to the release cardiac muscle  $(275)$ . In the latter, mechanical restitution, indicating the transfer of calcium from the uptake sites of the sarcoplasmic reticulum to the release store reaches its maximum after  $0.7$  to  $1.0$  s  $(164,$ tion, indicating the transfer of calcium from the uptake<br>sites of the sarcoplasmic reticulum to the release store,<br>reaches its maximum after 0.7 to 1.0 s (164, 97, 311, 419).<br>Accordingly, the latent period of the rested s sites of the sarcoplasmic reticulum to the release store, reaches its maximum after 0.7 to 1.0 s (164, 97, 311, 419).<br>Accordingly, the latent period of the rested state contraction can be regarded as an expression of the d reaches its maximum aft<br>Accordingly, the latent<br>traction can be regarde<br>between sequestration of<br>availability as activator.<br>B. Tun-Companent Con *B. Two-Component Contraction*<br>*B. Two-Component Contractions*<br>*B. Two-Component Contractions*<br>Contractions with two component tween sequestration of inflowing calcium and its first<br>
inflability as activator.<br>
Two-Component Contractions<br>
Contractions with two components, an early and a late<br>
e, sometimes occur during regular stimulation at very<br>

availability as activator.<br>
B. Two-Component Contractions calculation at the common calcular contractions with two components, an early and a late retione, sometimes occur during regular stimulation at very SR<br>
low frequen B. Two-Component Contractions<br>Contractions with two components, an early and a lat<br>one, sometimes occur during regular stimulation at ver-<br>low frequencies (7). The two components become espe-<br>cially distinct if they are st B. Two-Component Contractions can be contractions of the contractions with two components, an early and a late one, sometimes occur during regular stimulation at very Silow frequencies (7). The two components become espec Contractions with two components, an early and a late<br>one, sometimes occur during regular stimulation at very<br>low frequencies (7). The two components become espe-<br>cially distinct if they are strengthened by the addition of low frequencies (7). The two components become especially distinct if they are strengthened by the addition of less<br>drugs that increase cyclic AMP levels (328, 344, 345, 22, pec<br>24, 46, 255, 417, 111, 323, 248). Two-compo cially distinct if they are strengthened by the addition of drugs that increase cyclic AMP levels  $(328, 344, 345, 224, 46, 255, 417, 111, 323, 248)$ . Two-component contractions can also be observed when the action potent drugs that increase cyclic AMP levels (328, 344, 24, 46, 255, 417, 111, 323, 248). Two-component tions can also be observed when the action pot prolonged after most of the calcium of the bathition has been replaced by stro , 46, 255, 417, 111, 323, 248). Two-component contrac-<br>nns can also be observed when the action potential is<br>olonged after most of the calcium of the bathing solu-<br>n has been replaced by strontium  $(56, 207)$ .<br>The two com

tions can also be observed when the action potential is<br>prolonged after most of the calcium of the bathing solu-<br>tion has been replaced by strontium (56, 207).<br>The two components of these contractions should not<br>be confuse prolonged after most of the calcium of the bathing solution has been replaced by strontium  $(56, 207)$ .<br>The two components of these contractions should not the confused with the "phasic" and "tonic" components to of contr tion has been replaced by strontium (56, 207).<br>The two components of these contractions should not<br>be confused with the "phasic" and "tonic" components<br>of contraction observed in frog cardiac muscle during<br>prolonged depola The two components of these contractions should not the confused with the "phasic" and "tonic" components to of contraction observed in frog cardiac muscle during during the phasic (transient) component has the same covol be confused with the "phasic" and "tonic" components to logical for the contraction observed in frog cardiac muscle during duraprolonged depolarizing clamp pulses (146, 392, 99, 239). prefine the phasic (transient) compon of contraction observed in frog cardiac muscle during<br>prolonged depolarizing clamp pulses (146, 392, 99, 239).<br>Since the phasic (transient) component has the same<br>voltage dependence as the calcium current (175) and<br>both a prolonged depolarizing clamp pulses  $(146, 392, 99, 239)$ . P<br>Since the phasic (transient) component has the same covitage dependence as the calcium current  $(175)$  and all<br>both are inhibited by calcium channel blockers  $(M$ 

increasing the intracellular cyclic AMP level (215, 60, contractions of the frog heart are, in contrast to those of 381).<br>
the mammalian heart, directly activated by Ca entering<br>
The constancy of the latent period of the ER<br>contractions of the frog heart are, in contrast to those of<br>the mammalian heart, directly activated by Ca entering ER<br>contractions of the frog heart are, in contrast to those of<br>the mammalian heart, directly activated by Ca entering<br>via I<sub>Ca</sub>. The generation of tonic (sustained) contractions ER<br>contractions of the frog heart are, in contrast to those of<br>the mammalian heart, directly activated by Ca entering<br>via I<sub>Ca</sub>. The generation of tonic (sustained) contractions<br>is attributed to a calcium transfer mechanis contractions of the frog heart are, in contrast to those of<br>the mammalian heart, directly activated by Ca entering<br>via  $I_{Ca}$ . The generation of tonic (sustained) contractions<br>is attributed to a calcium transfer mechanism from I<sub>Ca</sub>. The generation for the influence of sodium on the tonic force of sodium on the tonic force is attributed to a calcium transfer mechanism different from I<sub>Ca</sub> (99). The influence of sodium on the tonic force de via  $I_{Ca}$ . The generation of tonic (sustained) contractions<br>is attributed to a calcium transfer mechanism different<br>from  $I_{Ca}$  (99). The influence of sodium on the tonic force<br>development at inside positive potentials m is attributed to a calcium transfer mechanism differe<br>from  $I_{Ca}$  (99). The influence of sodium on the tonic for<br>development at inside positive potentials makes it see<br>likely that the tonic components are activated by cal likely that the tonic components are activated by calcium<br>derived from Na-Ca exchange (391, 87, 11, 176, 82).<br>In mammalian cardiac muscle a terminal contracture-

with this view is the finding that, in skinned cardiac ing calcium is a matter of discussion. In heart muscle of cells, the SR that is wrapped around individual myofibrils mammals, unlike that of frogs, the contracture fo development at inside positive potentials makes it seem<br>likely that the tonic components are activated by calcium<br>derived from Na-Ca exchange (391, 87, 11, 176, 82).<br>In mammalian cardiac muscle a terminal contracture-<br>like likely that the tonic components are activated by calcium<br>derived from Na-Ca exchange (391, 87, 11, 176, 82).<br>In mammalian cardiac muscle a terminal contracture-<br>like component is observed if the period of depolarization<br>o derived from 1va-Ca exchange (351, 87, 11, 170, 82).<br>In mammalian cardiac muscle a terminal contracture-<br>like component is observed if the period of depolarization<br>outlasts the triggered contraction. This is true whether<br>t In mammanan cardiac muscle a terminal contracture-<br>like component is observed if the period of depolarization<br>outlasts the triggered contraction. This is true whether<br>the action potential is prolonged pharmacologically (2 outlasts the triggered contraction. This is true whether action potential is prolonged pharmacologically (203, 202, 253) or the membrane potential is controlled by voltage clamping (272, 421, 55, 294, 271, 103). It has be outlasts the triggered contraction. This is true whether<br>the action potential is prolonged pharmacologically (203,<br>202, 253) or the membrane potential is controlled by<br>voltage clamping (272, 421, 55, 294, 271, 103). It has the action potential is prolonged pharmacologically (203, 202, 253) or the membrane potential is controlled by voltage clamping (272, 421, 55, 294, 271, 103). It has been found that, during the prolonged depolarization, t 202, 253) or the membrane potential is controlled by voltage clamping (272, 421, 55, 294, 271, 103). It has been found that, during the prolonged depolarization, the tonic component is controlled by both intracellular sod voltage clamping (272, 421, 55, 294, 271, 103). It has been<br>found that, during the prolonged depolarization, the<br>tonic component is controlled by both intracellular so-<br>dium activity ( $a_{Na}^i$ ) and membrane potential in a found that, during the prolonged depolarization, the tonic component is controlled by both intracellular so-<br>dium activity  $(a_{N_a}^i)$  and membrane potential in a manner<br>consistent with Na-Ca exchange (103; see section V). tonic component is controlled by both intracellular so-<br>dium activity  $(a^i_{N_a})$  and membrane potential in a manner<br>consistent with Na-Ca exchange (103; see section V).<br>Whether the "tonic" contracture-like component is acdium activity  $(a_{N_a})$  and membrane potential in a man<br>consistent with Na-Ca exchange (103; see section<br>Whether the "tonic" contracture-like component is<br>tivated directly by the prolonged transmembrane upt<br>of calcium or vi consistent with Na-Ca exchange (103; see section V<br>Whether the "tonic" contracture-like component is *i*<br>tivated directly by the prolonged transmembrane upta<br>of calcium or via a sustained release from the intrac<br>lular stor ing calcium is a matter of discussion. In heart muscle of calcium or via a sustained release from the intracel-<br>lular store which continuously is sequestering the inflow-<br>ing calcium is a matter of discussion. In heart mus of calcium or via a sustained release from the intracel-<br>lular store which continuously is sequestering the inflow-<br>ing calcium is a matter of discussion. In heart muscle of<br>mammals, unlike that of frogs, the contracture f lular store which continuously is sequestering the inflowing calcium is a matter of discussion. In heart muscle of mammals, unlike that of frogs, the contracture force of these "tonic" components is usually considerably lo ing calcium is a matter of discussion. In heart muscle of mammals, unlike that of frogs, the contracture force of these "tonic" components is usually considerably lower than the peak force of the triggered contraction (55, mammals, unlike that of frogs, the contracture force of these "tonic" components is usually considerably lower than the peak force of the triggered contraction (55, 253). However, the tonic components may be followed after these "tonic" components is usually considerably lower<br>than the peak force of the triggered contraction (55, 253).<br>However, the tonic components may be followed after<br>repolarization by aftercontractions (103), and the peak than the peak force of the triggered contraction (55, 253).<br>However, the tonic components may be followed after<br>repolarization by aftercontractions (103), and the peak<br>force of the first regular systole after such a "tonic repolarization by aftercontractions (103), and the peak<br>force of the first regular systole after such a "tonic"<br>component is always considerably stronger than the con-<br>tracture force (421).<br>In contrast, the two-component c repolarization by aftercontractions (103), and the peak<br>force of the first regular systole after such a "tonic"<br>component is always considerably stronger than the con-<br>tracture force (421).<br>In contrast, the two-component

component is always considerably stronger than the con-<br>tracture force (421).<br>In contrast, the two-component contraction of mam-<br>malian cardiac muscle under the conditions of increased<br> $I_{C_a}$  and low frequency stimulatio tracture force (421).<br>In contrast, the two-component contraction of mam-<br>malian cardiac muscle under the conditions of increased<br> $I_{C_a}$  and low frequency stimulation consists of two distinct<br>phasic components. Only the e In contrast, the two-component contraction of mam-<br>malian cardiac muscle under the conditions of increased<br> $I_{C_a}$  and low frequency stimulation consists of two distinct<br>phasic components. Only the early component depends malian cardiac muscle under the conditions of increased  $I_{C_a}$  and low frequency stimulation consists of two distinct phasic components. Only the early component depends on the amount of previously stored calcium. There  $I_{Ca}$  and low frequency stimulation consists of two distinct<br>phasic components. Only the early component depends<br>on the amount of previously stored calcium. There is an<br>inflection of the force trace after about 100 ms, a phasic components. Only the early component depends<br>on the amount of previously stored calcium. There is an<br>inflection of the force trace after about 100 ms, and we<br>interpret this to be the point at which the inflowing<br>cal on the amount of previously stored calcium. There is an inflection of the force trace after about 100 ms, and we interpret this to be the point at which the inflowing calcium taken up from the longitudinal sarcoplasmic ret inflection of the force trace after about 100 ms, and we interpret this to be the point at which the inflowing calcium taken up from the longitudinal sarcoplasmic reticulum starts to be released by the release sites of the interpret this to be the point at which the inflowing<br>calcium taken up from the longitudinal sarcoplasmic<br>reticulum starts to be released by the release sites of the<br>SR. The release is ended with the repolarization of the<br> calcium taken up from the longitudinal sarcoplasmic<br>reticulum starts to be released by the release sites of the<br>SR. The release is ended with the repolarization of the<br>cell membrane which apparently closes the calcium re-<br> reticulum starts to be released by the release sites of the SR. The release is ended with the repolarization of the cell membrane which apparently closes the calcium re-<br>lease channels of the junctionally associated SR. De SR. The release is ended with the repolarization of the cell membrane which apparently closes the calcium release channels of the junctionally associated SR. Depending on the length of the action potential, the two contrac cell membrane which apparently closes the calcium re-<br>lease channels of the junctionally associated SR. De-<br>pending on the length of the action potential, the two<br>contraction components may be distinctly separated, or<br>they dease channels of the junctionally associated SR. Depending on the length of the action potential, the two<br>contraction components may be distinctly separated, of<br>they may fuse together into a contraction plateau (fig<br>3). T pending on the length of the action potential, the two<br>contraction components may be distinctly separated, or<br>they may fuse together into a contraction plateau (fig.<br>3). The duration of the action potential, therefore, con contraction components may be distinctly separated, or<br>they may fuse together into a contraction plateau (fig.<br>3). The duration of the action potential, therefore, con-<br>trols the duration of the late contraction peak and<br>t they may fuse together into a contraction plateau (fig.<br>3). The duration of the action potential, therefore, con-<br>trols the duration of the late contraction peak and<br>thereby the amount of total calcium released. The time<br>t 3). The duration of the action potential, therefore, controls the duration of the late contraction peak and thereby the amount of total calcium released. The time to peak of the late component is linearly related to the d trols the duration of the late contraction peak and thereby the amount of total calcium released. The time to peak of the late component is linearly related to the duration of the action potential, and this relation is pre thereby the amount of total calcium released. The time<br>to peak of the late component is linearly related to the<br>duration of the action potential, and this relation is<br>preserved in the presence of catecholamines (24, 345) o to peak of the late component is linearly related to the duration of the action potential, and this relation is preserved in the presence of catecholamines (24, 345) or cesium (323). The late component is reduced or even a duration of the action potential, and this relation is<br>preserved in the presence of catecholamines (24, 345) or<br>cesium (323). The late component is reduced or even<br>abolished if the duration of the action potential is de-<br>c preserved in the presence of catecholamines (24, 345) or cesium (323). The late component is reduced or even abolished if the duration of the action potential is decreased toward physiological values by increasing the freq



PHARMACOLOGICAL REVIEWS



FIG. 3. Two-component contractions. Superimposed action potentials and contraction curves of a guinea pig papillary muscle in the presence of 10  $\mu$ mol/liter of norepinephrine. The numbers indicate: 1, rested state contra

## *C. Cyclic AMP and Phosphodiesterase Inhibitors*

<sup>21.</sup> (345).<br>
<sup>31</sup> (345).<br>
Cyclic AMP and Phosphodiesterase Inhibitors<br>
1. Cyclic AMP. That the formation of cyclic AMP by<br>
tivation of adenylate cyclase plays a decisive role in 2. Cyclic AMP and Phosphodiesterase Inhibitors<br>
2. Cyclic AMP. That the formation of cyclic AMP by<br>
activation of adenylate cyclase plays a decisive role in<br>
the inotropic effect of catecholamines was deduced early 1. Cyclic AMP. That the formation of cyclic AMP by<br>activation of adenylate cyclase plays a decisive role in<br>the inotropic effect of catecholamines was deduced early<br>from the correlation between the increase in cyclic AMP<br> From the correlation between the increase in cyclic AMP by<br>activation of adenylate cyclase plays a decisive role in<br>the inotropic effect of catecholamines was deduced early<br>from the correlation between the increase in cyc 1. Cyclic AMP. That the formation of cyclic AMP by<br>activation of adenylate cyclase plays a decisive role in<br>the inotropic effect of catecholamines was deduced early<br>from the correlation between the increase in cyclic AMP<br> the inotropic effect of catecholamines was deduced early<br>from the correlation between the increase in cyclic AMP<br>and the inotropic effect (372). Isoproterenol was found<br>to be 5 to 10 times more potent than epinephrine or<br> the motropic enect of catecholamines was deduced early<br>from the correlation between the increase in cyclic AMP<br>and the inotropic effect (372). Isoproterenol was found<br>to be 5 to 10 times more potent than epinephrine or<br>nor and the inotropic effect (372). Isoproterenol was found<br>to be 5 to 10 times more potent than epinephrine or<br>norepinephrine in stimulating the formation of cyclic<br>AMP by preparations from dog ventricle, whereas di-<br>chloroi to be 5 to 10 times more potent than epinephrine correpinephrine in stimulating the formation of cycli<br>AMP by preparations from dog ventricle, whereas dehoroisoproterenol (DCI) behaved as an antagonis<br>which indicates the more pinepin in summating the formation of cyclic<br>
AMP by preparations from dog ventricle, whereas di-<br>
chloroisoproterenol (DCI) behaved as an antagonist<br>
which indicates the involvement of  $\beta$ -adrenoceptor stim-<br>
ulati evident that the activation of glycogen phosphorylase by<br>cyclic AMP is not responsible for the inotropic effect<br>(250, 224) Protein phosphorylation was found to be of special interest. 8-(4-Chlorophenyl)thio-cyclic AMP<br>(250 ulation. It was also observed that the formation of cyclic AMP was reduced by acetylcholine and carbachol (372).<br>From kinetic studies in the isolated heart it soon became evident that the activation of glycogen phosphoryla AMP was reduced by acetylcholine and carbachol (372). From kinetic studies in the isolated heart it soon became<br>evident that the activation of glycogen phosphorylase by<br>cyclic AMP is not responsible for the inotropic effe From kinetic studies in the isolated heart it soon became<br>evident that the activation of glycogen phosphorylase by<br>cyclic AMP-is not responsible for the inotropic effect<br>(259, 334). Protein phosphorylation was found to be evident that the activation of glycogen phosphorylase by<br>cyclic AMP is not responsible for the inotropic effect<br>(259, 334). Protein phosphorylation was found to be<br>catalyzed by cyclic AMP-dependent protein kinase (402)<br>in cyclic AMP is not responsible for the inotropic effect (259, 334). Protein phosphorylation was found to be catalyzed by cyclic AMP-dependent protein kinase (402) is in membrane particles not only from the sarcoplasmic par (259, 334). Protein phosphorylation was found to catalyzed by cyclic AMP-dependent protein kinase (40 in membrane particles not only from the sarcoplasm reticulum (208) but also from the cell surface (420). T association catalyzed by cyclic AMP-dependent protein kinase (402) is about 18 times as effective on protein kinase as the<br>in membrane particles not only from the sarcoplasmic<br>reticulum (208) but also from the cell surface (420). The in membrane particles not only from the sarcoplasmic reticulum (208) but also from the cell surface (420). The association of this phosphorylation with a cyclic AMP-dependent modulation of calcium influx (403) led to the reticulum (208) but also from the cell surface (420). The association of this phosphorylation with a cyclic AMP-<br>dependent modulation of calcium influx (403) led to the<br>proposal that a cyclic AMP-dependent protein kinase<br>p association of this phosphorylation with a cyclic AMP-<br>dependent modulation of calcium influx  $(403)$  led to the<br>proposal that a cyclic AMP-dependent protein kinase<br>phosphorylates a sarcolemmal calcium channel protein,<br>th dependent modulation of calcium influx  $(403)$  led to the<br>proposal that a cyclic AMP-dependent protein kinase<br>phosphorylates a sarcolemmal calcium channel protein,<br>thus producing a conformational change that makes the<br>cha proposal that a cyclic AMP-dependent protein kinase<br>phosphorylates a sarcolemmal calcium channel protein,<br>thus producing a conformational change that makes the<br>channel available for voltage activation (366, 385).<br>Changes phosphorylates a sarcolemmal calcium channel protein, methus producing a conformational change that makes the both channel available for voltage activation (366, 385). of Changes in the configuration of the action potenti thus producing a conformational change that makes the both channel available for voltage activation (366, 385). of Changes in the configuration of the action potential,  $I_{Ca}$ , as and contraction produced by injection of channel available for voltage activation  $(366, 385)$ .<br>Changes in the configuration of the action potential,  $I_{Cs}$ , and contraction produced by injection of cyclic AMP and subunits of cyclic AMP-dependent protein kinase Changes in the configuration of the action potential,  $I_{\text{Ca}}$ , as been and contraction produced by injection of cyclic AMP and hydro subunits of cyclic AMP-dependent protein kinase into group cardiac myocytes support th and contraction produced by injection of cyclic AMP and<br>subunits of cyclic AMP-dependent protein kinase into<br>cardiac myocytes support the hypothesis that phospho-<br>rylation of a protein within, or close to, the calcium<br>chan subunits of cyclic AMP-dependent protein kinase into ground cardiac myocytes support the hypothesis that phospho-<br>rylation of a protein within, or close to, the calcium low<br>channel by cyclic AMP-dependent protein kinase i cardiac inyocytes support the hypothesis that phosphorylation of a protein within, or close to, the calcium channel by cyclic AMP-dependent protein kinase is indeed the mechanism of calcium channel modulation by  $\beta$ -adre channel by cyclic AMP-dependent protein kinase is in-<br>deed the mechanism of calcium channel modulation by<br> $\beta$ -adrenoceptor stimulation (298, 62, 193). An elegant cell<br>proof of the key role of cyclic AMP formation in incr deed the mechanism of calcium channel modulation by  $\alpha$   $\beta$ -adrenoceptor stimulation (298, 62, 193). An elegant corroof of the key role of cyclic AMP formation in increasing  $I_{Ca}$  was provided by photochemically produc  $\beta$ -adrenoceptor stimulation (298, 62, 193). An elegar proof of the key role of cyclic AMP formation in increasing  $I_{C_a}$  was provided by photochemically producing a intracellular concentration jump of cyclic AMP. The w proof of the key role of cyclic AMP formation in increas-<br>ing L<sub>Ca</sub> was provided by photochemically producing an within the cell (219, 220).<br>intracellular concentration jump of cyclic AMP. This 3. Phosphodiesterase inhibi

**CALCIUM MOBILIZATION AND CARDIAC INOTROPIC MECHANISMS** 195<br>
yield cyclic AMP upon irradiation (332). Concentration jumps of cyclic AMP, following single brief light flashes, ROIAC INOTROPIC MECHANISMS 195<br>
yield cyclic AMP upon irradiation (332). Concentration<br>
jumps of cyclic AMP, following single brief light flashes,<br>
increased the amplitude and the duration of the action EXECUTE INCREDUCE MECHANISMS<br>
increased the amplitude and the duration of the action<br>
pioneers of cyclic AMP, following single brief light flashes,<br>
increased the amplitude and the duration of the action<br>
potentials, incr yield cyclic AMP upon irradiation (332). Concentration<br>jumps of cyclic AMP, following single brief light flashes,<br>increased the amplitude and the duration of the action<br>potentials, increased  $I_{Ca}$ , and simultaneously—in f yield cyclic AMP upon irradiation (332). Concentration<br>jumps of cyclic AMP, following single brief light flashes,<br>increased the amplitude and the duration of the action<br>potentials, increased  $I_{Cs}$ , and simultaneously—in (332). potentials, increased  $I_{Ca}$ , and simultaneously—in frog<br>heart trabeculae—increased the force of contraction<br>(332).<br>Cyclic AMP also facilitates calcium uptake into the<br>SR (350) and calcium extrusion through the sarcolemma heart trabeculae-increased the force of contraction

FIG. 3. Two-component contractions. Superimposed action poten-<br>tials and contraction curves of a guinea pig papillary muscle in the<br>presence of 10  $\mu$ mol/liter of norepinephrine. The *numbers* indicate: 1,<br>rested state c heart trabeculae—increased the force of contraction (332).<br>
Cyclic AMP also facilitates calcium uptake into the<br>
SR (350) and calcium extrusion through the sarcolemmal<br>
calcium pump (see section VI A), thereby accelerating (332). Cyclic AMP also facilitates calcium uptake into the SR (350) and calcium extrusion through the sarcolemmal calcium pump (see section VI A), thereby accelerating the relaxation of heart muscle. Several findings indi Cyclic AMP also facilitates calcium uptake into the SR (350) and calcium extrusion through the sarcolemmal calcium pump (see section VI A), thereby accelerating the relaxation of heart muscle. Several findings indicate th SR (350) and calcium extrusion through the sarcolemmal<br>calcium pump (see section VI A), thereby accelerating<br>the relaxation of heart muscle. Several findings indicate<br>that the modulation of the SR calcium pump parallels<br>p calcium pump (see section VI A), thereby accelerating<br>the relaxation of heart muscle. Several findings indicate<br>that the modulation of the SR calcium pump parallels<br>phosphorylation and dephosphorylation of a  $M_r$  22,000<br>p the relaxation of heart muscle. Several maings matcate<br>that the modulation of the SR calcium pump parallels<br>phosphorylation and dephosphorylation of a  $M_r$  22,000<br>polymeric membrane protein, phospholamban (378). The<br>phosp phosphorylation and dephosphorylation of a  $M_r$  22,000<br>polymeric membrane protein, phospholamban (378). The<br>phosphorylation of phospholamban is catalyzed by cyclic<br>AMP-dependent protein kinase (208). Recent results<br>sugges polymeric membrane protein, phospholamban (378). The<br>phosphorylation of phospholamban is catalyzed by cyclic<br>AMP-dependent protein kinase (208). Recent results<br>suggest that, in normal cardiac SR, phospholamban in<br>the depho AMP-dependent protein kinase (208). Recent results AMP-dependent protein kinase  $(208)$ . Recausses that, in normal cardiac SR, phospher the dephosphorylated state acts as a supprecalcium pump and that phosphorylation of phanes serves to reverse the suppression  $(182)$ .<br>2. ggest that, in normal cardiac SR, phospholamban in<br> *2. dephosphorylated state acts as a suppressor of the*<br>
lcium pump and that phosphorylation of phospholam-<br> *2. Cyclic AMP derivatives.* Cyclic AMP applied to the<br> *2. C* calcium pump and that phosphorylation of phospholam-

which indicates the involvement of  $\beta$ -adrenoceptor stim-<br>ulation. It was also observed that the formation of cyclic  $\beta$ -aximal cyclic AMP (dbcAMP; 226, 354, 328). The half-maximal<br>AMP was reduced by acetylcholine and c calcium pump and that phosphorylation of phospholam-<br>ban serves to reverse the suppression  $(182)$ .<br>2. Cyclic AMP derivatives. Cyclic AMP applied to the<br>extracellular fluid is unable to produce a positive ino-<br>tropic effe ban serves to reverse the suppression  $(182)$ .<br>
2. Cyclic AMP derivatives. Cyclic AMP applied to the<br>
extracellular fluid is unable to produce a positive ino-<br>
tropic effect  $(313)$  because it is destroyed intracellularly 2. Cyclic AMP derivatives. Cyclic AMP applied to the extracellular fluid is unable to produce a positive inotropic effect (313) because it is destroyed intracellularly by a phosphodiesterase at a rate much faster than its extracellular fluid is unable to produce a positive ino-<br>tropic effect (313) because it is destroyed intracellularly<br>by a phosphodiesterase at a rate much faster than its<br>rate of entry (334). However, several derivatives o rate of entry (334). However, several derivatives of cyclic AMP which are resistant to enzymatic degradation have been found to elicit catecholamine-like positive inotropic effects when applied extracellularly. The first a by a phosphodiesterase at a rate much faster than its<br>rate of entry (334). However, several derivatives of cyclic<br>AMP which are resistant to enzymatic degradation have<br>been found to elicit catecholamine-like positive inot rate of entry (334). However, several derivatives of cyclic AMP which are resistant to enzymatic degradation have been found to elicit catecholamine-like positive inotropic effects when applied extracellularly. The first AMP which are resistant to enzymatic degradation have<br>been found to elicit catecholamine-like positive inotropi<br>effects when applied extracellularly. The first and mos<br>widely used was the  $N^6-2'-O$ -dibutyryl derivative c<br> been found to elicit catecholamine-like positive inotropic<br>effects when applied extracellularly. The first and most<br>widely used was the  $N^2$ -2'-O-dibutyryl derivative of<br>cyclic AMP (dbcAMP; 226, 354, 328). The half-maxim effects when applied extracellularly. The first and most<br>widely used was the  $N^6$ -2'-O-dibutyryl derivative of<br>cyclic AMP (dbcAMP; 226, 354, 328). The half-maximal<br>effective concentration is about 1 mmol/liter of dbcAMP. widely used was the  $N^6$ -2'-O-dibutyryl derivative of cyclic AMP (dbcAMP; 226, 354, 328). The half-maximal effective concentration is about 1 mmol/liter of dbcAMP.<br>The same potency was observed with the 8-substituted cyc clic AMP (dbcAMP; 226, 354, 328). The half-maximal<br>fective concentration is about 1 mmol/liter of dbcAMP.<br>he same potency was observed with the 8-substituted<br>clic AMP derivatives 8-thio-benzyl-cyclic AMP (112).<br>A few of th

effective concentration is about 1 mmol/liter of dbcAMP.<br>The same potency was observed with the 8-substituted<br>cyclic AMP derivatives 8-thio-benzyl-cyclic AMP (112).<br>A few of the 8-substituted cyclic AMP derivatives are<br>of The same potency was observed with the 8-substituted<br>cyclic AMP derivatives 8-thio-benzyl-cyclic AMP (112).<br>A few of the 8-substituted cyclic AMP derivatives are<br>of special interest. 8-(4-Chlorophenyl)thio-cyclic AMP<br>is ab cyclic AMP derivatives 8-thio-benzyl-cyclic AMP (112).<br>A few of the 8-substituted cyclic AMP derivatives are<br>of special interest. 8-(4-Chlorophenyl)thio-cyclic AMP<br>is about 18 times as effective on protein kinase as the<br>pa A few of the 8-substituted cyclic AMP derivatives are<br>of special interest. 8-(4-Chlorophenyl)thio-cyclic AMP<br>is about 18 times as effective on protein kinase as the<br>parent cyclic AMP (266). On isolated guinea pig papillary of special interest. 8-(4-Chlorophenyl)thio-cyclic AMI<br>is about 18 times as effective on protein kinase as th<br>parent cyclic AMP (266). On isolated guinea pig papillar<br>muscles 8-(4-chlorophenyl)thio-cyclic AMP was foun<br>to is about 18 times as effective on protein kinase as the parent cyclic AMP (266). On isolated guinea pig papillary muscles 8-(4-chlorophenyl)thio-cyclic AMP was found to be about 25 times as potent as dbcAMP with a half-ma parent cyclic AMP (266). On isolated guinea pig papillary<br>muscles 8-(4-chlorophenyl)thio-cyclic AMP was found<br>to be about 25 times as potent as dbcAMP with a half-<br>maximally effective concentration, log EC<sub>50</sub>, of -4.4,<br>f muscles 8-(4-chlorophenyl)thio-cyclic AMP was found<br>to be about 25 times as potent as dbcAMP with a half-<br>maximally effective concentration, log EC<sub>50</sub>, of -4.4,<br>followed by the 8-tertiary butyl-thio-cyclic AMP with a<br>mea to be about 25 times as potent as dbcAMP with a half-<br>maximally effective concentration, log  $EC_{50}$ , of  $-4.4$ ,<br>followed by the 8-tertiary butyl-thio-cyclic AMP with a<br>mean log  $EC_{50}$  of  $-4.0$  (220). The inotropic pote followed by the 8-tertiary butyl-thio-cyclic AMP with a mean log  $EC_{50}$  of  $-4.0$  (220). The inotropic potency of both compounds was further increased to log  $EC_{50}$  values of  $-5.66$  and  $-5.38$ , respectively, when they followed by the 8-tertiary butyl-thio-cyclic AMP with a mean log  $EC_{50}$  of  $-4.0$  (220). The inotropic potency of both compounds was further increased to log  $EC_{50}$  values of  $-5.66$  and  $-5.38$ , respectively, when they mean log EC<sub>50</sub> of  $-4.0$  (220). The inotropic potency of<br>both compounds was further increased to log EC<sub>50</sub> values<br>of  $-5.66$  and  $-5.38$ , respectively, when they were applied<br>as benzyl esters (220). Neutralization of th hydroxyl residue of 8-substituted cyclic AMP by a benzyl<br>group yielded lipophilic cyclic AMP benzyl esters which<br>produced their positive inotropic effect at 20 to 100 times of  $-5.66$  and  $-5.38$ , respectively, when they were applied<br>as benzyl esters (220). Neutralization of the phosphate<br>hydroxyl residue of 8-substituted cyclic AMP by a benzyl<br>group yielded lipophilic cyclic AMP benzyl este as benzyl esters (220). Neutralization of the phosphate<br>hydroxyl residue of 8-substituted cyclic AMP by a benzyl<br>group yielded lipophilic cyclic AMP benzyl esters which<br>produced their positive inotropic effect at 20 to 100 hydroxyl residue of 8-substituted cyclic AMP by a benzyl<br>group yielded lipophilic cyclic AMP benzyl esters which<br>produced their positive inotropic effect at 20 to 100 times<br>lower concentrations than the respective cyclic A group yielded lipophilic cyclic AMP benzyl esters which<br>produced their positive inotropic effect at 20 to 100 times<br>lower concentrations than the respective cyclic AMP<br>salts. The lipophilic benzyl esters of cyclic AMP can produced their positive inotropic effect at 20 to 100 times<br>lower concentrations than the respective cyclic AMP<br>salts. The lipophilic benzyl esters of cyclic AMP can be<br>considered as transport forms for cyclic AMP across t lower concentrations than the respective cyclic AMP salts. The lipophilic benzyl esters of cyclic AMP can be considered as transport forms for cyclic AMP across the cell membrane, which gain their biological activity throu salts. The lipophilic benzyl<br>considered as transport form<br>cell membrane, which ga<br>through cyclic AMP release<br>within the cell (219, 220).<br>3. Phosphodiesterase in maidered as transport forms for cyclic AMP across the<br> *3.* Phosphodiesterase *inhibitors.* Substances which<br> *3. Phosphodiesterase inhibitors.* Substances which<br>
imulate adenylate cyclase should be potentiated in their cell membrane, which gain their biological activity<br>through cyclic AMP released by spontaneous hydrolysis<br>within the cell (219, 220).<br>3. Phosphodiesterase inhibitors. Substances which<br>stimulate adenylate cyclase should be

through cyclic AMP released by spontaneous hydrolysis<br>within the cell (219, 220).<br>3. Phosphodiesterase inhibitors. Substances which<br>stimulate adenylate cyclase should be potentiated in their<br>inotropic effects by drugs whic

REITER<br>the phosphodiesterase that converts cyclic 3',5'-AMP to curre<br>the inactive adenosine 5'-phosphate. Methylxanthines prev R<br>the phosphodiesterase that converts cyclic 3',5'-AMP t<br>the inactive adenosine 5'-phosphate. Methylxanthine<br>are competitive inhibitors of this phosphodiesterase (64) REIT<br>the phosphodiesterase that converts cyclic 3',5'-AMP to<br>the inactive adenosine 5'-phosphate. Methylxanthines<br>are competitive inhibitors of this phosphodiesterase (64);<br>and it has been shown that theophylline and, less the phosphodiesterase that converts cyclic 3',5'-AMP the inactive adenosine 5'-phosphate. Methylxanthine are competitive inhibitors of this phosphodiesterase (64 and it has been shown that theophylline and, less effectivel the inactive adenosine 5'-phosphate. Methylxanthines<br>are competitive inhibitors of this phosphodiesterase (64);<br>and it has been shown that theophylline and, less effec-<br>tively, caffeine at concentrations at which they them the inactive adenosine 5'-phosphate. Methylxanthines pare competitive inhibitors of this phosphodiesterase  $(64)$ ; and it has been shown that theophylline and, less effectively, caffeine at concentrations at which they th are competitive inhibitors of this phosphodiesterase (64);<br>and it has been shown that theophylline and, less effec-<br>tively, caffeine at concentrations at which they them-<br>selves are inotropically ineffective potentiate the and it has been shown that theophylline and, less effectively, caffeine at concentrations at which they them-<br>selves are inotropically ineffective potentiate the cardiac minotropic response to norepinephrine (313). In high tively, caffeine at concentrations at which they themselves are inotropically ineffective potentiate the cardiac inotropic response to norepinephrine (313). In higher concentrations, the methylxanthines would be expected t selves are inotropically ineffective potentiate the cardiac<br>inotropic response to norepinephrine (313). In higher from<br>concentrations, the methylxanthines would be expected auto<br>increase cardiac force in a catecholamine-li inotropic response to norepinephrine  $(313)$ . In higher from concentrations, the methylxanthines would be expected auto increase cardiac force in a catecholamine-like manner, where if their activity as phosphodiesterase i concentrations, the methylxanthines would be expected<br>to increase cardiac force in a catecholamine-like manner,<br>if their activity as phosphodiesterase inhibitors were<br>sufficiently selective. However, both caffeine  $(40)$  to increase cardiac force in a catecholamine-like manne<br>if their activity as phosphodiesterase inhibitors we<br>sufficiently selective. However, both caffeine (40) an<br>theophylline (218) affect the onset and the relaxation<br>pha sufficiently selective. However, both caffeine (40) and patheophylline (218) affect the onset and the relaxation morphase of the contraction curve in a way distinctly different from that characteristic for catecholamines. theophylline (218) affect the onset and the relaxat<br>phase of the contraction curve in a way distinctly dif<br>ent from that characteristic for catecholamines. T<br>points to additional effects besides the inhibition of<br>phosphodi phase of the contraction curve in a way distinctly differ-<br>
ent from that characteristic for catecholamines. This<br>
co<br>
points to additional effects besides the inhibition of the<br>
co<br>
phosphodiesterase (see section IV E). S ent from that characteristic for catecholamines. This<br>points to additional effects besides the inhibition of the<br>phosphodiesterase (see section IV E). So far, 1-methyl-<br>3-isobutylxanthine (IBMX), which is about 15 times as points to additional effects besides the inhibition of the<br>
phosphodiesterase (see section IV E). So far, 1-methyl-<br>
3-isobutylxanthine (IBMX), which is about 15 times as<br>
SF<br>
potent as theophylline as a phosphodiesterase phosphodiesterase (see section IV E). So far, 1-methyl-<br>3-isobutylxanthine (IBMX), which is about 15 times as SI<br>potent as theophylline as a phosphodiesterase inhibitor<br>(21), is the only xanthine derivative that has been 3-isobutylxanthine (IBMX), which is about 15 times a<br>potent as theophylline as a phosphodiesterase inhibito<br>(21), is the only xanthine derivative that has been found<br>to mimic the effects of isoproterenol in the extent of i potent as theophylline as a phosphodiesterase inhibito (21), is the only xanthine derivative that has been found to mimic the effects of isoproterenol in the extent of iteration of the contraction IBMX seems to be devoid o

to mimic the effects of isoproterenol in the extent of its<br>inotropic effect and the abbreviation of the contraction.<br>IBMX seems to be devoid of other effects (218, 227).<br>In recent years several new agents including bipyrid motropic enect and the abbreviation of the contraction.<br>
IBMX seems to be devoid of other effects (218, 227).<br>
In recent years several new agents including bipyridine<br>
and pyridazinone derivatives have been developed that<br> In recent years several new agents including bipyridin<br>and pyridazinone derivatives have been developed tha<br>possess phosphodiesterase-inhibiting activity and pro<br>duce positive inotropic effects in the heart (for review<br>see and pyridazinone derivatives have been developed that possess phosphodiesterase-inhibiting activity and produce positive inotropic effects in the heart (for review, see ref. 122). These agents also apparently have addition possess phosphodiesterase-inhibiting activity and pro-<br>duce positive inotropic effects in the heart (for review,<br>see ref. 122). These agents also apparently have addi-<br>dional effects which might influence their therapeutic duce positive inotropic effects in the heart (for review, see ref. 122). These agents also apparently have additional effects which might influence their therapeutic usefulness (360, 410, 343, 335, 113). It has been found see Fel. 122). These agents also apparently have additional effects which might influence their therapeutic usefulness (360, 410, 343, 335, 113). It has been found that functional subclasses of the cyclic AMP-specific phos usefulness (360, 410, 343, 335, 113). It has been found belt that functional subclasses of the cyclic AMP-specific allembrosphodiesterase (PDE III) exist in ventricular muscle; ran these may be either membrane bound or so that functional subclasses of the cyclic AMP-specific<br>phosphodiesterase (PDE III) exist in ventricular muscle;<br>these may be either membrane bound or soluble (409).<br>Differences in their intracellular localization might be<br>r phosphodiesterase (PDE III) exist in ventricular musc<br>these may be either membrane bound or soluble (40<br>Differences in their intracellular localization might<br>responsible for species differences that exist in the ca<br>diotoni tors. **ISONATE:** Interpretes that exist in<br> **IV. Calcium Release Mechanisms**<br> **IV. Calcium Release Mechanisms**<br> **IC.** Dersus Current-dependent Calcium diotonic responses to various phosphodiesterase inhibi-<br> *A. Voltage- versus Current-dependent Calcium Release*<br>
In voltage-clamp experiments the relation between<br>
In voltage-clamp experiments the relation between

IV. Calcium Release Mechanisms<br>Voltage-versus Current-dependent Calcium Release<br>In voltage-clamp experiments the relation between<br>embrane potential and force development has been IV. Calcium Release Mechanisms<br>
A. Voltage-versus Current-dependent Calcium Release<br>
In voltage-clamp experiments the relation between<br>
membrane potential and force development has been<br>
studied in an effort to determine A. Voltage- versus Current-dependent Calcium Release<br>In voltage-clamp experiments the relation between<br>membrane potential and force development has been<br>studied in an effort to determine whether Ca entering by sign<br>way of A. Voltage- versus Current-uependent Cultum Release<br>In voltage-clamp experiments the relation between<br>membrane potential and force development has been<br>studied in an effort to determine whether Ca entering by<br>way of the se In voltage-clamp experiments the relation between<br>membrane potential and force development has been<br>studied in an effort to determine whether Ca entering by<br>way of the second inward current not only replenishes<br>the intrace membrane potential and force development has bee<br>studied in an effort to determine whether Ca entering b<br>way of the second inward current not only replenishe<br>the intracellular calcium pools but also triggers the re<br>lease o studied in an effort to determine whether Ca entering by<br>way of the second inward current not only replenishes SR,<br>the intracellular calcium pools but also triggers the re-calc<br>lease of stored calcium. In addition to the m way of the second inward current not only replenishes<br>the intracellular calcium pools but also triggers the re-<br>lease of stored calcium. In addition to the methodological wide<br>difficulties in obtaining homogeneous voltage the intracellular calcium pools but also triggers the re-<br>lease of stored calcium. In addition to the methodological we<br>difficulties in obtaining homogeneous voltage control in the<br>multicellular preparations (190), these e lease of stored calcium. In addition to the methodological widerficulties in obtaining homogeneous voltage control in the multicellular preparations (190), these experiments have in the problem of uncertainty about the ext difficulties in obtaining homogeneous voltage control in<br>multicellular preparations (190), these experiments have<br>the problem of uncertainty about the extent of filling of<br>the calcium release store, which depends upon a va multicellular preparations (190), these experiments have the problem of uncertainty about the extent of filling the calcium release store, which depends upon a varie of factors, including resting membrane potential, procus the problem of uncertainty about the extent of filling of<br>the calcium release store, which depends upon a variety<br>of factors, including resting membrane potential, pre-<br>vious stimulation pattern, outside calcium concentrat the calcium release store, which depends upon a variety is step of factors, including resting membrane potential, pre-<br>vious stimulation pattern, outside calcium concentration, It as<br>temperature, clamp duration, and the nu of factors, including resting membrane potential, pre-<br>vious stimulation pattern, outside calcium concentration, It<br>temperature, clamp duration, and the number of depo-<br>alarizations. The role of the SR becomes visible if, vious stimulation pattern, outside calcium concentration, It<br>temperature, clamp duration, and the number of depo-<br>larizations. The role of the SR becomes visible if, as in<br>the records of Beeler and Reuter (23), the develop temperature, clamp duration, and the number of depo-<br>larizations. The role of the SR becomes visible if, as in<br>the records of Beeler and Reuter (23), the developed Tl<br>force increases with the number of similar voltage clam

sufficiently selective. However, both caffeine (40) and parallels between  $I_{C_a}$  and force of contraction indicate a theophylline (218) affect the onset and the relaxation modulation by  $I_{C_a}$  of the release itself or o REITER<br>to current itself seems to be influenced by the number of<br>les previous contractions or pattern of stimulation. Simurda ER<br>current itself seems to be influenced by the number of<br>previous contractions or pattern of stimulation. Simurda<br>and coworkers (352) observed a decrease of  $I_{Ca}$  under ER<br>current itself seems to be influenced by the number of<br>previous contractions or pattern of stimulation. Simurda<br>and coworkers (352) observed a decrease of  $I_{Ca}$  under<br>conditions of a mechanical staircase, reflecting t current itself seems to be influenced by the number of<br>previous contractions or pattern of stimulation. Simurda<br>and coworkers (352) observed a decrease of  $I_{Ca}$  under<br>conditions of a mechanical staircase, reflecting the current itself seems to be influenced by the number of<br>previous contractions or pattern of stimulation. Simurda<br>and coworkers (352) observed a decrease of  $I_{Ca}$  under<br>conditions of a mechanical staircase, reflecting the previous contractions or pattern of stimulation. Simurda<br>and coworkers (352) observed a decrease of  $I_{Ca}$  under<br>conditions of a mechanical staircase, reflecting the in-<br>creasing amount of calcium released from the SR and and coworkers (352) observed a decrease of  $L_{ca}$  under<br>conditions of a mechanical staircase, reflecting the in-<br>creasing amount of calcium released from the SR and its<br>modulating effect on  $L_{Ca}$ . Therefore, it is diffic conditions of a mechanical staircase, reflecting the increasing amount of calcium released from the SR and its modulating effect on  $I_{Ca}$ . Therefore, it is difficult to judge from the voltage-force relationships publishe modulating effect on  $I_{Ca}$ . Therefore, it is difficult to judge<br>from the voltage-force relationships published by various<br>authors working under different experimental conditions<br>whether the observed effects are directly modulating effect on  $I_{Ca}$ . Therefore, it is difficult to judge<br>from the voltage-force relationships published by various<br>authors working under different experimental conditions<br>whether the observed effects are directly from the voltage-force relationships published by various<br>authors working under different experimental conditions<br>whether the observed effects are directly or indirectly<br>voltage related. In other words, it is uncertain wh authors working under different experimental conditions<br>whether the observed effects are directly or indirectly<br>voltage related. In other words, it is uncertain whether<br>parallels between  $I_{Ca}$  and force of contraction in whether the observed effects are directly or indirectly<br>voltage related. In other words, it is uncertain whether<br>parallels between  $I_{C_a}$  and force of contraction indicate a<br>modulation by  $I_{C_a}$  of the release itself or voltage related. In other words, it is uncertain whether<br>parallels between  $I_{C_a}$  and force of contraction indicate a<br>modulation by  $I_{C_a}$  of the release itself or of the filling of<br>the release stores. Since in the mamm parallels between  $I_{Ca}$  and force of contraction indicate a modulation by  $I_{Ca}$  of the release itself or of the filling of the release stores. Since in the mammalian heart, in contrast to the frog heart, there appears n modulation by  $I_{Ca}$  of the release itself or of the filling of<br>the release stores. Since in the mammalian heart, in<br>contrast to the frog heart, there appears not to be direct<br>coupling between inflowing calcium and contra the release stores. Since<br>contrast to the frog heart,<br>coupling between inflowin<br>results are bound to depe:<br>SR is filled with calcium.<br>In the steady state, wh ntrast to the frog heart, there appears not to be direct<br>upling between inflowing calcium and contraction, the<br>sults are bound to depend on the extent to which the<br> $\lambda$  is filled with calcium.<br>In the steady state, where o

(21), is the only xanthine derivative that has been found constant filling of the SR proportional to the strength of<br>to mimic the effects of isoproterenol in the extent of its<br>including  $I_{Ca}$  at the chosen clamp potentia coupling between inflowing calcium and contraction, the results are bound to depend on the extent to which the SR is filled with calcium.<br>
In the steady state, where one might expect a rather constant filling of the SR pr results are bound to depend on the extent to which the<br>SR is filled with calcium.<br>In the steady state, where one might expect a rather<br>constant filling of the SR proportional to the strength of<br> $I_{Ca}$  at the chosen clamp SR is filled with calcium.<br>In the steady state, where one might expect a rather<br>constant filling of the SR proportional to the strength of<br> $I_{C_a}$  at the chosen clamp potential, almost all authors have<br>found a parallelism In the steady state, where one might expect a rather constant filling of the SR proportional to the strength of  $I_{Ca}$  at the chosen clamp potential, almost all authors have found a parallelism between  $I_{Ca}$  and force of constant filling of the SR proportional to the strength of  $I_{C_a}$  at the chosen clamp potential, almost all authors have found a parallelism between  $I_{C_a}$  and force of contraction at depolarizations up to zero potentia  $I_{Ca}$  at the chosen clamp potential, almost all authors have<br>found a parallelism between  $I_{Ca}$  and force of contraction<br>at depolarizations up to zero potential. With further<br>depolarizations to inside positive values, th found a parallelism between  $I_{Ca}$  and force of contraction<br>at depolarizations up to zero potential. With further<br>depolarizations to inside positive values, the force of<br>contraction usually remained more or less constant, at depolarizations up to zero potential. With further depolarizations to inside positive values, the force of contraction usually remained more or less constant, not following the decline of  $I_{C_a}$  and indicating a relea depolarizations to inside positive values, the force of contraction usually remained more or less constant, not following the decline of  $I_{Ca}$  and indicating a release of stored calcium independent of  $I_{Ca}$  (134, 23, 29 contraction usually remained more or less constant, not<br>following the decline of  $I_{C_a}$  and indicating a release of<br>stored calcium independent of  $I_{C_a}$  (134, 23, 294, 383, 186).<br>A few papers on multicellular preparatio stored calcium independent of  $I_{Ca}$  (134, 23, 294, 383, 186).<br>A few papers on multicellular preparations (271, 238, 260) and one on single heart cells (245) have presented bell-shaped voltage-force curves which run rough stored calcium independent of  $I_{Ca}$  (134, 23, 294, 383, 186).<br>A few papers on multicellular preparations (271, 238, 260) and one on single heart cells (245) have presented<br>bell-shaped voltage-force curves which run rough A few papers on multicellular preparations (271, 238, 260) and one on single heart cells (245) have presented bell-shaped voltage-force curves which run roughly parallel to the voltage- $I_{Ca}$  curves in the positive voltag 260) and one on single heart cells (245) have presented<br>bell-shaped voltage-force curves which run roughly par-<br>allel to the voltage- $I_{Ca}$  curves in the positive voltage<br>range. As a possible explanation of the divergence bell-shaped voltage-force curves which run roughly parallel to the voltage-I<sub>Ca</sub> curves in the positive voltage range. As a possible explanation of the divergence of their results, Morad and Goldman (271) pointed to the lo allel to the voltage- $I_{C_a}$  curves in the positive voltage<br>range. As a possible explanation of the divergence of<br>their results, Morad and Goldman (271) pointed to the<br>lower experimental temperature in contrast to that us range. As a possible explanation of the divergence of their results, Morad and Goldman  $(271)$  pointed to the lower experimental temperature in contrast to that used by other authors  $(24-25^{\circ}C, \text{ refs. } 271 \text{ and } 260; \text{ "room$ their results, Morad and Goldman (271) pointed to the lower experimental temperature in contrast to that used<br>by other authors (24–25°C, refs. 271 and 260; "room<br>temperature," refs. 238 and 245 versus 35–37°C, the<br>others). by other authors (24–25°C, refs. 271 and 260; "room<br>temperature," refs. 238 and 245 versus 35–37°C, the<br>others). This could indicate that the storage capability<br>of the release sites of the SR in the mammalian heart is<br>redu by other authors (24–25°C, refs. 271 and 260; "room<br>temperature," refs. 238 and 245 versus 35–37°C, the<br>others). This could indicate that the storage capability<br>of the release sites of the SR in the mammalian heart is<br>redu temperature," refs. 238 and 245 versus 35–37°C, the others). This could indicate that the storage capability of the release sites of the SR in the mammalian heart is reduced at low temperatures. Experimental evidence for s others). This could indicate that the storage capability<br>of the release sites of the SR in the mammalian heart is<br>reduced at low temperatures. Experimental evidence for<br>such an assumption is provided by the rapid cooling<br> of the release sites of the SR in the mammalian heart is<br>reduced at low temperatures. Experimental evidence for<br>such an assumption is provided by the rapid cooling<br>contractures which are activated without depolarization<br>b reduced at low temperatures. Experimental evidence for<br>such an assumption is provided by the rapid cooling<br>contractures which are activated without depolarization<br>by an abrupt Ca<sup>2+</sup> leak from the SR (228, 58). If cooling<br> contractures which are activated without depolarization<br>by an abrupt  $Ca^{2+}$  leak from the SR (228, 58). If cooling<br>significantly slows the active calcium uptake into the<br>SR, an uncompensated calcium leak will reduce the<br> by an abrupt  $Ca^{2+}$  leak from the SR (228, 58). If cooling significantly slows the active calcium uptake into the SR, an uncompensated calcium leak will reduce the calcium content of the release compartments. Consistent significantly slows the active calcium uptake into the SR, an uncompensated calcium leak will reduce the calcium content of the release compartments. Consistent with the release sites being empty at low temperatures is the SR, an uncompensated calcium leak will reduce the calcium content of the release compartments. Consistent with the release sites being empty at low temperatures is the finding of Kitazawa (210) that, at  $25^{\circ}$ C, the cha calcium content of the release compartments. Consistent<br>with the release sites being empty at low temperatures is<br>the finding of Kitazawa (210) that, at 25°C, the change<br>in force of contraction of mammalian ventricular mu which the felease sites being empty at low demperatures is<br>the finding of Kitazawa (210) that, at 25°C, the change<br>in force of contraction of mammalian ventricular muscle<br>induced by a change in the outside calcium concent the finding of Kitazawa (210) that, at 25°C, the change<br>in force of contraction of mammalian ventricular muscle<br>induced by a change in the outside calcium concentration<br>is synchronous with the change in  $[Ca^{2+}]$  at the ce in force of contraction of mammalian ventricular muscle<br>induced by a change in the outside calcium concentration<br>is synchronous with the change in  $[Ca^{2+}]$  at the cell<br>surface. (see also ref. 6 for comparable results at 2 induced by a change in the outside calcium concentrat<br>is synchronous with the change in  $[Ca^{2+}]$  at the surface. (see also ref. 6 for comparable results at 21<sup>°</sup><br>It appears, therefore, that at 25<sup>°</sup>C the contractions<br>acti is synchronous with the change in  $[Ca^{2+}]$  at the celevation surface. (see also ref. 6 for comparable results at  $21^{\circ}$ C) It appears, therefore, that at  $25^{\circ}$ C the contractions are activated by calcium entering the c surface. (see also ref. 6 for comparable results at  $21^{\circ}$ C).<br>It appears, therefore, that at  $25^{\circ}$ C the contractions are<br>activated by calcium entering the cell during depolari-<br>zation via  $I_{Ca}$  and presumably consis It appears, therefore, that at  $25^{\circ}\text{C}$  the contractions are<br>activated by calcium entering the cell during depolari-<br>zation via  $I_{\text{Ca}}$  and presumably consist of late components.<br>The bell-shaped curves in the aboveactivated by calcium entering the cell during depolarization via  $I_{C_a}$  and presumably consist of late components.<br>The bell-shaped curves in the above-mentioned papers would then correspond to those obtained in single ce

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CALCIUM MOBILIZATION AN<br>SR are empty, and the calcium that activates contraction is "directly" derived from  $I_{Ca}$  and leads to let CALCIUM MOBILIZATION AND SR are empty, and the calcium that activates contraction is "directly" derived from  $I_{Ca}$  and leads to late-appearing contractions (see below, and ref. 186). In line CALCIUM MOBILIZATION AND CARDI<br>SR are empty, and the calcium that activates contraction<br>is "directly" derived from  $I_{Ca}$  and leads to late-<br>compearing contractions (see below, and ref. 186). In line<br>with this reasoning i SR are empty, and the calcium that activates contraction is "directly" derived from  $I_{Ca}$  and leads to late-appearing contractions (see below, and ref. 186). In line with this reasoning is the bell-shaped voltage depende SR are empty, and the calcium that activates contraction is "directly" derived from  $I_{Ca}$  and leads to late appearing contractions (see below, and ref. 186). In line with this reasoning is the bell-shaped voltage depende appearing contractions (see below, and ref. 186). In line<br>with this reasoning is the bell-shaped voltage dependence<br>of  $[Ca^{2+}]_i$  transients observed in single guinea pig ven-<br>tricular cells at 37°C by means of the fluore appearing contractions (see below, and ref. 186). In line contraction components presumably because, as a result<br>with this reasoning is the bell-shaped voltage dependence of partial diastolic depolarization of the sarcole with this reasoning is the bell-shaped voltage dependence of  $\int$  of  $[Ca^{2+}]$ ; transients observed in single guinea pig ven-<br>tricular cells at 37°C by means of the fluorescent  $Ca^{2+}$  des<br>indicator fura-2 (16). The cells of  $[Ca^{2+}]_i$  transients observed in single guinea pig ven<br>tricular cells at 37°C by means of the fluorescent  $Ca^2$ <br>indicator fura-2 (16). The cells were voltage clampe<br>from a holding potential of  $-40$  mV, which is a ver tricular cells at 37°C by means of the fluorescent  $Ca^{2+}$  indicator fura-2 (16). The cells were voltage clamped from a holding potential of  $-40$  mV, which is a very unfavorable condition for Ca storage in SR release com indicator fura-2 (16). The cells were voltage clamped<br>from a holding potential of  $-40$  mV, which is a very<br>unfavorable condition for Ca storage in SR release com-<br>partments in spite of "conditioning" clamp pulses (186,<br>3 from a holding potential of  $-40$  mV, which is a very be unfavorable condition for Ca storage in SR release compartments in spite of "conditioning" clamp pulses (186, aft 399; see section IV C). Therefore, it is quite pos unfavorable condition for Ca storage<br>partments in spite of "conditioning"<br>399; see section IV C). Therefore, it<br>the transients of fluorescence were<br>voltage-dependent calcium influx.<br>The filling state of the SR is The filling state of "conditioning" clamp pulses (186, after the SR is quite possible that cover the state of fluorescence were caused directly by the politage-dependent calcium influx. The filling state of the SR is also

399; see section IV C). Therefore, it is quite possible that<br>the transients of fluorescence were caused directly by the<br>voltage-dependent calcium influx.<br>The filling state of the SR is also pertinent to the<br>question of wh the transients of fluorescence were caused directly by the voltage-dependent calcium influx.<br>The filling state of the SR is also pertinent to the question of whether calcium release can be triggered a potentials negative voltage-dependent calcium influx. at<br>
The filling state of the SR is also pertinent to the<br>
question of whether calcium release can be triggered at<br>
potentials negative to the  $I_{Ca}$  threshold. Beeler and Reu-<br>
ter (in th The filling state of the SR is also pertinent to the from question of whether calcium release can be triggered at 20 potentials negative to the  $L_{c_a}$  threshold. Beeler and Reuter (in their fig. 4, ref. 23) observed that question of whether calcium release can be triggered at  $20 \text{ m/s}$ <br>potentials negative to the  $I_{Ca}$  threshold. Beeler and Reu-<br>ter (in their fig. 4, ref. 23) observed that appreciable force ulum,<br>of contraction was activ potentials negative to the  $I_{C_a}$  threshold. Beeler and Reuter (in their fig. 4, ref. 23) observed that appreciable force und of contraction was activated at  $-54$  mV only after the v sixth depolarization to  $+19$  mV, i. ter (in their fig. 4, ref. 23) observed that appreciable fo<br>of contraction was activated at  $-54$  mV only after  $\cdot$ <br>sixth depolarization to  $+19$  mV, i.e., only after the<br>was filled with releasable calcium as a result of of contraction was activated at  $-54$  mV only after the sixth depolarization to  $+19$  mV, i.e., only after the SF was filled with releasable calcium as a result of repeated previous activation of calcium inward current. A sixth depolarization to  $+19$  mV, i.e., only after the SR lower was filled with releasable calcium as a result of repeated the previous activation of calcium inward current. Accordingly, Gibbons and Fozzard (141) found th was filled with releasable calcium as a result of repeated<br>previous activation of calcium inward current. Accord-<br>ingly, Gibbons and Fozzard (141) found that the con-<br>straction threshold was altered by a shift of the stead previous activation of calcium inward current. Accordingly, Gibbons and Fozzard (141) found that the contraction threshold was altered by a shift of the steady shift of the steady to about 20 mV more positive values after ingly, Gibbons and Fozzard (141) found that the contraction threshold was altered by a shift of the steady membrane voltage. The voltage-force relation was shifted to about 20 mV more positive values after a shift of the traction threshold was altered by a shift of the steady<br>membrane voltage. The voltage-force relation was shifted<br>to about 20 mV more positive values after a shift of the<br>holding potential from  $-78$  to  $-61$  mV. This indi inembrane voltage. I he voltage-force relation was sinted<br>to about 20 mV more positive values after a shift of the<br>holding potential from  $-78$  to  $-61$  mV. This indicates<br>that (a) the amount of calcium available in the s holding potential from  $-78$  to  $-61$  mV. This indicates that (a) the amount of calcium available in the storage site for release (the degree of recovery or repriming) channel depends on the "diastolic" membrane potential that (*a*) the amount of calcium available in the storage<br>site for release (the degree of recovery or repriming)<br>depends on the "diastolic" membrane potential (see also<br>section IV C), and (*b*) the release of activator ca site for release (the degree of recovery or repriming)<br>depends on the "diastolic" membrane potential (see also<br>section IV C), and (b) the release of activator calcium<br>from a filled store upon depolarization from a membran depends on the "diastolic" membrane potential (see also <br>section IV C), and (b) the release of activator calcium<br>from a filled store upon depolarization from a membrane<br>potential of about -80 mV is not triggered by  $I_{Ca}$ section IV C), and (b) the release of activator calcium<br>from a filled store upon depolarization from a membrane<br>potential of about -80 mV is not triggered by  $I_{Ca}$  flowing<br>through L-type channels, since strong contractio from a filled store upon depolarization from a membrane<br>potential of about -80 mV is not triggered by  $I_{C_a}$  flowing<br>through L-type channels, since strong contractions are<br>elicited at potentials as low as -60 mV, far bel potential of about  $-60$  in v is not triggered by  $1<sub>Ca</sub>$  nowing<br>through L-type channels, since strong contractions are<br>elicited at potentials as low as  $-60$  mV, far below the<br>threshold for this current (see also refs elicited at potentials as low as  $-60$  mV, far below the<br>threshold for this current (see also refs. 384, 353, and<br>186). Simurda and coworkers (353) observed a slow in-<br>ward current associated with strong contractions at v threshold for this current (see also refs. 384, 353,  $i$  186). Simurda and coworkers (353) observed a slow ward current associated with strong contractions at vages negative to the threshold of  $I_{Ca}$ . The current var in 186). Simurda and coworkers (353) observed a slow in-<br>ward current associated with strong contractions at volt-<br>ages negative to the threshold of  $I_{Ca}$ . The current varied<br>in parallel with the strength of contraction, bo ward current associated with strong contractions at volt-<br>ages negative to the threshold of  $I_{Ca}$ . The current varied<br>in parallel with the strength of contraction, both depend-<br>ing on the extent to which preceding activi ages negative to the threshold of  $I_{Ca}$ . The current var<br>in parallel with the strength of contraction, both depen<br>ing on the extent to which preceding activity had fil<br>the release stores. They related this current  $(I_{\rm sic$ in parallel with the strength of contraction, both depending on the extent to which preceding activity had filled value with the release stores. They related this current  $(I_{\rm sic})$  to the with calcium discharge from the st ing on the extent to which preceding activity had fil<br>the release stores. They related this current  $(I_{\rm sic})$  to<br>calcium discharge from the stores. Evidence for a con<br>bution of a current induced by calcium release from<br>SR the release stores. They related this current  $(I_{\text{sic}})$  to the calcium discharge from the stores. Evidence for a contribution of a current induced by calcium release from the SR to the second inward current in mammalian calcium discharge from the stores. Evention of a current induced by calcium SR to the second inward current in rular cells has also been obtained by  $(206;$  see sections IV B 4 and V A). Calcium release cannot be expected bution of a current induced by calcium release from the SR to the second inward current in mammalian ventric-<br>ular cells has also been obtained by others (254, 98, 125, 206; see sections IV B 4 and V A).<br>Calcium release ca SR to the second inward current in mammalian ventric-<br>ular cells has also been obtained by others (254, 98, 125,<br>206; see sections IV B 4 and V A).<br>Calcium release cannot be expected under conditions<br>which favor the empty

ular cells has also been obtained by others (254, 98, 125<br>206; see sections IV B 4 and V A).<br>Calcium release cannot be expected under condition<br>which favor the empty state of release sites. A rationa<br>method to provide empt 206; see sections IV B 4 and V A).<br>Calcium release cannot be expected under conditions combined to provide empty state of release sites. A rational by<br>method to provide empty release compartments in voltions<br>age-clamp exp Calcium release cannot be expected under conditions<br>which favor the empty state of release sites. A rational<br>method to provide empty release compartments in volt-<br>age-clamp experiments at a temperature of  $35^{\circ}$ C was<br>us which favor the empty state of release sites. A rational b method to provide empty release compartments in volt-<br>age-clamp experiments at a temperature of  $35^{\circ}$ C was a used by Isenberg et al. (186). They elicited contr method to provide empty release compartments in volt-<br>age-clamp experiments at a temperature of  $35^{\circ}$ C was<br>used by Isenberg et al. (186). They elicited contractions ele<br>of single myocytes isolated from guinea pig or bo age-clamp experiments at a temperature of  $35^{\circ}$ C was a used by Isenberg et al. (186). They elicited contractions esting of single myocytes isolated from guinea pig or bovine hypertricles by clamp steps from a holding p used by Isenberg et al. (186). They elicited contractions est of single myocytes isolated from guinea pig or bovine heretricles by clamp steps from a holding potential of  $-45$  mV (solution containing 20 mmol/liter of KCl of single myocytes isolated from guinea pig or bovit ventricles by clamp steps from a holding potential of  $-wV$  (solution containing 20 mmol/liter of KCl). The contractions were of slow onset, lagging the start depolariza

SUIAC INOTROPIC MECHANISMS<br>sented pure late contraction components. Under these<br>conditions the ventricular cell is unable to produce early conditions the ventricular cell is unable to produce early<br>conditions the ventricular cell is unable to produce early<br>contraction components presumably because, as a result contraction components. Under these<br>sented pure late contraction components. Under these<br>conditions the ventricular cell is unable to produce early<br>contraction components presumably because, as a result<br>of partial diastoli sented pure late contraction components. Under these<br>conditions the ventricular cell is unable to produce early<br>contraction components presumably because, as a result<br>of partial diastolic depolarization of the sarcolemma, sented pure late contraction components. Under these<br>conditions the ventricular cell is unable to produce early<br>contraction components presumably because, as a result<br>of partial diastolic depolarization of the sarcolemma, conditions the ventricular cell is unable to produce early contraction components presumably because, as a result of partial diastolic depolarization of the sarcolemma, the calcium has leaked from the release stores. The contraction components presumably because, as a result<br>of partial diastolic depolarization of the sarcolemma, the<br>calcium has leaked from the release stores. The curve<br>describing the voltage dependence of these contractio of partial diastolic depolarization of the sarcolemma, the calcium has leaked from the release stores. The curve describing the voltage dependence of these contractions is bell shaped and parallel to that of  $I_{Ca}$ , presu calcium has leaked from the release stores. The curve<br>describing the voltage dependence of these contractions<br>is bell shaped and parallel to that of  $I_{Ca}$ , presumably<br>because it is the calcium carried by  $I_{Ca}$  which, af describing the voltage dependence of these contractions<br>is bell shaped and parallel to that of  $I_{Ca}$ , presumably<br>because it is the calcium carried by  $I_{Ca}$  which, after its<br>uptake into the longitudinal part of the SR, i is bell shaped and parallel to that of  $I_{Ca}$ , presumably<br>because it is the calcium carried by  $I_{Ca}$  which, after its<br>uptake into the longitudinal part of the SR, is released<br>after some delay into the cytosol. Early (fas because it is the calcium carried by  $I_{Ca}$  which, after its uptake into the longitudinal part of the SR, is released after some delay into the cytosol. Early (fast) contraction components were obtained in myocytes when, uptake into the longitudinal part of the SR, is released<br>after some delay into the cytosol. Early (fast) contraction<br>components were obtained in myocytes when, from a<br>potential of  $-80$  mV during the intervals between bea after some delay into the cytosol. Early (fast) contraction<br>components were obtained in myocytes when, from a<br>potential of  $-80$  mV during the intervals between beats<br>at 0.5 or 1.0 Hz, increasing clamp steps were induced<br> components were obtained in myocytes when, from a<br>potential of  $-80$  mV during the intervals between beats<br>at  $0.5$  or  $1.0$  Hz, increasing clamp steps were induced<br>from an intermediate  $-45$  mV holding potential lasting<br> potential of  $-80$  mV during the intervals between beat at  $0.5$  or  $1.0$  Hz, increasing clamp steps were induce from an intermediate  $-45$  mV holding potential lastin  $20$  ms. These contractions, elicited by calcium rele at  $0.5$  or  $1.0$  Hz, increasing clamp steps were induced<br>from an intermediate  $-45$  mV holding potential lasting<br> $20$  ms. These contractions, elicited by calcium release<br>from presumably filled stores of the sarcoplasmic from an intermediate  $-45$  mV holding potential last 20 ms. These contractions, elicited by calcium rele<br>from presumably filled stores of the sarcoplasmic ret<br>ulum, must be regarded as normal contractions wh<br>voltage depen 20 ms. These contractions, elicited by calcium release<br>from presumably filled stores of the sarcoplasmic retic-<br>ulum, must be regarded as normal contractions whose<br>voltage dependence should be representative for physio-<br>lo from presumably filled stores of the sarcoplasmic retic-<br>ulum, must be regarded as normal contractions whose<br>voltage dependence should be representative for physio-<br>logical excitation-contraction coupling. The contraction ulum, must be regarded as normal contractions wh<br>voltage dependence should be representative for phys<br>logical excitation-contraction coupling. The contract<br>threshold of these early contractions was obviously m<br>negative th voltage dependence should be representative for physiological excitation-contraction coupling. The contraction threshold of these early contractions was obviously more negative than  $-45$  mV (extrapolation of the voltagelogical excitation-contraction coupling. The contraction<br>threshold of these early contractions was obviously more<br>negative than  $-45$  mV (extrapolation of the voltage-<br>shortening velocity curve in fig. 4 of ref. 186 to ze threshold of these early contractions was obviously more<br>negative than  $-45$  mV (extrapolation of the voltage-<br>shortening velocity curve in fig. 4 of ref. 186 to zero<br>shortening velocity gives an estimated value of  $-60$  negative than  $-45$  mV (extrapolation of the voltage-<br>shortening velocity curve in fig. 4 of ref. 186 to zero<br>shortening velocity gives an estimated value of  $-60$  mV),<br>and the voltage dependence of these contractions was shortening velocity curve in fig. 4 of ref. 186 to zero<br>shortening velocity gives an estimated value of  $-60$  mV),<br>and the voltage dependence of these contractions was<br>not bell shaped; maximal early contractions were ob-<br> shortening velocity gives an estimated value of  $-60$  mV),<br>and the voltage dependence of these contractions was<br>not bell shaped; maximal early contractions were ob-<br>tained at strongly positive potentials  $(+100$  mV) where<br> and the voltage dependence of these contractions was<br>not bell shaped; maximal early contractions were ob-<br>tained at strongly positive potentials  $(+100 \text{ mV})$  where<br>there should be no calcium current through the calcium<br>ch tained at strongly positive potentials (+100 mV) where ere should be no calcium current through the calcium<br>annels (20, 289).<br>Calcium-induced Calcium Release<br>1. Oscillatory contractions in skinned fibers. Ford and<br>dolsky (132) and Endo et al. (109) reported independ-

channels (20, 289).<br>
B. Calcium-induced Calcium Release<br>
1. Oscillatory contractions in skinned fibers. Ford<br>
Podolsky (132) and Endo et al. (109) reported indepently that, under certain facilitating conditions, calc B. Calcium-induced Calcium Release<br>
1. Oscillatory contractions in skinned fibers. Ford and<br>
Podolsky (132) and Endo et al. (109) reported independ-<br>
ently that, under certain facilitating conditions, calcium<br>
ions can ac B. Calcium-induced Calcium Release<br>
1. Oscillatory contractions in skinned fibers. Ford and<br>
Podolsky (132) and Endo et al. (109) reported independ-<br>
ently that, under certain facilitating conditions, calcium<br>
ions can ac 1. Oscillatory contractions in skinned fibers. Ford and Podolsky (132) and Endo et al. (109) reported independently that, under certain facilitating conditions, calcium ions can actually induce a release of stored calcium Podolsky (132) and Endo et al. (109) reported independently that, under certain facilitating conditions, calcium<br>ions can actually induce a release of stored calcium from<br>the SR of skeletal muscle fibers which have been me ently that, under certain facilitating conditions, calcium<br>ions can actually induce a release of stored calcium from<br>the SR of skeletal muscle fibers which have been me-<br>chanically deprived of the sarcolemma (skinned fiber the SR of skeletal muscle fibers which have been methe SR of skeletal muscle fibers which have been mechanically deprived of the sarcolemma (skinned fibers, Natori, ref. 280). Endo et al. (109) observed spontaneous oscillatory contractions suggesting that calcium release i chanically deprived of the sarcolemma (skinned fibe Natori, ref. 280). Endo et al. (109) observed spontaneo oscillatory contractions suggesting that calcium release is a regenerative process in which Ca itself causes t rel Natori, ref. 280). Endo et al. (109) observed spontaneous oscillatory contractions suggesting that calcium release is a regenerative process in which Ca itself causes the release of Ca from the SR. Essentially the same obs oscillatory contractions suggesting that calcium release<br>is a regenerative process in which Ca itself causes the<br>release of Ca from the SR. Essentially the same obser-<br>vations have been made in mammalian heart muscle cells is a regenerative process in which Ca itself causes the release of Ca from the SR. Essentially the same observations have been made in mammalian heart muscle cells with disrupted or removed sarcolemma but not in those of release of Ca from the SR. Essentially the same obs<br>vations have been made in mammalian heart muscle c<br>with disrupted or removed sarcolemma but not in th<br>of the frog heart  $(42-44, 118, 119, 83)$ . The cyclic c<br>tractions w vations have been made in mammalian heart muscle cells<br>with disrupted or removed sarcolemma but not in those<br>of the frog heart  $(42-44, 118, 119, 83)$ . The cyclic con-<br>trations were inhibited in the presence of high conce with disrupted or removed sarcol<br>of the frog heart  $(42-44, 118, 11)$ <br>tractions were inhibited in the pictrations of a Ca buffer, and the<br>SR was destroyed by a detergent.<br>2. Aftercontractions. The inde tractions were inhibited in the presence of high concentrations of a Ca buffer, and they were abolished if the SR was destroyed by a detergent.<br>2. Aftercontractions. The independence of oscillatory contractions from the st

trations of a Ca buffer, and they were abolished if the<br>SR was destroyed by a detergent.<br>2. Aftercontractions. The independence of oscillatory<br>contractions from the stimulation of the sarcolemma had<br>been observed earlier i SR was destroyed by a detergent.<br>
2. Aftercontractions. The independence of oscillation<br>
contractions from the stimulation of the sarcolemma h<br>
been observed earlier in intact multicellular preparation<br>
in which damped for 2. Aftercontractions. The independence of oscillatory<br>contractions from the stimulation of the sarcolemma had<br>been observed earlier in intact multicellular preparations<br>in which damped force oscillations (aftercontractions contractions from the stimulation of the sarcolemma had<br>been observed earlier in intact multicellular preparations<br>in which damped force oscillations (aftercontractions)<br>appeared without accompanying action potentials afte been observed earlier in intact multicellular preparations<br>in which damped force oscillations (aftercontractions)<br>appeared without accompanying action potentials after<br>electrically triggered contractions under conditions o in which damped force oscillations (aftercontractions)<br>appeared without accompanying action potentials a<br>electrically triggered contractions under conditions<br>high calcium load (318). These aftercontractions were<br>garded as appeared without accompanying action potentials after<br>electrically triggered contractions under conditions of<br>high calcium load (318). These aftercontractions were<br>regarded as an example of electromechanical dissocia-<br>tion electrically triggered contractions under conditions of<br>high calcium load (318). These aftercontractions were<br>regarded as an example of electromechanical dissocia-<br>tion, of decoupling of contraction from excitation of the high calcium load (318). These aftercontractions were regarded as an example of electromechanical dissociation, of decoupling of contraction from excitation of the sarcolemmal membrane, and they were envisaged as being th

198<br>
loaded stores of the SR (318–320, 57). By increasing<br>
diastolic mechanical activity they change myocardial<br>
t RE<br>
198<br>
loaded stores of the SR (318–320, 57). By increasing<br>
diastolic mechanical activity they change myocardial<br>
diastolic compliance (53, 212, 126). While aftercontrac-198<br>loaded stores of the SR (318–320, 57). By incre<br>diastolic mechanical activity they change myoca<br>diastolic compliance (53, 212, 126). While aftercontions are not elicited by action potentials they ma loaded stores of the SR (318–320, 57). By increasing mediastolic mechanical activity they change myocardial tandiastolic compliance (53, 212, 126). While aftercontractories are not elicited by action potentials they may be loaded stores of the SR (318-320, 57). By increasing mechanical oscillation amplitude, it enhances the spon-<br>diastolic mechanical activity they change myocardial taneous frequency of  $Ca^{2+}$  release, but ryanodine sup-<br>di diastolic compliance  $(53, 212, 126)$ . While aftercontractions are not elicited by action potentials they may be accompanied, under certain conditions, by oscillations of the membrane potential (oscillatory afterpotential diastolic compliance  $(53, 212, 126)$ . While aftercontrac-<br>tions are not elicited by action potentials they may be<br>accompanied, under certain conditions, by oscillations of rele<br>the membrane potential (oscillatory afterpo tions are not elicited by action potentials they may be accompanied, under certain conditions, by oscillations of the membrane potential (oscillatory afterpotentials) which are thought to be secondary events caused by intr accompanied, under certain conditions, by oscillations<br>the membrane potential (oscillatory afterpotentia<br>which are thought to be secondary events caused<br>intracellularly released calcium (see section IV B<br>Because of their r the membrane potential (oscillatory afterpotentials) which are thought to be secondary events caused by intracellularly released calcium (see section IV B 4).<br>Because of their resemblance to the oscillatory contractions of intracellularly released calcium (see section IV B 4).<br>Because of their resemblance to the oscillatory contractions of skinned muscle fibers, aftercontractions are swidely considered to represent a manifestation of cal-<br>c Because of their resemblance to the osci-<br>tions of skinned muscle fibers, afterc<br>widely considered to represent a manif<br>cium-induced calcium release in the intac<br>(94, 118, 142, 107, 79, 47, 297, 369, 4).<br>3. Asynchronous ca

widely considered to represent a manifestation of calcium-induced calcium release in the intact cardiac muscle the (94, 118, 142, 107, 79, 47, 297, 369, 4). Currely and  $3.$  Asynchronous calcium release. Under conditions cium-induced calcium release in the intact cardiac muscle  $(94, 118, 142, 107, 79, 47, 297, 369, 4)$ .<br>3. Asynchronous calcium release. Under conditions of high Ca<sup>2+</sup> loading in a sodium-free solution, Glitsch and Pott  $($ (94, 118, 142, 107, 79, 47, 297, 369, 4). cu<br>3. Asynchronous calcium release. Under conditions of  $I_T$ <br>high Ca<sup>2+</sup> loading in a sodium-free solution, Glitsch and the<br>Pott (142) observed spontaneous fluctuations of an in-<br> 3. Asynchronous calcium release. Under conditions of high  $Ca^{2+}$  loading in a sodium-free solution, Glitsch and Pott  $(142)$  observed spontaneous fluctuations of an increased resting force of guinea pig atrial trabeculae high Ca<sup>2+</sup> loading in a sodium-free solution, Glitsch and the Pott  $(142)$  observed spontaneous fluctuations of an increased resting force of guinea pig atrial trabeculae. The afluctuations were thought to result from sp creased resting force of guinea pig atrial trabeculae. The atrial tissue, other workers have not observed a reversal<br>fluctuations were thought to result from spontaneous in  $I_{TI}$  and have suggested that  $I_{TI}$  may result creased resting force of guinea pig atrial trabeculae. The<br>fluctuations were thought to result from spontaneous<br>oscillations with asynchronous cycles in different parts<br>of the muscles which contributed to the increased res fluctuations were thought to result from spontaneous is<br>oscillations with asynchronous cycles in different parts<br>of the muscles which contributed to the increased resting 1<br>force. Since caffeine inhibited the fluctuations oscillations with asynchronous cycles in different parts<br>of the muscles which contributed to the increased resting<br>force. Since caffeine inhibited the fluctuations and si-<br>multaneously reduced the mean resting force, it s of the muscles which contributed to the increased resting<br>force. Since caffeine inhibited the fluctuations and si-<br>multaneously reduced the mean resting force, it seems<br>likely that asynchronous  $Ca^{2+}$  release from differ force. Since caffeine inhibited the fluctuations and si-<br>multaneously reduced the mean resting force, it seems<br>likely that asynchronous  $Ca^{2+}$  release from different<br>parts of the SR was responsible for the random motion. likely that asynchronous  $Ca^{2+}$  release from different parts of the SR was responsible for the random motion.<br>The latter could be interrupted by an electrically triglikely that asynchronous  $Ca^{2+}$  release from different relation parts of the SR was responsible for the random motion. circle latter could be interrupted by an electrically trig-weigred twitch which was followed by after parts of the SR was responsible for the random motic<br>The latter could be interrupted by an electrically tr<br>gered twitch which was followed by aftercontractio<br>and "hyper-relaxations" (200, 309). This was probable<br>due to the The latter could be interrupted by an electrically tri-<br>gered twitch which was followed by aftercontraction<br>and "hyper-relaxations" (200, 309). This was probab-<br>due to the synchronization of the spontaneous oscill<br>tions in and "hyper-relaxations" (200, 309). This was probably<br>due to the synchronization of the spontaneous oscilla-<br>tions in different cells as suggested from similar obser-<br>vations with rat papillary muscles by Stern et al. (36 d "hyper-relaxations" (200, 309). This was probably<br>e to the synchronization of the spontaneous oscilla-<br>ons in different cells as suggested from similar obser-<br>tions with rat papillary muscles by Stern et al. (369).<br>That

due to the synchronization of the spontaneous oscilla-<br>tions in different cells as suggested from similar obser-<br>vations with rat papillary muscles by Stern et al. (369). of<br>That  $[Ca^{2+}]_i$  can fluctuate in intact, unstim tions in different cells as suggested from similar observations with rat papillary muscles by Stern et al.  $(369)$ . ol<br>That  $[Ca^{2+}]_i$  can fluctuate in intact, unstimulated car-<br>diac muscle preparations has been shown by vations with rat papillary muscles by Stern et al. (369). That  $[Ca^{2+}]_i$  can fluctuate in intact, unstimulated cardiac muscle preparations has been shown by means of sthe photoprotein aequorin (297, 415, 4) and in single That  $[Ca^{2+}]_i$  can fluctuate in intact, unstimulated car-<br>diac muscle preparations has been shown by means of suf<br>the photoprotein aequorin (297, 415, 4) and in single<br>heart cells by both fura-2 fluorescence (414) and ae duate muscle preparations has been shown by means of summer<br>the photoprotein aequorin (297, 415, 4) and in single 5. (<br>heart cells by both fura-2 fluorescence (414) and aequorin lation<br>(105). Such oscillations of  $[Ca^{2+}]$ heart cells by both fura-2 fluorescence (414) and aequorin latio (105). Such oscillations of  $[Ca^{2+}]_i$  had previously been skel inferred from observations of laser light scattering from SR quiescent muscle (231). The spo (105). Such oscillations of  $[Ca^{2+}]_i$  had previously been slinferred from observations of laser light scattering from Squiescent muscle (231). The spontaneous  $Ca^{2+}$ -dependent oscillations vary with species in a manner inferred from observations of laser light scattering from<br>quiescent muscle (231). The spontaneous  $Ca^{2+}$ -depend-<br>ent oscillations vary with species in a manner similar to<br>that for  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from quiescent muscle (231). The spontaneous  $Ca^{2+}$ -dependent oscillations vary with species in a manner similar to that for  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from the SR of mechanically skinned cardiac cells (120): Unstimul ent oscillations vary with species in a manner similar to<br>that for  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from the SR of<br>mechanically skinned cardiac cells (120): Unstimulated<br>rat and canine tissues exhibit spontaneous oscill mechanically skinned cardiac cells (120): Unstimulated<br>rat and canine tissues exhibit spontaneous oscillations<br>even when extracellular calcium is as low as 2 mmol/<br>liter, whereas in rabbit ventricle the calcium concentra-<br> rat and canine tissues exhibit spontaneous oscillations rat and canine tissues exhibit spontaneous oscillations<br>even when extracellular calcium is as low as 2 mmol/<br>liter, whereas in rabbit ventricle the calcium concentra-<br>tion must be considerably higher for oscillations to o even when extracellular calcium is as low as 2 mm<br>liter, whereas in rabbit ventricle the calcium concent<br>tion must be considerably higher for oscillations to occ<br>frog cardiac tissues do not exhibit oscillations even un<br>hi liter, whereas in rabbit ventricle the calcium concentrion must be considerably higher for oscillations to occurrog cardiac tissues do not exhibit oscillations even und high  $Ca^{2+}$ -loading conditions  $(230)$ —a fact that tion must be considerably higher for oscillations to occur; lafrog cardiac tissues do not exhibit oscillations even under shigh Ca<sup>2+</sup>-loading conditions (230)—a fact that presum-<br>ably reflects the paucity of their SR. Th frog cardiac tissues do not exhibit oscillations even und<br>high Ca<sup>2+</sup>-loading conditions (230)—a fact that presur<br>ably reflects the paucity of their SR. The general obse<br>vation that oscillations of cytosolic Ca<sup>2+</sup> are ab high Ca<sup>2+</sup>-loading conditions (230)—a fact that presumably reflects the paucity of their SR. The general observation that oscillations of cytosolic Ca<sup>2+</sup> are abolished by caffeine and ryanodine, both inhibitors of sarco ably reflects the paucity of their SR. The general observation that oscillations of cytosolic  $Ca^{2+}$  are abolished by caffeine and ryanodine, both inhibitors of sarco-plasmic reticulum function, supports the hypothesis t vation that oscillations of cytosolic  $Ca^{2+}$  are abolished  $Ca^{2+}$ <br>by caffeine and ryanodine, both inhibitors of sarco-<br>as a plasmic reticulum function, supports the hypothesis that caln<br>the oscillations of muscle force by caffeine and ryanodine, both inhibitors of saplasmic reticulum function, supports the hypothesis the oscillations of muscle force arise from a Ca-depent release of Ca from the SR (415, 4, 387). Howeve regard to the disc plasmic reticulum function, supports the hypothesis that calmodulin-dependent phosphorylation of the cardiac SR<br>the oscillations of muscle force arise from a Ca-depend-<br>ent release of Ca from the SR (415, 4, 387). However the oscillations of muscle force arise from a Ca-depend-<br>ent release of Ca from the SR (415, 4, 387). However, in<br>regard to the discussion on the mechanism of excitation-<br>contraction coupling, it is noteworthy that there a ent release of Ca from the SR  $(415, 4, 387)$ . However, in regard to the discussion on the mechanism of excitation-<br>contraction coupling, it is noteworthy that there are no<br>distinct differences in the influence of the two

ER<br>mechanical oscillation amplitude, it enhances the sportaneous frequency of Ca<sup>2+</sup> release, but ryanodine sup ER<br>mechanical oscillation amplitude, it enhances the spon-<br>taneous frequency of  $Ca^{2+}$  release, but ryanodine sup-<br>presses both frequency and amplitude (230). ER<br>mechanical oscillation amplitude, it enhances<br>taneous frequency of  $Ca^{2+}$  release, but ryand<br>presses both frequency and amplitude (230).<br>4. Oscillatory afterpotentials. The oscillator *echanical oscillation amplitude*, it enhances the spon-<br>neous frequency of Ca<sup>2+</sup> release, but ryanodine sup-<br>esses both frequency and amplitude (230).<br>4. *Oscillatory afterpotentials*. The oscillatory calcium<br>lease, besi

widely considered to represent a manifestation of cal-<br>cium-induced calcium release in the intact cardiac muscle<br>(34, 118, 142, 107, 79, 47, 297, 369, 4).<br> $(34, 118, 142, 107, 79, 47, 297, 369, 4)$ <br>*3. Asynchronous calciu* mechanical oscillation amplitude, it enhances the spon-<br>taneous frequency of  $Ca^{2+}$  release, but ryanodine sup-<br>presses both frequency and amplitude (230).<br>4. Oscillatory afterpotentials. The oscillatory calcium<br>release, taneous frequency of  $Ca^{2+}$  release, but ryanodine suppresses both frequency and amplitude (230).<br>4. Oscillatory afterpotentials. The oscillatory calcium<br>release, besides inducing oscillatory contractions, also<br>leads und presses both frequency and amplitude (230).<br>4. Oscillatory afterpotentials. The oscillatory calcium<br>release, besides inducing oscillatory contractions, also<br>leads under appropriate experimental conditions to os-<br>cillatory 4. Oscillatory afterpotentials. The oscillatory calcium<br>release, besides inducing oscillatory contractions, also<br>leads under appropriate experimental conditions to os-<br>cillatory afterpotentials or afterdepolarizations of t release, besides inducing oscillatory contractions, also<br>leads under appropriate experimental conditions to os-<br>cillatory afterpotentials or afterdepolarizations of the<br>sarcolemma (51, 201, 188, 322, 279, 127, 195, 101, 25 leads under appropriate experimental conditions to oscillatory afterpotentials or afterdepolarizations of the sarcolemma (51, 201, 188, 322, 279, 127, 195, 101, 25 244, 194). In cardiac Purkinje fibers, this may grow intsu cillatory afterpotentials or afterdepolarizations of the<br>sarcolemma (51, 201, 188, 322, 279, 127, 195, 101, 257,<br>244, 194). In cardiac Purkinje fibers, this may grow into<br>sustained rhythmic activity (390, 128, 88). The mem sarcolemma (51, 201, 188, 322, 279, 127, 195, 101, 257, 244, 194). In cardiac Purkinje fibers, this may grow into sustained rhythmic activity (390, 128, 88). The membrane current underlying these afterdepolarizations is t 244, 194). In cardiac Purkinje fibers, this may grow into sustained rhythmic activity (390, 128, 88). The membrane current underlying these afterdepolarizations is thought to be the calcium-activated transient inward curr sustained rhythmic activity (390, 128, 88). The membrane current underlying these afterdepolarizations is thought to be the calcium-activated transient inward current  $(I_{TI})$  (236). The finding in Purkinje fibers that  $I_{TI$ brane current underlying these afterdepolarizations is<br>thought to be the calcium-activated transient inward<br>current  $(I_{TI})$  (236). The finding in Purkinje fibers that<br> $I_{TI}$  showed a reversal potential at about  $-5$  mV sup thought to be the calcium-activated transient inward<br>current  $(I_{TI})$  (236). The finding in Purkinje fibers that<br> $I_{TI}$  showed a reversal potential at about  $-5$  mV supported<br>the suggestion of a calcium-activated nonselecti  $I_{TI}$  showed a reversal potential at about  $-5$  mV supported Fri subwear a veveral potential at about  $-$  in  $W$  supported that the suggestion of a calcium-activated nonselective cation<br>channel (196, 66). However, in studies on ventricular and<br>atrial tissue, other workers have not channel (196, 66). However, in studies on ventricular and abolished after blockade of the inward calcium current atrial tissue, other workers have not observed a reversal<br>in  $I_{TI}$  and have suggested that  $I_{TI}$  may result from an<br>electrogenic sodium-calcium exchange (13, 262, 292, 140,<br>124). Lipp and Pott (242) found a reversal of in  $I_{TI}$  and have suggested that  $I_{TI}$  may result from an electrogenic sodium-calcium exchange (13, 262, 292, 140, 124). Lipp and Pott (242) found a reversal of  $I_{TI}$  to be abolished after blockade of the inward calciu electrogenic sodium-calcium exchange (13, 262, 292, 140, 124). Lipp and Pott (242) found a reversal of  $I_{TI}$  to be abolished after blockade of the inward calcium current ( $I_{Ca}$ ) by D 600. The authors assumed that the ap 124). Lipp and Pott (242) found a reversal of  $I_{TI}$  to be abolished after blockade of the inward calcium current  $(I_{Ca})$  by D 600. The authors assumed that the apparent reversal of  $I_{TI}$  is caused by intracellularly rele abolished after blockade of the inward calcium current  $(I_{Ca})$  by D 600. The authors assumed that the apparent reversal of  $I_{TI}$  is caused by intracellularly released calcium which inactivates  $I_{Ca}$ . This would be in acc ( $I_{Ca}$ ) by D 600. The authors assumed that the apparent reversal of  $I_{TI}$  is caused by intracellularly released calcium which inactivates  $I_{Ca}$ . This would be in accordance with an earlier observation by Bogdanov and c reversal of  $I_{TI}$  is caused by intracellularly released ca<br>cium which inactivates  $I_{Ca}$ . This would be in accordance<br>with an earlier observation by Bogdanov and coworke:<br>(47) of an inhibition of the slow-response action cium which inactivates  $I_{Ca}$ . This would be in accordariation with an earlier observation by Bogdanov and cowork (47) of an inhibition of the slow-response action potent during the aftercontraction. Consistent with the i with an earlier observation by Bogdanov and coworkers  $(47)$  of an inhibition of the slow-response action potential during the aftercontraction. Consistent with the interpretation that afterdepolarizations are caused by e (47) of an inhibition of the slow-response action potentia<br>during the aftercontraction. Consistent with the inter<br>pretation that afterdepolarizations are caused by electro<br>genic sodium-calcium exchange (section  $V$  A) is during the aftercontraction. Consistent with the inter-<br>pretation that afterdepolarizations are caused by electro-<br>genic sodium-calcium exchange (section V A) is the<br>observation that they are totally absent in spite of po pretation that afterdepolarizations are caused by electro-<br>genic sodium-calcium exchange (section V A) is the<br>observation that they are totally absent in spite of pow-<br>erful aftercontractions if cardiac muscles are kept fo observation that they are totally absent in spite of pow-<br>erful aftercontractions if cardiac muscles are kept for a<br>sufficiently long time in sodium-free solution (252, 70).<br>5. Oscillatory calcium release from isolated SR

skeletal muscle and  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from erful aftercontractions if cardiac muscles are kept for a<br>sufficiently long time in sodium-free solution (252, 70).<br>5. Oscillatory calcium release from isolated SR. Oscillations in calcium release from isolated SR vesicle sufficiently long time in sodium-free solution (252, 70).<br>
5. Oscillatory calcium release from isolated SR. Oscillations in calcium release from isolated SR vesicles of<br>
skeletal muscle and Ca<sup>2+</sup>-induced release of Ca<sup>2+</sup> 5. Oscillatory calcium release from isolated SR. Oscillations in calcium release from isolated SR vesicles of skeletal muscle and  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from SR vesicles of cardiac muscle have been observed by lations in calcium release from isolated SR vesicles of  $\frac{32}{27}$ <br>skeletal muscle and  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from SR vesicles of cardiac muscle have been observed by<br>several investigators (198, 197, 76). Alt skeletal muscle and  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from SR vesicles of cardiac muscle have been observed by several investigators (198, 197, 76). Although the  $Ca^{2+}$  release rates from isolated canine cardiac SR at 3 SR vesicles of cardiac muscle have been observed by<br>several investigators (198, 197, 76). Although the Ca<sup>2+</sup><br>release rates from isolated canine cardiac SR at 37°C<br>(76) were several orders of magnitude lower than the rate several investigators (198, 197, 76). Although the Ca<sup>2+</sup><br>release rates from isolated canine cardiac SR at 37°C<br>(76) were several orders of magnitude lower than the rate<br>of Ca<sup>2+</sup> release which occurs in muscle cells in v release rates from isolated canine cardiac SR at 37°C (76) were several orders of magnitude lower than the rate of  $Ca^{2+}$  release which occurs in muscle cells in vivo, this  $Ca^{2+}$  release phenomenon may be related to th (76) were several orders of magnitude lower than the i<br>of  $Ca^{2+}$  release which occurs in muscle cells in vivo,  $Ca^{2+}$  release phenomenon may be related to the Co<br>induced release of  $Ca^{2+}$  in skinned cardiac cells. The of Ca<sup>2+</sup> release which occurs in muscle cells in vivo, this Ca<sup>2+</sup> release phenomenon may be related to the Ca<sup>2+</sup>-<br>induced release of Ca<sup>2+</sup> in skinned cardiac cells. The Ca<sup>2+</sup><br>release from the SR vesicles (containing Ca<sup>2+</sup> release phenomenon may be related to the Ca<sup>2+</sup>-<br>induced release of Ca<sup>2+</sup> in skinned cardiac cells. The Ca<sup>2+</sup><br>release from the SR vesicles (containing both subpopu-<br>lations, i.e., from longitudinal and junctional induced release of Ca<sup>2+</sup> in skinned cardiac cells. The Ca<sup>2+</sup><br>release from the SR vesicles (containing both subpopu-<br>lations, i.e., from longitudinal and junctional SR) is<br>specifically inhibited by ruthenium red, with an release from the SR vesicles (containing both subpopulations, i.e., from longitudinal and junctional SR) is specifically inhibited by ruthenium red, with an  $EC_{50}$  of 80 nmol/liter (77). Calmodulin has no effect on the r lations, i.e., from longitudinal and junctional SR) is<br>specifically inhibited by ruthenium red, with an  $EC_{50}$  of<br>80 nmol/liter (77). Calmodulin has no effect on the rate<br>or extent of the release, although reuptake of th specifically inhibited by ruthenium red, with an  $EC_{50}$  of 80 nmol/liter (77). Calmodulin has no effect on the rate or extent of the release, although reuptake of the released  $Ca^{2+}$  is faster in the presence of calmodu 80 nmol/liter (77). Calmodulin has no effect on the rate<br>or extent of the release, although reuptake of the released<br>Ca<sup>2+</sup> is faster in the presence of calmodulin, presumably<br>as a result of enhanced Ca<sup>2+</sup> transport acti (75).  $a^{2+}$  is faster in the presence of calmodulin, presumably<br>a result of enhanced  $Ca^{2+}$  transport activity due to<br>lmodulin-dependent phosphorylation of the cardiac SR<br>5).<br>In regard to the molecular mechanism of  $Ca^{2+}$ -i

as a result of enhanced  $Ca^{2+}$  transport activity due to calmodulin-dependent phosphorylation of the cardiac SR (75).<br>
In regard to the molecular mechanism of  $Ca^{2+}$ -induced release of  $Ca^{2+}$  it is important that the calmodulin-dependent phosphorylation of the cardiac SR (75).<br>
In regard to the molecular mechanism of  $Ca^{2+}$ -induced<br>
release of  $Ca^{2+}$  it is important that the  $Ca^{2+}$  release is<br>
not accompanied by a reduction in ATP (75). In regard to the molecular mechanism of  $Ca^{2+}$ -induced release of  $Ca^{2+}$  it is important that the  $Ca^{2+}$  release is not accompanied by a reduction in ATP hydrolysis and that  $Ca^{2+}$  influx proceeds during the per In regard to the molecular mechanism of  $Ca^{2+}$ -induced<br>release of  $Ca^{2+}$  it is important that the  $Ca^{2+}$  release is<br>not accompanied by a reduction in ATP hydrolysis and<br>that  $Ca^{2+}$  influx proceeds during the period of

PHARM<br>REV

**a**spet

CALCIUM MOBILIZATION AND CARDIA<br>reversal or cessation of inward  $Ca^{2+}$  pumping. This in and<br>turn suggests that  $Ca^{2+}$  release is not mediated through con CALCIUM MOBILIZATION AND CARE<br>reversal or cessation of inward  $Ca^{2+}$  pumping. This in at<br>turn suggests that  $Ca^{2+}$  release is not mediated through co<br>the  $Ca^{2+}$  pump protein, but occurs through a separate CALCIUM MOBILIZATION AND CAR<br>reversal or cessation of inward  $Ca^{2+}$  pumping. This in<br>turn suggests that  $Ca^{2+}$  release is not mediated through<br>the  $Ca^{2+}$  pump protein, but occurs through a separate<br>efflux pathway. The reversal or cessation of inward  $Ca^{2+}$  pumping. This in a<br>turn suggests that  $Ca^{2+}$  release is not mediated through c<br>the  $Ca^{2+}$  pump protein, but occurs through a separate<br>efflux pathway. The  $Ca^{2+}$  efflux is elicite reversal or cessation of inward  $Ca^{2+}$  pumping. This in and<br>turn suggests that  $Ca^{2+}$  release is not mediated through con<br>the  $Ca^{2+}$  pump protein, but occurs through a separate T<br>efflux pathway. The  $Ca^{2+}$  efflux is e turn suggests that  $Ca^{2+}$  release is not mediated through<br>the  $Ca^{2+}$  pump protein, but occurs through a separate<br>efflux pathway. The  $Ca^{2+}$  efflux is elicited by relatively<br>low  $Ca^{2+}$  concentrations and is significant the Ca<sup>2+</sup> pump protein, but occurs through a separate efflux pathway. The Ca<sup>2+</sup> efflux is elicited by relatively low Ca<sup>2+</sup> concentrations and is significantly inhibited by elevations of  $[Ca^{2+}]_o$ . Both the rate and th efflux pathway. The Ca<sup>2+</sup> efflux is elicited by relatively de<br>low Ca<sup>2+</sup> concentrations and is significantly inhibited by fro<br>elevations of  $[Ca^{2+}]_o$ . Both the rate and the extent of net co<br>Ca<sup>2+</sup> release from SR vesicl low Ca<sup>2+</sup> concentrations and is significantly inhibited by<br>elevations of  $[Ca^{2+}]_o$ . Both the rate and the extent of net co<br>Ca<sup>2+</sup> release from SR vesicles loaded to approximately the<br>the same total Ca<sup>2+</sup> content depend elevations of  $[Ca^{2+}]_o$ . Both the rate and the extent of net  $Ca^{2+}$  release from SR vesicles loaded to approximately the same total  $Ca^{2+}$  content depend on the  $[Ca^{2+}]_o$  at the onset of release. Since the  $Ca^{2+}$  tra  $Ca^{2+}$  release from SR vesicles loaded to approximately<br>the same total  $Ca^{2+}$  content depend on the  $[Ca^{2+}]_o$  at the<br>onset of release. Since the  $Ca^{2+}$  transport ATPase of the<br>SR, which accounts for more than half the onset of release. Since the Ca<sup>2+</sup> transport ATPase of the SR, which accounts for more than half the SR membrane mass, is the only known Ca<sup>2+</sup>-binding protein with a Ca<sup>2+</sup> affinity high enough to bind much Ca<sup>2+</sup> at the onset of release. Since the Ca<sup>2+</sup> transport ATPase of the SR, which accounts for more than half the SR membrane mass, is the only known Ca<sup>2+</sup>-binding protein with a Ca<sup>2+</sup> affinity high enough to bind much Ca<sup>2+</sup> at the SR, which accounts for more than half the SR membrane<br>mass, is the only known  $Ca^{2+}$ -binding protein with a  $Ca^{2+}$  of about<br>affinity high enough to bind much  $Ca^{2+}$  at the concentrations that trigger release (91), one mass, is the only known  $Ca^{2+}$ -binding protein with a  $Ca^{2+}$  of a<br>affinity high enough to bind much  $Ca^{2+}$  at the concen-<br>trations that trigger release (91), one might assume that<br>it is the active uptake of  $Ca^{2+}$  int affinity high enough to bind much  $Ca^{2+}$  at the concentrations that trigger release (91), one might assume that under<br>it is the active uptake of  $Ca^{2+}$  into a  $Ca^{2+}$ -loaded SR. The<br>which evokes the release and not an e trations that trigger release (91), one might assume t<br>it is the active uptake of  $Ca^{2+}$  into a  $Ca^{2+}$ -loaded<br>which evokes the release and not an effect of  $Ca^{2+}$ <br>channel gate at the outside of the SR. However, for<br>und it is the active uptake of  $Ca^{2+}$  into a  $Ca^{2+}$ -loaded SR which evokes the release and not an effect of  $Ca^{2+}$  at a channel gate at the outside of the SR. However, for an understanding of the elementary processes of  $Ca$ which evokes the release and not an effect of  $Ca^{2+}$  at a channel gate at the outside of the SR. However, for an understanding of the elementary processes of  $Ca^{2+}$ -in-<br>duced release of  $Ca^{2+}$  the variables involved—th of  $Ca^{2+}$  loading and the relation between the  $Ca^{2+}$  concentrations inside and outside of the SR—will have to be independently controlled, since they all change as the  $[Ca^{2+}]$  outside the SR is varied (115, 67).<br>6. Do centrations inside and outside of the SR—will have to<br>be independently controlled, since they all change as the<br> $[Ca^{2+}]$  outside the SR is varied (115, 67).<br>6. Does the depolarization-induced contraction result<br>from calciu

centrations inside and outside of the SR—will have to<br>be independently controlled, since they all change as the<br> $[Ca^{2+}]$  outside the SR is varied (115, 67).<br>6. Does the depolarization-induced contraction result<br>from calci be independently controlled, since they all change as the  $[Ca^{2+}]$  outside the SR is varied (115, 67).<br>6. Does the depolarization-induced contraction result<br>from calcium-induced calcium release? Although it seems<br>very lik b. Does the aepotarization-induced contraction result has been increased by a few simulated twitches, the from calcium-induced calcium release? Although it seems latency is greatly reduced.<br>
very likely that aftercontract 6. Does the depolarization-induced contraction result from calcium-induced calcium release? Although it seems<br>very likely that aftercontractions result from a  $Ca^{2+}$ <br>induced  $Ca^{2+}$  release, it is an open question whethe from calcium-induced calcium release? Although it see<br>very likely that aftercontractions result from a Cs<br>induced Ca<sup>2+</sup> release, it is an open question whether<br>regular contraction of mammalian heart muscle is transpared very likely that aftercontractions result from a  $Ca^{2+}$ -<br>induced  $Ca^{2+}$  release, it is an open question whether the<br>regular contraction of mammalian heart muscle is trig-<br>gered by the fast initial component of transsarc induced  $Ca^{2+}$  release, it is an open question whether the regular contraction of mammalian heart muscle is trig-<br>gered by the fast initial component of transsarcolemmal  $Ca^{2+}$  flux (114, 116). What seems to be consiste regular contraction of mammalian heart muscle is triggered by the fast initial component of transsarcolemmal  $Ca^{2+}$  flux (114, 116). What seems to be consistent, at first sight, with such a mechanism is that in the skinn gered by the fast initial component of transsarcolemmal  $Ca^{2+}$  flux (114, 116). What seems to be consistent, at first sight, with such a mechanism is that in the skinned fiber, which consists of myofilaments surrounded b Ca<sup>2+</sup> flux (114, 116). What seems to be consistent, at affirst sight, with such a mechanism is that in the skinned the fiber, which consists of myofilaments surrounded by SR, of a rapid increase in  $[Ca^{2+}]$  produces a co first sight, with such a mechanism is that in the skinned the<br>fiber, which consists of myofilaments surrounded by SR, of r<br>a rapid increase in  $[Ca^{2+}]$  produces a contraction (116). dev<br>However, if the  $[Ca^{2+}]$  in this pr fiber, which consists of myofilaments surrounded by SR, of released calcium and evidenced by the velocity of force<br>a rapid increase in  $[Ca^{2+}]$  produces a contraction (116). development (fig. 4). Therefore, it would be di a rapid increase in  $[Ca^{2+}]$  produces a contraction (116). dev<br>However, if the  $[Ca^{2+}]$  in this preparation is not reduced beli<br>to the original loading concentration after the twitch, a ing<br>new contraction will now appear However, if the  $[Ca^{2+}]$  in this preparation is not reduced<br>to the original loading concentration after the twitch, a<br>new contraction will now appear a few seconds later (at<br> $22^{\circ}$ C) and, according to the prevailing con to the original loading concentration after the twitch<br>new contraction will now appear a few seconds later<br> $22^{\circ}$ C) and, according to the prevailing conditions,<br>oscillating cycle of  $Ca^{2+}$  uptake and release may be<br>duc new contraction will now appear a few seconds later (at 22°C) and, according to the prevailing conditions, an oscillating cycle of Ca<sup>2+</sup> uptake and release may be induced as seen in fig. 4 of Fabiato (ref. 116). The appe 22°C) and, according to the prevailing conditions, a oscillating cycle of  $Ca^{2+}$  uptake and release may be in duced as seen in fig. 4 of Fabiato (ref. 116). The appean ance of such a cyclic repetition of the contraction oscillating cycle of Ca<sup>2+</sup> uptake and release may be in-<br>duced as seen in fig. 4 of Fabiato (ref. 116). The appear-<br>ance of such a cyclic repetition of the contraction is<br>inhibited only if, as in Fabiato's usual experime duced as seen in fig. 4 of Fabiato (ref. 116). The appearance of such a cyclic repetition of the contraction is inhibited only if, as in Fabiato's usual experimental procedure, the cytosolic  $[Ca^{2+}]$  is reduced immediatel ance of such a cyclic repetition of the contraction is<br>inhibited only if, as in Fabiato's usual experimental<br>procedure, the cytosolic  $[Ca^{2+}]$  is reduced immediately<br>after the  $Ca^{2+}$ -induced contraction, i.e., after the inhibited only if, as in Fabiato's usual experimen<br>procedure, the cytosolic  $[Ca^{2+}]$  is reduced immediat<br>after the  $Ca^{2+}$ -induced contraction, i.e., after the fi<br>part of the oscillation cycle. Therefore, it seems unlik<br>t procedure, the cytosolic  $[Ca^{2+}]$  is reduced immediately after the  $Ca^{2+}$ -induced contraction, i.e., after the first part of the oscillation cycle. Therefore, it seems unlikely that there are fundamentally different rele part of the oscillation cycle. Therefore, it seems unlikely<br>that there are fundamentally different release mecha-<br>nisms between the first contraction which is "triggered"<br>by a fast increase in  $[Ca^{2+}]$  and the consecutive part of the oscillation cycle. Therefore, it seems unlikely<br>that there are fundamentally different release mecha-<br>nisms between the first contraction which is "triggered"<br>by a fast increase in  $[Ca^{2+}]$  and the consecutive that there are fundamentally different release mechanisms between the first contraction which is "triggered" by a fast increase in  $[Ca^{2+}]$  and the consecutive spontaneous contractions. The situation seems quite similar a by a fast increase in  $[Ca^{2+}]$  and the consecutive spontaneous contractions. The situation seems quite similar as in calcium release from isolated SR vesicles (see previous section), and in isolated cardiac myocytes under by a fast increase in  $[Ca^{2+}]$  and the consecutive spontaneous contractions. The situation seems quite similar as in calcium release from isolated SR vesicles (see previous section), and in isolated cardiac myocytes under neous contractions. The situation seems quite similar as<br>in calcium release from isolated SR vesicles (see previous<br>section), and in isolated cardiac myocytes under condi-<br>tions of electrochemical shunting across the exter section), and in isolated cardiac myocytes under condi-<br>tions of electrochemical shunting across the external<br>membrane (83). In these myocytes, phasic contractile<br>activation occurs independently of sarcolemmal excita-<br>tio section), and in isolated cardiac myocytes under cor-<br>tions of electrochemical shunting across the exter-<br>membrane (83). In these myocytes, phasic contrac-<br>activation occurs independently of sarcolemmal excu-<br>tion at  $Ca^{2$ tions of electrochemical shunting across the external<br>membrane (83). In these myocytes, phasic contractile<br>activation occurs independently of sarcolemmal excita-<br>tion at  $Ca^{2+}$  concentrations sustaining calcium accumu-<br>l membrane (83). In these myocytes, phasic contractile activation occurs independently of sarcolemmal excitation at  $Ca^{2+}$  concentrations sustaining calcium accumulation in the SR, as proven by electron probe analysis.  $Ca^{$ 

RDIAC INOTROPIC MECHANISMS 199<br>and a rate-limiting factor for the occurrence of phasic<br>contractile activation (83).<br>That the actual  $Ca^{2+}$  uptake into the SR might play a CONTROPIC MECHANISS<br>and a rate-limiting factor for<br>contractile activation (83).<br>That the actual  $Ca^{2+}$  uptal

channel gate at the outside of the SR. However, for an<br>understanding of the elementary processes of  $Ca^{2+}$ -in-<br>duced release of  $Ca^{2+}$  the variables involved—the extent<br>of  $Ca^{2+}$  to prevent much force development. And duced release of  $Ca^{2+}$  the variables involved—the extent<br>of  $Ca^{2+}$  loading and the relation between the  $Ca^{2+}$  con-<br>centrations inside and outside of the SR—will have to<br>be independently controlled, since they all cha IAC INOTROPIC MECHANISMS 199<br>
od a rate-limiting factor for the occurrence of phasic<br>
intractile activation (83).<br>
That the actual Ca<sup>2+</sup> uptake into the SR might play a<br>
ccisive role in Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release can and a rate-limiting factor for the occurrence of phasic<br>contractile activation (83).<br>That the actual Ca<sup>2+</sup> uptake into the SR might play a<br>decisive role in Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release can be inferred<br>from the time-depe and a rate-limiting factor for the occurrence of phasic<br>contractile activation (83).<br>That the actual Ca<sup>2+</sup> uptake into the SR might play a<br>decisive role in Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release can be inferred<br>from the time-depe contractile activation (83).<br>That the actual Ca<sup>2+</sup> uptake into the SR might play a<br>decisive role in Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release can be inferred<br>from the time-dependent appearance of the Ca<sup>2+</sup>-induced<br>contractions in f That the actual Ca<sup>2+</sup> uptake into the SR might play a decisive role in Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release can be inferred from the time-dependent appearance of the Ca<sup>2+</sup>-induced contractions in figs. 6, 10, and 12 of Fabiato decisive role in  $Ca^{2+}$ -induced  $Ca^{2+}$  release can be inferred<br>from the time-dependent appearance of the  $Ca^{2+}$ -induced<br>contractions in figs. 6, 10, and 12 of Fabiato (116). With<br>the increase in the number of mixed fas from the time-dependent appearance of the  $Ca^{2+}$ -induced<br>contractions in figs. 6, 10, and 12 of Fabiato (116). With<br>the increase in the number of mixed fast and slow  $Ca^{2+}$ -<br>loading pulses, the contraction response is n contractions in figs. 6, 10, and 12 of Fabiato (116). With<br>the increase in the number of mixed fast and slow  $Ca^{2+}$ -<br>loading pulses, the contraction response is not only in-<br>creased ("graded response"), but also the late the increase in the number of mixed fast and slow  $Ca^{2+}$ -loading pulses, the contraction response is not only increased ("graded response"), but also the latency of its appearance is drastically reduced from an original loading pulses, the contraction response is not only in-<br>creased ("graded response"), but also the latency of its<br>appearance is drastically reduced from an original value<br>of about 1000 ms. These results have a striking sim creased ("graded response"), but also the latency of its<br>appearance is drastically reduced from an original value<br>of about 1000 ms. These results have a striking similarity<br>to the behavior of the intact guinea pig papilla appearance is drastically reduced from an original value<br>of about 1000 ms. These results have a striking similarity<br>to the behavior of the intact guinea pig papillary muscle<br>under rested state conditions described in sect of about 1000 ms. These results have a striking similarity<br>to the behavior of the intact guinea pig papillary muscle<br>under rested state conditions described in section III A.<br>They illustrate very clearly that, when  $Ca^{2+}$ to the behavior of the intact guinea pig papillary muscle under rested state conditions described in section III A. They illustrate very clearly that, when  $Ca^{2+}$  enters the cell at a rate similar to that during the plat under rested state conditions described in section III A.<br>They illustrate very clearly that, when  $Ca^{2+}$  enters the<br>cell at a rate similar to that during the plateau of the<br>action potential, the SR is capable of taking i They illustrate very clearly that, when  $Ca^{2+}$  enters the cell at a rate similar to that during the plateau of the action potential, the SR is capable of taking it up fast enough to prevent much force development. And th cell at a rate similar to that during the plateau of the action potential, the SR is capable of taking it up fast enough to prevent much force development. And they are a strong argument against the idea that, in the rest action potential, the SIV is capable of taking it up fast<br>enough to prevent much force development. And they<br>are a strong argument against the idea that, in the rested<br>state contraction, force development results from the are a strong argument against the idea that, in the rested<br>state contraction, force development results from the<br>diffusion of  $Ca^{2+}$  directly from the surface membrane to<br>the myofibrils. Fabiato's results also show that, state contraction, force development results from the diffusion of  $Ca^{2+}$  directly from the surface membrane to the myofibrils. Fabiato's results also show that, when the SR is relatively poorly loaded with  $Ca^{2+}$ ,  $Ca^{2$ cell at a rate similar to that during the plateau of the<br>action potential, the SR is capable of taking it up fast<br>ecouponent. And they<br>encoupon trove development. And they<br>are a strong argument against the idea that, in t the myofibrils. Fabiato's re<br>SR is relatively poorly loo<br>release occurs with a long l<br>has been increased by a<br>latency is greatly reduced.<br>The wide variation in R is relatively poorly loaded with  $Ca^{2+}$ ,  $Ca^{2+}$ -induced lease occurs with a long latency, whereas when loading as been increased by a few simulated twitches, the tency is greatly reduced. The wide variation in latency

release occurs with a long latency, whereas when loading<br>has been increased by a few simulated twitches, the<br>latency is greatly reduced.<br>The wide variation in latency of the  $Ca^{2+}$ -induced<br>contraction in skinned fibers s has been increased by a few simulated twitches, and intency is greatly reduced.<br>The wide variation in latency of the  $Ca^{2+}$ -inducontraction in skinned fibers seems not to be consist with the mechanical behavior of the in latency is greatly reduced.<br>The wide variation in latency of the  $Ca^{2+}$ -induced contraction in skinned fibers seems not to be consistent with the mechanical behavior of the intact cell. Repetitive electrical stimulations The wide variation in latency of the  $Ca^{2+}$ -induced<br>contraction in skinned fibers seems not to be consistent<br>with the mechanical behavior of the intact cell. Repeti-<br>tive electrical stimulations usually induce contractio contraction in skinned fibers seems not to be consistent<br>with the mechanical behavior of the intact cell. Repeti-<br>tive electrical stimulations usually induce contractions<br>after a latency which remains constant irrespective with the mechanical behavior of the intact cell. Repetitive electrical stimulations usually induce contractions after a latency which remains constant irrespective of the inotropic state which is determined by the amount o tive electrical stimulations usually induce contractions<br>
after a latency which remains constant irrespective of<br>
the inotropic state which is determined by the amount<br>
of released calcium and evidenced by the velocity of after a latency which remains constant irrespective of<br>the inotropic state which is determined by the amount<br>of released calcium and evidenced by the velocity of force<br>development (fig. 4). Therefore, it would be difficult the inotropic state which is determined by the amount<br>of released calcium and evidenced by the velocity of force<br>development (fig. 4). Therefore, it would be difficult to<br>believe that calcium fluxes through the sarcolemma ing the action potential, regardless of whether they occur



fig. 4. The effect of increasing calcium load on the contractile<br>behavior of mammalian ventricular muscle. Superimposed force records<br>of a guinea pig papillary muscle in the presence of dihydroouabain. *a*,<br>steady-state ef behavior of mammalian ventricular muscle. Superimposed force records of a guinea pig papillary muscle in the presence of dihydroouabain.  $a$ , steady-state effects;  $b$ , effects of 120  $\mu$ mol/liter of dihydroouabain as a (321).

200<br>through calcium channels or via Na-Ca exchange, are me<br>primarily involved in the depolarization-induced Ca<sup>2+</sup> be 200 RET<br>through calcium channels or via Na-Ca exchange, are<br>primarily involved in the depolarization-induced  $Ca^{2+}$ <br>release. release. rough calcium channels or via Na-Ca exchange, are imarily involved in the depolarization-induced  $Ca^2$  lease.<br>Fabiato points out that the observation of a well-veloped  $Ca^{2+}$ -induced release of  $Ca^{2+}$  in skinned car

through calcium channels or via Na-Ca exchange, are<br>primarily involved in the depolarization-induced  $Ca^{2+}$ <br>release.<br>Fabiato points out that the observation of a well-<br>developed  $Ca^{2+}$ -induced release of  $Ca^{2+}$  in skin primarily involved in the depolarization-induced  $Ca^{2+}$  belease.<br>
Fabiato points out that the observation of a well-<br>
developed  $Ca^{2+}$ -induced release of  $Ca^{2+}$  in skinned car-<br>
diac cells in which all superficial coup release.<br>Fabiato points out that the observation of a we<br>developed  $Ca^{2+}$ -induced release of  $Ca^{2+}$  in skinned ca<br>diac cells in which all superficial couplings are remov<br>proves that the release was not from the terminal Fabiato points out that the observation of a well-reduced developed  $Ca^{2+}$ -induced release of  $Ca^{2+}$  in skinned car-<br>diac cells in which all superficial couplings are removed C<br>proves that the release was not from the t developed  $Ca^{2+}$ -induced release of  $Ca^{2+}$  in skinned cardiac cells in which all superficial couplings are removed<br>proves that the release was not from the terminal cister-<br>nae (116). The absence or paucity of junctiona diac cells in which all superficial couplings are removed<br>proves that the release was not from the terminal cister-<br>nae (116). The absence or paucity of junctional SR in<br>the skinned preparations can also be deduced from t proves that the release was not from the terminal cister-<br>nae (116). The absence or paucity of junctional SR in from<br>the skinned preparations can also be deduced from their br-<br>low sensitivity to ruthenium red and ryanodi nae (116). The absence or paucity of junctional SR<br>the skinned preparations can also be deduced from th<br>low sensitivity to ruthenium red and ryanodine (11<br>substances which specifically act on  $Ca^{2+}$  channels of t<br>junctio the skinned preparations can also be deduced from th<br>low sensitivity to ruthenium red and ryanodine (11<br>substances which specifically act on  $Ca^{2+}$  channels of t<br>junctional SR (356, 130, 307; see section IV D). The<br>fore, low sensitivity to ruthenium red and ryanodine (117),<br>substances which specifically act on  $Ca^{2+}$  channels of the<br>junctional SR (356, 130, 307; see section IV D). There-<br>fore, the  $Ca^{2+}$  release in skinned fibers must b substances which specifically act on  $Ca^{2+}$  channels of the junctional SR (356, 130, 307; see section IV D). Therefore, the  $Ca^{2+}$  release in skinned fibers must be considered to occur from the free longitudinal SR thro nctional SR (356, 130, 307; see section IV D). The, the Ca<sup>2+</sup> release in skinned fibers must be coned to occur from the free longitudinal SR through o<sup>2+</sup> channels than those specific for the junctional There are two ess

fore, the  $Ca^{2+}$  release in skinned fibers must be conserved to occur from the free longitudinal SR through ot  $Ca^{2+}$  channels than those specific for the junctional ST here are two essentials of a normal action potenti ered to occur from the free longitudinal SR through other  $Ca^{2+}$  channels than those specific for the junctional SR.<br>There are two essentials of a normal action potential-<br>triggered release mechanism which apparently nec  $Ca^{2+}$  channels than those specific for the junctional SR.<br>There are two essentials of a normal action potential-<br>triggered release mechanism which apparently necessi-<br>tate the junctional connection between the sarcolemm There are two essentials of a normal action potentitiggered release mechanism which apparently necestate the junctional connection between the sarcolem and the adjacent junctional SR, and which therefore cannot be met by triggered release mechanism which apparently necessi-<br>tate the junctional connection between the sarcolemma and<br>and the adjacent junctional SR, and which therefore u<br>cannot be met by  $Ca^{2+}$ -induced  $Ca^{2+}$  release as dem tate the junctional connection between the sarcolem<br>and the adjacent junctional SR, and which thereficannot be met by  $Ca^{2+}$ -induced  $Ca^{2+}$  release as demostrated either in skinned fibers or in aftercontractions<br>intact and the adjacent junctional SR, and which therefore ur cannot be met by  $Ca^{2+}$ -induced  $Ca^{2+}$  release as demon-<br>strated either in skinned fibers or in aftercontractions of of<br>intact cells. (a) The release has to be swit cannot be met by  $Ca^{2+}$ -induced  $Ca^{2+}$  release as demon-<br>strated either in skinned fibers or in aftercontractions of of filling of the junctional SR.<br>intact cells. (a) The release has to be switched on instan-<br>taneously intact cells. ( $a$ ) The release has to be switched on instantaneously with a short and constant latency. ( $b$ ) The release mechanism has to be switched off again with the repolarization of the sarcolemma. I have already d intact cells. ( $a$ ) The release has to be switched on instant taneously with a short and constant latency. ( $b$ ) The release mechanism has to be switched off again with the repolarization of the sarcolemma. I have already taneously with a short and constant latency. (b) The release mechanism has to be switched off again with the repolarization of the sarcolemma. I have already discussed the question of the mechanical latency. The influ-<br>en repolarization of the sarcolemma. I have already dis-<br>cussed the question of the mechanical latency. The influ-<br>extracellular potassium<br>ence of the repolarization on the duration of the release<br>concentration, one studies repolarization of the sarcolemma. I have already discussed the question of the mechanical latency. The influence of the repolarization on the duration of the release and consequently on the time to peak force becomes evide cussed the question of the mechanical latency. The in<br>ence of the repolarization on the duration of the rele<br>and consequently on the time to peak force becon<br>evident when the duration of the action potential is eit<br>prolong ence of the repolarization on the duration of the release cand consequently on the time to peak force becomes mevident when the duration of the action potential is either hypolonged, as in rested state contractions by cat and consequently on the time to peak force becomes mevident when the duration of the action potential is either lum<br>prolonged, as in rested state contractions by catechol-<br>amines (24, 345) or cesium (323; see section III evident when the duration of the action potential is either<br>prolonged, as in rested state contractions by catechol-<br>mamines (24, 345) or cesium (323; see section III B), or<br>shortened with increasing  $Ca^{2+}$  load. Conseque amines (24, 345) or cesium (323; see section III B), or<br>sintervals), the contractions of ventricular muscle have<br>shortened with increasing  $Ca^{2+}$  load. Consequently, as only a late and no early peak (346, 255, 417, 186). amines (24, 345) or cesium (323; see section III B), or shortened with increasing  $Ca^{2+}$  load. Consequently, as shown in fig. 4b, a digitalis-induced increase in  $Ca^{2+}$  load causes a progressive shortening of the time t shortened with increasing  $Ca^{2+}$  load. Consequently, as<br>shown in fig. 4b, a digitalis-induced increase in  $Ca^{2+}$  load<br>causes a progressive shortening of the time to peak force<br>despite an unchanged rate of force developm shown in fig. 4b, a digitalis-induced increase in  $Ca^{2+}$  load<br>causes a progressive shortening of the time to peak force<br>despite an unchanged rate of force development as evi-<br>dent from the unchanged steepness of the isom causes a progressive shortening of the time to peak force<br>despite an unchanged rate of force development as evident from the unchanged steepness of the isometric do<br>contraction curve, indicating that the initial  $Ca^{2+}$  r despite an unchanged rate of force development as evident from the unchanged steepness of the isometric contraction curve, indicating that the initial  $Ca^{2+}$  release is probably not inhibited. This is in accordance with dent from the unchanged steepness of the isometric contraction curve, indicating that the initial  $Ca^{2+}$  release is probably not inhibited. This is in accordance with the finding that the diminution of force development contraction curve, indicating that the initial  $Ca^{2+}$  release<br>is probably not inhibited. This is in accordance with the<br>finding that the diminution of force development under<br>comparable conditions of Ca overload is not a is probably not inhibited. This is in accordance with the finding that the diminution of force development under comparable conditions of Ca overload is not accompanied by a decrease of the systolic Ca signal as estimated finding that the diminution of force development under<br>comparable conditions of Ca overload is not accompanied<br>by a decrease of the systolic Ca signal as estimated from<br>the peak systolic light signal measured with aequorin by a decrease of the systolic Ca signal as estimated from<br>the peak systolic light signal measured with aequorin (5).<br>The unabated maximal rate of force development pre-<br>cludes a reduced Ca sensitivity of the contractile ap by a decrease of the systolic Ca signal as estimated from<br>the peak systolic light signal measured with acquorin  $(5)$ .<br>The unabated maximal rate of force development pre-<br>cludes a reduced Ca sensitivity of the contractile the peak systolic light signal measured with aequorin (The unabated maximal rate of force development picludes a reduced Ca sensitivity of the contractile appratus as a cause for the shortening of the time to pe force and The unabated maximal rate of force development pre-<br>cludes a reduced Ca sensitivity of the contractile appa-<br>ratus as a cause for the shortening of the time to peak<br>force and the resulting decline of the contraction amplicludes a reduced Ca sensitivity of the contractile apparatus as a cause for the shortening of the time to peak<br>force and the resulting decline of the contraction ampli-<br>tude. The abbreviation of the ascending slope of the<br> ratus as a cause for the shortening of the time to peartion-dependent of the contraction amplement tude. The abbreviation of the ascending slope of the contraction-dependent closing of the Ca release chan-<br>repolarization-d force and the resulting decline of the contraction amplitude. The abbreviation of the ascending slope of the contraction curve very likely results from an earlier repolarization-dependent closing of the Ca release channels tude. The abbreviation of the ascending slope of the<br>contraction curve very likely results from an earlier<br>repolarization-dependent closing of the Ca release chan-<br>nels which would accelerate the impact of the fast Ca<br>upta contraction curve very likely results from an earlier repolarization-dependent closing of the Ca release channels which would accelerate the impact of the fast Ca uptake system of the SR on the Ca release from the contract repolarization-dependent closing of the Ca release chan-<br>nels which would accelerate the impact of the fast Ca<br>uptake system of the SR on the Ca release from the (m<br>contractile proteins. A shortening of the action potenti uptake system of the SR on the Ca release from the (mmol/l)<br>contractile proteins. A shortening of the action potential FIG. 5. Influence of potassium and stimulation frequency on cal-<br>duration in mammalian heart muscle le uptake system of the SR on the Ca release from the contractile proteins. A shortening of the action potential duration in mammalian heart muscle leads generally to an abbreviation of the time to, and consequently to a redu contractile proteins. A shortening of the action potent<br>duration in mammalian heart muscle leads generally<br>an abbreviation of the time to, and consequently to<br>reduction of, the contraction peak as was demonstrat<br>by Morad a

ER<br>ments. The rate of force development in fig. 4*b* begins to<br>be reduced only if the resting force is increased by about ER<br>ments. The rate of force development in fig. 4b begins to<br>be reduced only if the resting force is increased by about<br>100%, indicating that the increase in diastolic  $[Ca^{2+}]_i$ ER<br>ments. The rate of force development in fig. 4b begins to<br>be reduced only if the resting force is increased by about<br>100%, indicating that the increase in diastolic  $[Ca^{2+}]_i$ <br>reduces the rate of  $Ca^{2+}$  release and/or ments. The rate of force development in fig. 4b begins to be reduced only if the resting force is increased by about 100%, indicating that the increase in diastolic  $[Ca^{2+}]$ ; reduces the rate of  $Ca^{2+}$  release and/or the ments. The rate of force de<br>be reduced only if the resti<br>100%, indicating that the<br>reduces the rate of  $Ca^{2+}$  rel<br>of the contractile proteins.<br>Considering the availab reduced only if the resting force is increased by about 0%, indicating that the increase in diastolic  $[Ca^{2+}]_i$  duces the rate of  $Ca^{2+}$  release and/or the Ca sensitivity the contractile proteins.<br>Considering the availa 100%, indicating that the increase in diastolic  $[Ca^{2+}]$ ;<br>reduces the rate of  $Ca^{2+}$  release and/or the Ca sensitivity<br>of the contractile proteins.<br>Considering the available evidence, one obtains the<br>following picture of

reduces the rate of  $Ca^{2+}$  release and/or the Ca sensitivit<br>of the contractile proteins.<br>Considering the available evidence, one obtains the<br>following picture of the different modes of  $Ca^{2+}$  release<br>from the SR in the of the contractile proteins.<br>Considering the available evidence, one obtains following picture of the different modes of  $Ca^{2+}$  rele<br>from the SR in the intact cell. At normal resting me<br>brane potentials, spontaneous cont Considering the available evidence, one obtains following picture of the different modes of  $Ca^{2+}$  rel from the SR in the intact cell. At normal resting m brane potentials, spontaneous contractions or after tractions (i. following picture of the different modes of  $Ca^{2+}$  release<br>from the SR in the intact cell. At normal resting mem-<br>brane potentials, spontaneous contractions or aftercon-<br>tractions (i.e., contractions not induced by depol from the SR in the intact cell. At normal resting mem-<br>brane potentials, spontaneous contractions or aftercon-<br>tractions (i.e., contractions not induced by depolariza-<br>tion) are the result of  $Ca^{2+}$ -induced release of  $Ca$ brane potentials, spontaneous contractions or aftercon-<br>tractions (i.e., contractions not induced by depolariza-<br>tion) are the result of  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from<br>a heavily loaded SR, which probably takes pl tractions (i.e., contractions not induced by depolariza-<br>tion) are the result of  $Ca^{2+}$ -induced release of  $Ca^{2+}$  from<br>a heavily loaded SR, which probably takes place mainly<br>through channels other than those involved in a heavily loaded SR, which probably takes place mainly through channels other than those involved in the depolarization-induced release of  $Ca^{2+}$ . These contractions are usually smaller than the electrically triggered co a heavily loaded SR, which probably takes place main<br>through channels other than those involved in the d<br>polarization-induced release of  $Ca^{2+}$ . These contraction<br>are usually smaller than the electrically triggered co<br>tr through channels other than those involved in the de-<br>polarization-induced release of  $Ca^{2+}$ . These contractions<br>are usually smaller than the electrically triggered con-<br>traction (418). It is only by depolarization of th polarization-induced release of  $Ca^{2+}$ . These contractions<br>are usually smaller than the electrically triggered con-<br>traction (418). It is only by depolarization of the sarco-<br>lemma that the Ca channels of the release com are usually smaller than the electrically triggered con-<br>traction (418). It is only by depolarization of the sarco-<br>lemma that the Ca channels of the release compartments<br>are effectively opened by a mechanism which is sti traction (418). It is only by depolarization of the sarco-<br>lemma that the Ca channels of the release compartments<br>are effectively opened by a mechanism which is still not<br>understood in detail (see section IV C), and the ca lemma that the Ca channels of the are effectively opened by a mech understood in detail (see section is released through these channels of filling of the junctional SR. *C. Voltage-dependent Caccion IV C)*, and is released through these channels according of the junctional SR.<br>*C. Voltage-dependent Calcium Release*<br>More insight into the mechanism by wh

released through these channels according to the state<br>filling of the junctional SR.<br>Voltage-dependent Calcium Release<br>More insight into the mechanism by which the release<br>pre of the sarcoplasmic reticulum releases calcium of filling of the junctional SR.<br>C. Voltage-dependent Calcium Release<br>More insight into the mechanism by which the release<br>store of the sarcoplasmic reticulum releases calcium can<br>be obtained if, by varying the extracellul C. Voltage-dependent Calcium Release<br>
More insight into the mechanism by which the release<br>
store of the sarcoplasmic reticulum releases calcium can<br>
be obtained if, by varying the extracellular potassium<br>
concentration, concentration, one studies the release<br>More insight into the mechanism by which the release<br>store of the sarcoplasmic reticulum releases calcium can<br>be obtained if, by varying the extracellular potassium<br>concentration, one More insight into the mechanism by which the release<br>store of the sarcoplasmic reticulum releases calcium can<br>be obtained if, by varying the extracellular potassium<br>concentration, one studies the relation between resting<br>m store of the sarcoplasmic reticulum releases calcium can<br>be obtained if, by varying the extracellular potassium<br>concentration, one studies the relation between resting<br>membrane potential and early contraction peak. In sobe obtained if, by varying the extracellular potassium<br>concentration, one studies the relation between resting<br>membrane potential and early contraction peak. In so-<br>lutions with a potassium concentration higher than 8<br>mmol concentration, one studies the relation between resting<br>membrane potential and early contraction peak. In so-<br>lutions with a potassium concentration higher than 8<br>mmol/liter and at low contraction frequencies (10- or 5-<br>s membrane potential and early contraction peak. In solutions with a potassium concentration higher than 8 mmol/liter and at low contraction frequencies (10- or 5-<br>s intervals), the contractions of ventricular muscle have<br>on flutions with a potassium concentration higher than 8<br>mmol/liter and at low contraction frequencies (10- or 5-<br>s intervals), the contractions of ventricular muscle have<br>only a late and no early peak (346, 255, 417, 186).<br>H s intervals), the contractions of ventricular muscle have<br>only a late and no early peak (346, 255, 417, 186).<br>However, when these contractions are followed by a<br>stimulus after a 1-s interval, the resulting test beat shows<br> only a late and no early peak (346, 255, 417, 186).<br>However, when these contractions are followed by a<br>stimulus after a 1-s interval, the resulting test beat shows<br>an early contraction peak in addition to the late one, as<br> However, when these contractions are followed by a<br>stimulus after a 1-s interval, the resulting test beat shows<br>an early contraction peak in addition to the late one, as<br>does a regular low frequency contraction at the norm stimulus after a 1-s interval, the resulting test beat shows<br>an early contraction peak in addition to the late one, as<br>does a regular low frequency contraction at the normal<br>potassium concentration of 5.9 mmol/liter (fig. an early contraction peak in addition to the late one, as<br>does a regular low frequency contraction at the normal<br>potassium concentration of 5.9 mmol/liter (fig. 5). This<br>indicates that the release store was filled (reprim



(mmol/l)<br>FIG. 5. Influence of potassium and stimulation frequency on cal-<br>cium stored in release compartments. Contractions of a guinea pig<br>papillary muscle in the presence of 3  $\mu$ mol/liter of norepinephrine at<br>0.2 Hz f cium stored in release compartments. Contractions of a guinea p<br>papillary muscle in the presence of  $3 \mu$ mol/liter of norepinephrine<br>0.2 Hz frequency; test contraction after an interval of 800 ms (so<br>stimulation pattern a



tween regular beats at low frequency showed that the CALCIUM MOBILIZATION AND CARDI<br>contraction. Test contractions at various intervals be-<br>tween regular beats at low frequency showed that the<br>ability of the muscle to produce early contraction com-CALCIUM MOBILIZATION AND<br>contraction. Test contractions at various intervals be<br>tween regular beats at low frequency showed that th<br>ability of the muscle to produce early contraction com-<br>ponents is lost in a few seconds ( contraction. Test contractions at various intervals be-<br>tween regular beats at low frequency showed that the<br>ability of the muscle to produce early contraction com-<br>ponents is lost in a few seconds (346, 255, 417) and that contraction. Test contractions at various intervals be-<br>tween regular beats at low frequency showed that the<br>ability of the muscle to produce early contraction com-<br>ponents is lost in a few seconds  $(346, 255, 417)$  and t tween regular beats at low frequency showed that the ability of the muscle to produce early contraction components is lost in a few seconds (346, 255, 417) and that the rate of loss depends on the extracellular potassium ability of the muscle to produce early contraction com-<br>ponents is lost in a few seconds  $(346, 255, 417)$  and that  $Ca^{2+}$ <br>the rate of loss depends on the extracellular potassium SR/<br>concentration, i.e., on the resting m ponents is lost in a few seconds (346, 255, 417) and that  $Ca^{2}$ <br>the rate of loss depends on the extracellular potassium SR,<br>concentration, i.e., on the resting membrane potential that<br>(in the range between  $-77$  mV and the rate of loss depends on the extracellular potassium Sconcentration, i.e., on the resting membrane potential the range between  $-77$  mV and  $-59$  mV at [K]<sub>0</sub> of 8 for 16 mmol/liter, respectively; ref. 399). Increases concentration, i.e., on the resting membrane potential the (in the range between  $-77$  mV and  $-59$  mV at [K]<sub>o</sub> of 8 for 16 mmol/liter, respectively; ref. 399). Increases in actively<sup>2+</sup>]<sub>o</sub> or [Ca<sup>2+</sup>]<sub>o</sub> prevent the po (in the range between  $-77$  mV and  $-59$  mV at  $[K]_0$  of 8 or 16 mmol/liter, respectively; ref. 399). Increases in  $[Mg^{2+}]_0$  or  $[Ca^{2+}]_0$  prevent the potassium-induced loss of the early contraction component without alt or 16 mmol/liter, respectively; ref. 399). Increases in  $[Mg^{2+}]_o$  or  $[Ca^{2+}]_o$  prevent the potassium-induced loss of the early contraction component without altering the effect of potassium on the transmembrane potentia [Mg<sup>2+</sup>]<sub>o</sub> or [Ca<sup>2+</sup>]<sub>o</sub> prevent the potassium-induced loss<br>the early contraction component without altering t<br>effect of potassium on the transmembrane potent<br>(399). These results have been interpreted as follows.<br>low e the early contraction component without altering the calciu<br>effect of potassium on the transmembrane potential heavy<br>(399). These results have been interpreted as follows. At of bot<br>low extracellular  $K^+$  concentrations, effect of potassium on the transmembrane potential (399). These results have been interpreted as follows. At low extracellular  $K^+$  concentrations, i.e., during hyperpolarization, there is only a small leakage of calcium (399). These results have been interpreted as follows. At low extracellular  $K^+$  concentrations, i.e., during hyper-<br>polarization, there is only a small leakage of calcium<br>from the store of the SR in cardiac muscle. Ther low extracellular  $K^+$  concentrations, i.e., during hyper-<br>polarization, there is only a small leakage of calcium fiec<br>from the store of the SR in cardiac muscle. Therefore tide<br>enough calcium remains in the SR to cause polarization, there is only a small leakage of calcium firm the store of the SR in cardiac muscle. Therefore tien ough calcium remains in the SR to cause a distinct dearly contraction component. As  $[K^+]_o$  is elevated and from the store of the SR in cardiac muscle. Therefore<br>enough calcium remains in the SR to cause a distinct<br>early contraction component. As  $[K^+]_o$  is elevated and<br>membrane potential is made less negative, a voltage<br>sensor enough calcium remains in the SR to cause a distinct dearly contraction component. As  $[K^+]_o$  is elevated and comembrane potential is made less negative, a voltage usensor is affected by the membrane potential in a manner early contraction component. As  $[K^+]_o$  is elevated and comembrane potential is made less negative, a voltage uis<br>sensor is affected by the membrane potential in a manner flu<br>that opens some sarcomplasmic reticulum channe membrane potential is made less negative, a voltage<br>sensor is affected by the membrane potential in a manner<br>that opens some sarcomplasmic reticulum channels. This<br>reduces the amount of stored calcium available for the<br>ear sensor is affected by the membrane potential in a manner flue that opens some sarcomplasmic reticulum channels. This IV reduces the amount of stored calcium available for the relearly contraction component. The effect of t that opens some sarcomplasmic reticulum channels. This IV I<br>reduces the amount of stored calcium available for the rele<br>early contraction component. The effect of the divalent the<br>cations is to change a surface potential ( reduces the amount of stored calcium available for the relearly contraction component. The effect of the divalent the cations is to change a surface potential (163) of the sarcolemma and thus alter the electric field sense early contraction component. The effect of the dival<br>cations is to change a surface potential (163) of<br>sarcolemma and thus alter the electric field sensed<br>the voltage sensor. Consistent with this hypothesis is<br>observation cations is to change a surface potential (163) of the the sarcolemma and thus alter the electric field sensed by prethe voltage sensor. Consistent with this hypothesis is the brobservation made by Mascher (252) in partiall sarcolemma and thus alter the electric field sensed by pro<br>the voltage sensor. Consistent with this hypothesis is the briobservation made by Mascher (252) in partially depolar-<br>ized (18.9 mmol/liter of KCl) cat papillary the voltage sensor. Consistent with this hypothesis is the brookservation made by Mascher (252) in partially depolarized (18.9 mmol/liter of KCl) cat papillary muscles which were kept in low sodium solution and, therefore observation made by Mascher  $(252)$  in partially depolarized  $(18.9 \text{ mmol/liter of KCl})$  cat papillary muscles which were kept in low sodium solution and, therefore, had  $Ca^{2+}$ -filled release stores. These muscles had lost the ab ized (18.9 mmol/liter of KCl) cat papillary muscles which Swere kept in low sodium solution and, therefore, had tion Ca<sup>2+</sup>-filled release stores. These muscles had lost the suggebility to respond with action potentials ( were kept in low sodium solution and, therefore, had  $Ca^{2+}$ -filled release stores. These muscles had lost the ability to respond with action potentials (and slow inward currents) to electrical stimuli and responded to st  $Ca<sup>2+</sup>$ -filled release stores. These muscles had lost ability to respond with action potentials (and slow ward currents) to electrical stimuli and responded stimuli of increasing strength with graded electrotonic displ ability to respond with action potentials (and slow in-<br>ward currents) to electrical stimuli and responded to<br>stimuli of increasing strength with graded electrotonic<br>responses. Small increments in the electrotonic displace ward currents) to electrical stimuli and responded<br>stimuli of increasing strength with graded electrotor<br>responses. Small increments in the electrotonic disple<br>ment of the membrane potential yielded marked<br>creases in the m tion. sponses. Small increments in the electrotonic displace-<br>ent of the membrane potential yielded marked in-<br>eases in the magnitude of the associated early contrac-<br>on.<br>It points to the similarity of the release mechanisms<br>ske ment of the membrane potential yielded marked increases in the magnitude of the associated early contraction.<br>It points to the similarity of the release mechanisms<br>in skeletal and in cardiac muscle that, in skeletal muscle

creases in the magnitude of the associated early contraction.<br>
It points to the similarity of the release mechanisms<br>
in skeletal and in cardiac muscle that, in skeletal muscle,<br>
a "slow" release of calcium has also been o ion.<br>It points to the similarity of the release mechanisms<br>in skeletal and in cardiac muscle that, in skeletal muscle,<br>a "slow" release of calcium has also been observed at<br>potassium concentrations above 8 mmol/liter but It points to the similarity of the release mechanisms evident in skeletal and in cardiac muscle that, in skeletal muscle, SF a "slow" release of calcium has also been observed at contracture threshold. Elevations of  $[K^+]$ in skeletal and in cardiac muscle that, in skeletal muscle, SR a "slow" release of calcium has also been observed at compotassium concentrations above 8 mmol/liter but still (363 below the contracture threshold. Elevation a "slow" release of calcium has also been observed at opotassium concentrations above 8 mmol/liter but still below the contracture threshold. Elevations of  $[K^+]$ , cause an increase in oxygen consumption (155) and in heat potassium concentrations above 8 mmol/liter but still (36;<br>below the contracture threshold. Elevations of  $[K^+]$ , cou<br>cause an increase in oxygen consumption (155) and in mes<br>heat production (358). These effects have been below the contracture threshold. Elevations of  $[K^+]$ , couplind cause an increase in oxygen consumption (155) and in messer heat production (358). These effects have been attributed tubular to an enhanced calcium sequestra cause an increase in oxygen consumption (155) and<br>heat production (358). These effects have been attribut<br>to an enhanced calcium sequestration secondary to a<br>augmentation of voltage-dependent calcium release fro<br>the sarcop heat production (358). These effects have been attributed<br>to an enhanced calcium sequestration secondary to an<br>augmentation of voltage-dependent calcium release from<br>the sarcoplasmic reticulum (293, 31) and a resultant<br>inc to an enhanced calcium sequestration secondary to an augmentation of voltage-dependent calcium release from the sarcoplasmic reticulum (293, 31) and a resultant increase in the intracellular calcium concentration (357). Fu the sarcoplasmic reticulum (293, 31) and a resultant<br>increase in the intracellular calcium concentration (357).<br>Furthermore, these effects were also inhibited by various<br>divalent cations (388).<br>Since the coupling mechanism e sarcoplasmic reticulum (293, 31) and a resultant<br>crease in the intracellular calcium concentration (357).<br>urthermore, these effects were also inhibited by various<br>valent cations (388).<br>Since the coupling mechanism betwee

increase in the intracellular calcium concentration (357).<br>
Furthermore, these effects were also inhibited by various<br>
divalent cations (388).<br>
Since the coupling mechanism between membrane po-<br>
tential and calcium leak fr Furthermore, these effects were also inhibited by various<br>divalent cations (388).<br>Since the coupling mechanism between membrane po-<br>tential and calcium leak from intracellular stores seems<br>to be as well developed in skelet divalent cations (388).<br>
Since the coupling mechanism between membrane p<br>
tential and calcium leak from intracellular stores seer<br>
to be as well developed in skeletal as in mammalii<br>
cardiac muscle, one is inclined to assu Since the coupling mechanism between membrane po-<br>tential and calcium leak from intracellular stores seems (IV<br>to be as well developed in skeletal as in mammalian the<br>cardiac muscle, one is inclined to assume that this mec tential and calcium leak from intracellular stores see<br>to be as well developed in skeletal as in mammal<br>cardiac muscle, one is inclined to assume that this me<br>anism serves, in both types of muscle, for the ra<br>release of ca to be as well developed in skeletal as in mammalian the cardiac muscle, one is inclined to assume that this mech-<br>anism serves, in both types of muscle, for the rapid release of calcium that is triggered by the fast depola

CALCIUM MOBILIZATION AND CARDIAC INOTROPIC MECHANISMS 201<br>contraction. Test contractions at various intervals be- reconcile with a mechanism other than passive diffusion reconcile with a mechanism other than passive diffusion<br>through activated calcium release channels of the juncthrough activated reconcile with a mechanism other than passive diffusion<br>through activated calcium release channels of the junc-<br>tional SR. The kinetic studies by Ikemoto et al. (180) o the concile with a mechanism other than passive diffusion<br>reconcile with a mechanism other than passive diffusion<br>through activated calcium release channels of the junc-<br>tional SR. The kinetic studies by Ikemoto et al. (1 reconcile with a mechanism other than passive diffusion<br>through activated calcium release channels of the junc-<br>tional SR. The kinetic studies by Ikemoto et al. (180) on<br>Ca<sup>2+</sup> release (induced by ionic replacement) from i reconcile with a mechanism other than passive diffusion<br>through activated calcium release channels of the junc-<br>tional SR. The kinetic studies by Ikemoto et al. (180) on<br>Ca<sup>2+</sup> release (induced by ionic replacement) from i tional SR. The kinetic studies by Ikemoto et al.  $(180)$  on  $Ca^{2+}$  release (induced by ionic replacement) from isolated SR/T-tubule complexes from skeletal muscle suggest that the linkage between sarcolemma and SR is req tional SR. The kinetic studies by Ikemoto et al. (180) on Ca<sup>2+</sup> release (induced by ionic replacement) from isolated SR/T-tubule complexes from skeletal muscle suggest that the linkage between sarcolemma and SR is require  $Ca^{2+}$  release (induced by ionic replacement) from isolated SR/T-tubule complexes from skeletal muscle suggest that the linkage between sarcolemma and SR is required for triggering rapid calcium release, whereas a direct SR/T-tubule complexes from skeletal muscle suggest<br>that the linkage between sarcolemma and SR is required<br>for triggering rapid calcium release, whereas a direct<br>activation of the SR membrane by (released) calcium or<br>drugs that the linkage between sarcolemma and SR is required<br>for triggering rapid calcium release, whereas a direct<br>activation of the SR membrane by (released) calcium or<br>drugs (caffeine and quercetin) leads to a relatively slow activation of the SR membrane by (released) calcium or drugs (caffeine and quercetin) leads to a relatively slow calcium release. Putative calcium release channels in heavy SR vesicles, derived from the terminal cisternae activation of the SR membrane by (released) calcium or<br>drugs (caffeine and quercetin) leads to a relatively slow<br>calcium release. Putative calcium release channels in<br>heavy SR vesicles, derived from the terminal cisternae<br> drugs (caffeine and quercetin) leads to a relatively sl<br>calcium release. Putative calcium release channels<br>heavy SR vesicles, derived from the terminal cisterr<br>of both skeletal (356) and cardiac (334a) muscle, whi<br>were inc calcium release. Putative calcium release channels<br>heavy SR vesicles, derived from the terminal cisterr<br>of both skeletal (356) and cardiac (334a) muscle, whi<br>were incorporated into planar lipid bilayers and iden<br>fied on th heavy SR vesicles, derived from the terminal cisternae<br>of both skeletal (356) and cardiac (334a) muscle, which<br>were incorporated into planar lipid bilayers and identi-<br>fied on the basis of their activation by adenine nucle of both skeletal (356) and cardiac (334a) muscle, which<br>were incorporated into planar lipid bilayers and identi-<br>fied on the basis of their activation by adenine nucleo-<br>tides, blockade by ruthenium red, and sensitivity fo were incorporated into planar lipid bilayers and ider<br>fied on the basis of their activation by adenine nucl-<br>tides, blockade by ruthenium red, and sensitivity<br>divalent cations, have been shown to exhibit a very la<br>conducta fied on the basis of their activation by adenine nucleotides, blockade by ruthenium red, and sensitivity for divalent cations, have been shown to exhibit a very large conductance. A large conductance is certainly a prerequ tides, blockade by ruthenium red, and sensitivity for divalent cations, have been shown to exhibit a very large conductance. A large conductance is certainly a prerequisite for a calcium channel that can mediate large ion divalent cations, have been shown to exhibit a very large conductance. A large conductance is certainly a prerequisite for a calcium channel that can mediate large ion fluxes on a millisecond time scale. Ryanodine (see se uisite for a calcium channel that can mediate large ion<br>fluxes on a millisecond time scale. Ryanodine (see section<br>IV D) was found to act as a specific ligand for the  $Ca^{2+}$ <br>release channels of the junctional SR (130). T fluxes on a millisecond time scale. Ryanodine (see sec IV D) was found to act as a specific ligand for the velease channels of the junctional SR (130). This let the isolation, from skeletal as from cardiac muscle the  $Ca^{2$ IV D) was found to act as a specific ligand for the  $Ca^{2+}$  release channels of the junctional SR (130). This led to the isolation, from skeletal as from cardiac muscle, of the  $Ca^{2+}$  release channel. It is a high-molecu release channels of the junctional SR (130). This led the isolation, from skeletal as from cardiac muscle,  $\chi$  the Ca<sup>2+</sup> release channel. It is a high-molecular-weigh protein whose structure is identical with that of th the isolation, from skeletal as from cardiac muscle, complete the Ca<sup>2+</sup> release channel. It is a high-molecular-weigh protein whose structure is identical with that of the feed bridging the gap between the sarcolemma and e Ca<sup>2+</sup> release channel. It is a high-molecular-weigotein whose structure is identical with that of the foreign of the same of same several mechanisms for a volt

rices, blockade by ruthenium red, and sensitivity for divalent cations, have been shown to exhibit a very large conductance. A large conductance is certainly a prerequisite for a calcium channel that can mediate large ion protein whose structure is identical with that of the feet<br>bridging the gap between the sarcolemma and the junc-<br>tional sarcoplasmic reticulum (183, 183a, 229a, 229b).<br>Several mechanisms for a voltage-dependent activa-<br>tio bridging the gap between the sarcolemma and the junctional sarcoplasmic reticulum (183, 183a, 229a, 229b).<br>Several mechanisms for a voltage-dependent activation of calcium release in skeletal muscle have been<br>suggested. Th tional sarcoplasmic reticulum (183, 183a, 229a, 229b).<br>Several mechanisms for a voltage-dependent activa-<br>tion of calcium release in skeletal muscle have been<br>suggested. The main hypotheses are electrical, chemical,<br>and me Several mechanisms for a voltage-dependent activation of calcium release in skeletal muscle have been suggested. The main hypotheses are electrical, chemical, and mechanical (for reviews, see refs. 368, 251, and 362). Elec tion of calcium release in skeletal muscle have been suggested. The main hypotheses are electrical, chemical, and mechanical (for reviews, see refs. 368, 251, and 362). Electrical coupling was thought to occur by a flow of suggested. The main hypotheses are electrical, chemical, and mechanical (for reviews, see refs. 368, 251, and 362). Electrical coupling was thought to occur by a flow of ionic current from the tubular space through pores ( and mechanical (for reviews, see refs. 368, 251, and 362).<br>
Electrical coupling was thought to occur by a flow of<br>
ionic current from the tubular space through pores (pil-<br>
lars) of the bridging structures into the SR, th Electrical coupling was thought to occur by a flow of<br>ionic current from the tubular space through pores (pil-<br>lars) of the bridging structures into the SR, thereby<br>inducing an electrical potential change across the SR<br>mem hypothesis could not be supported experimentally, since in membrane which would cause calcium release (256). This hypothesis could not be supported experimentally, since evidence for large changes in membrane potential of inducing an electrical potential change across the SR<br>membrane which would cause calcium release (256). This<br>hypothesis could not be supported experimentally, since<br>evidence for large changes in membrane potential of the<br>S membrane which would cause calcium release (256). This<br>hypothesis could not be supported experimentally, since<br>evidence for large changes in membrane potential of the<br>SR during calcium release was found neither in the ioni hypothesis could not be supported experimentally, sine<br>evidence for large changes in membrane potential of th<br>SR during calcium release was found neither in the ion<br>composition of the SR nor in relevant optical signa<br>(363, evidence for large changes in membrane potential of the SR during calcium release was found neither in the ionic composition of the SR nor in relevant optical signals (363, 295, 211, 19). A chemical excitation-contraction SR during calcium release was found neither in the ionic composition of the SR nor in relevant optical signals (363, 295, 211, 19). A chemical excitation-contraction coupling could possibly be accomplished by a diffusible composition of the SR nor in relevant optical signals (363, 295, 211, 19). A chemical excitation-contraction coupling could possibly be accomplished by a diffusible messenger substance which enters the fiber through the t (363, 295, 211, 19). A chemical excitation-contraction<br>coupling could possibly be accomplished by a diffusible<br>messenger substance which enters the fiber through the<br>tubular membrane (or is released by the membrane) and<br>a coupling could possibly be accomplished by a diffusible<br>messenger substance which enters the fiber through the<br>tubular membrane (or is released by the membrane) and<br>activates the SR.  $Ca^{2+}$  has long been considered as a<br> messenger substance which enters the fiber through the tubular membrane (or is released by the membrane) and activates the SR.  $Ca^{2+}$  has long been considered as *i* likely candidate for such messenger substance (for re tubular membrane (or is released by the membrane) and<br>activates the SR.  $Ca^{2+}$  has long been considered as a<br>likely candidate for such messenger substance (for re-<br>views, see refs. 30 and 135). According to this hypothes activates the SR.  $Ca^{2+}$  has long been considered as a likely candidate for such messenger substance (for reviews, see refs. 30 and 135). According to this hypothesis, small quantities of  $Ca^{2+}$  entering during depolari likely candidate for such messenger substance (for reviews, see refs. 30 and 135). According to this hypothesis, small quantities of  $Ca^{2+}$  entering during depolarization should trigger the release from the SR of the muc views, see refs. 30 and 135). According to this hypothesis,<br>small quantities of  $Ca^{2+}$  entering during depolarization<br>should trigger the release from the SR of the much larger<br>quantity of  $Ca^{2+}$  required for contraction should trigger the release from the SR of the much larger<br>quantity of  $Ca^{2+}$  required for contraction  $(Ca^{2+}$ -induced<br>release of  $Ca^{2+}$ ). As discussed in the previous sections<br>(IV A to IV B 6), it was found to be rathe should trigger the release from the SR of the much large quantity of  $Ca^{2+}$  required for contraction  $(Ca^{2+}$ -induce release of  $Ca^{2+}$ ). As discussed in the previous section (IV A to IV B 6), it was found to be rather u quantity of  $Ca^{2+}$  required for contraction  $(Ca^{2+}$ -induced release of  $Ca^{2+}$ ). As discussed in the previous sections (IV A to IV B 6), it was found to be rather unlikely that the normal, depolarization-induced, contra release of  $Ca^{2+}$ ). As discussed in the previous sections (IV A to IV B 6), it was found to be rather unlikely that the normal, depolarization-induced, contraction of mammalian cardiac muscle results from  $Ca^{2+}$ -induced (IV A to IV B 6), it was found to be rather unlikely that the normal, depolarization-induced, contraction of mammalian cardiac muscle results from  $Ca^{2+}$ -induced  $Ca^{2+}$ release. In skeletal muscle, the hypothesis appears



REITER<br>release signals have even been recorded from fibers which dif<br>had been bathed in 1 mmol/liter of EGTA for 2 days, a eve REITER<br>
release signals have even been recorded from fibers which diff<br>
had been bathed in 1 mmol/liter of EGTA for 2 days, a eve<br>
treatment which certainly should have caused them to the REITER<br>
release signals have even been recorded from fibers which different<br>
had been bathed in 1 mmol/liter of EGTA for 2 days, a even<br>
treatment which certainly should have caused them to the<br>
lose their tubular calcium release signals have even been recorded from fibers w.<br>had been bathed in 1 mmol/liter of EGTA for 2 day<br>treatment which certainly should have caused ther<br>lose their tubular calcium content (265). The experint<br>al analysis release signals have even been recorded from fibers which different cells including skinned muscles fibers (see, how-<br>had been bathed in 1 mmol/liter of EGTA for 2 days, a ever, ref. 274) led to the suggestion that  $\text{InsP$ had been bathed in 1 mmol/liter of EGTA for 2 days, a even<br>treatment which certainly should have caused them to the<br>lose their tubular calcium content (265). The experimentractal<br>analysis of the influence of extracellular treatment which certainly should have caused them<br>lose their tubular calcium content (265). The experimental analysis of the influence of extracellular  $Ca^{2+}$ <br>excitation-contraction coupling in skeletal muscle led<br>the vi lose their tubular calcium content (265). The experimental analysis of the influence of extracellular  $Ca^{2+}$  on excitation-contraction coupling in skeletal muscle led to the view that bound calcium is a requisite for the tal analysis of the influence of extracellular  $Ca^{2+}$  on Insercitation-contraction coupling in skeletal muscle led to is used the view that bound calcium is a requisite for the voltage-<br>sensing and force-controlling syst excitation-contraction coupling in skeletal muscle led to<br>the view that bound calcium is a requisite for the voltage-<br>sensing and force-controlling system residing in the tu-<br>bular membrane (247, 147, 246, 63, 61). Nickel the view that bound calcium is a requisite for the voltage-<br>sensing and force-controlling system residing in the tu-<br>bular membrane (247, 147, 246, 63, 61). Nickel ions can<br>apparently substitute for  $Ca^{2+}$  in this functi sensing and force-controlling system residing in the tu-<br>bular membrane  $(247, 147, 246, 63, 61)$ . Nickel ions can<br>apparently substitute for  $Ca^{2+}$  in this function  $(389, 68,$ <br>31). The removal of external Ca caused an a bular membrane  $(247, 147, 246, 63, 61)$ . Nickel ions c<br>apparently substitute for  $Ca^{2+}$  in this function  $(389, 631)$ . The removal of external Ca caused an accelerati<br>of force inactivation in skeletal muscle leading to 31). The removal of external Ca caused an acceleration of force inactivation in skeletal muscle leading to a shift of the steady-state potential dependence of force inactivation to more negative potentials  $(247, 147, 246$ 31). The removal of external Ca caused an acceleration<br>of force inactivation in skeletal muscle leading to a shift<br>of the steady-state potential dependence of force inacti-<br>vation to more negative potentials  $(247, 147, 2$ of force inactivation in skeletal muscle leading to a shift<br>of the steady-state potential dependence of force inacti-<br>vation to more negative potentials  $(247, 147, 246)$ . Sim-<br>ilar potential shifts were observed of the i of the steady-state potential dependence of force inactivation to more negative potentials  $(247, 147, 246)$ . Similar potential shifts were observed of the inactivation in curves of  $Ca^{2+}$  release (63) and intramembrane vation to more negative potentials  $(247, 147, 246)$ . Sim-<br>ilar potential shifts were observed of the inactivation inj<br>curves of  $Ca^{2+}$  release (63) and intramembrane charge ere<br>movement (61). Lüttgau and coworkers (246) ilar potential shifts were observed of the inactiva<br>curves of  $Ca^{2+}$  release (63) and intramembrane ch<br>movement (61). Lüttgau and coworkers (246) explai<br>the influence of  $Ca^{2+}$  on the potential dependence of<br>inactivatio curves of  $Ca^{2+}$  release (63) and intramembrane charge<br>movement (61). Lüttgau and coworkers (246) explained<br>the influence of  $Ca^{2+}$  on the potential dependence of the<br>inactivation curve by assuming a potential-dependent movement (61). Lüttgau and coworkers (246) explained aft<br>the influence of Ca<sup>2+</sup> on the potential dependence of the<br>inactivation curve by assuming a potential-dependent bin<br>binding of Ca<sup>2+</sup> to the potential sensor of for the influence of Ca<sup>2+</sup> on the potential dependence of the matrixation curve by assuming a potential-dependent binding of Ca<sup>2+</sup> to the potential sensor of force activation skin the T-tubular membrane, with a low affinity inactivation curve by assuming a potential-dependent<br>binding of  $Ca^{2+}$  to the potential sensor of force activation<br>in the T-tubular membrane, with a low affinity in the<br>depolarized inactivated state. A dissociation of  $Ca$ binding of  $Ca^{2+}$  to the potential sensor of force activation<br>in the T-tubular membrane, with a low affinity in the<br>depolarized inactivated state. A dissociation of  $Ca^{2+}$  is<br>assumed to turn the system into a secondary in the T-tubular membrane, with a low affinity in the previously by several investigators were explained as<br>depolarized inactivated state. A dissociation of  $Ca^{2+}$  is being induced by the depolarization of sealed-off T-<br> depolarized inactivated state. A dissociation of  $Ca^{2+}$  is b<br>assumed to turn the system into a secondary inactivated the<br>(paralyzed) state from which it only slowly recovers after lo<br>repolarization. This model would expl assumed to turn the system into a secondary inactivated (paralyzed) state from which it only slowly recovers after repolarization. This model would explain the failure, in skinned skeletal muscle fibers, to induce  $Ca^{2+}$ (paralyzed) state from which it only slowly recovers after log<br>repolarization. This model would explain the failure, in<br>skinned skeletal muscle fibers, to induce  $Ca^{2+}$  release<br>from the SR by depolarization of sealed-off repolarization. This model would explain the failure, in skinned skeletal muscle fibers, to induce  $Ca^{2+}$  release from the SR by depolarization of sealed-off transverse tubules after application of EGTA to their cytosoli skinned skeletal muscle fibers, to induce  $Ca^{2+}$  rele<br>from the SR by depolarization of sealed-off transve<br>tubules after application of EGTA to their cytosolic  $(401)$ . Since the membrane potential of these tubu<br>and, ther from the SR by depolarization of sealed-off transverse a<br>tubules after application of EGTA to their cytosolic side<br>(401). Since the membrane potential of these tubules than<br>and, therefore, their binding affinity for Ca<sup>2+</sup> tubules after application of EGTA to their cytosolic side (401). Since the membrane potential of these tubules and, therefore, their binding affinity for  $Ca^{2+}$  are presumably relatively low, it seems to be feasible that and, therefore, their binding affinity for  $Ca^{2+}$  are presum-<br>ably relatively low, it seems to be feasible that chelation<br>of dissociating  $Ca^{2+}$  by EGTA renders the potential<br>lisensor into a paralyzed state.<br>As to the n

ably relatively low, it seems to be feasible that chelation of dissociating  $Ca^{2+}$  by EGTA renders the potential lisensor into a paralyzed state.<br>As to the nature of the voltage sensors, the likelihood crists that they a of dissociating  $Ca^{2+}$  by EGTA renders the potential<br>sensor into a paralyzed state.<br>As to the nature of the voltage sensors, the likelihood<br>exists that they are identical with the high-affinity 1,4-<br>dihydropyridine bindi sensor into a paralyzed state.<br>
As to the nature of the voltage sensors, the likelihood<br>
exists that they are identical with the high-affinity 1,4-<br>
dihydropyridine binding sites (332a) which are abundant<br>
in skeletal tran As to the nature of the voltage sensors, the likelihood clo<br>exists that they are identical with the high-affinity  $1,4$ -<br>dihydropyridine binding sites (332a) which are abundant res<br>in skeletal transverse tubular membranes exists that they are identical with the high-affinity 1,4-<br>dihydropyridine binding sites (332a) which are abundant res<br>in skeletal transverse tubular membranes (47a). Al-<br>ca though most binding sites for the dihydropyridin dihydropyridine binding sites (332a) which are abundant<br>in skeletal transverse tubular membranes (47a). Al-<br>though most binding sites for the dihydropyridines are<br>not functional Ca channels (343a), it is possible that the<br> in skeletal transverse tubular membranes  $(47a)$ . Alcough most binding sites for the dihydropyridines are repond functional Ca channels  $(343a)$ , it is possible that the ible high-affinity receptors are channel-like prote though most binding sites for the dihydropyridines are not functional Ca channels (343a), it is possible that the high-affinity receptors are channel-like proteins that perform the voltage-sensing function and are coupled not functional Ca channels (343a), it is possible that the ible<br>high-affinity receptors are channel-like proteins that that<br>perform the voltage-sensing function and are coupled to spee<br>the calcium release channel by an unk high-affinity receptors are channel-like proteins that the perform the voltage-sensing function and are coupled to spite calcium release channel by an unknown mechanism. from the intact cell, the high-affinity binding depe perform the voltage-sensing function and are coupled to<br>the calcium release channel by an unknown mechanism.<br>In the intact cell, the high-affinity binding depends on<br>depolarization; negative potentials inhibit the binding<br> the calcium release channel by an unknown mechanism. frog s<br>In the intact cell, the high-affinity binding depends on pende<br>depolarization; negative potentials inhibit the binding tentia<br>(343a). Dihydropyridines in nanomola In the intact cell, the high-affinity binding depends on<br>depolarization; negative potentials inhibit the binding<br>(343a). Dihydropyridines in nanomolar concentrations<br>were found to inhibit charge movements and SR calcium<br>re depolarization; negative potentials inhibit the bindin<br>(343a). Dihydropyridines in nanomolar concentration<br>were found to inhibit charge movements and SR calciur<br>release in parallel (332a). The effect has a dependenc<br>on mem were found to inhibit charge movements and SR calcium<br>release in parallel (332a). The effect has a dependence<br>on membrane voltage analogous to that of specific bind-<br>ing of dihydropyridines. Since the blockade of sarcolemwere found to inhibit charge movements and SR calcium<br>release in parallel (332a). The effect has a dependence<br>on membrane voltage analogous to that of specific bind-<br>ing of dihydropyridines. Since the blockade of sarcolem release in parallel  $(332a)$ . The effect has a dependence mon membrane voltage analogous to that of specific bind-<br>ing of dihydropyridines. Since the blockade of sarcolem-S<br>mal calcium channels requires more than 100-fold on membrane voltage analogous to that of specific bind-<br>ing of dihydropyridines. Since the blockade of sarcolem-<br>mal calcium channels requires more than 100-fold higher<br>concentrations (see section III A),  $Ca^{2+}$  currents ing of dihydropyridines. Since the blockade of sarcolem<br>mal calcium channels requires more than 100-fold highe<br>concentrations (see section III A),  $Ca^{2+}$  currents through<br>the sarcolemma remain uninhibited at dihydropyrid mal calcium channels<br>concentrations (see set<br>the sarcolemma rema<br>concentrations high<br>affinity sites (343a).<br>The discovery that ncentrations (see section III A),  $Ca^{2+}$  currents through<br>e sarcolemma remain uninhibited at dihydropyridine<br>ncentrations high enough to bind nearly all high-<br>finity sites (343a).<br>The discovery that inositol 1,4,5-trisph the sarcolemma remain uninhibited at dihydropyridine heconcentrations high enough to bind nearly all high-<br>affinity sites (343a). com<br>The discovery that inositol 1,4,5-trisphosphate (InsP<sub>3</sub>) sm<br>mobilizes  $Ca^{2+}$  from the

ER<br>different cells including skinned muscles fibers (see, how<br>ever, ref. 274) led to the suggestion that  $\text{InsP}_3$  may b ereture the simulation of the suggestion that InsP<sub>3</sub> may be ever, ref. 274) led to the suggestion that InsP<sub>3</sub> may be the postulated chemical messenger for excitation-con-ER<br>different cells including skinned muscles fibers (see,<br>ever, ref. 274) led to the suggestion that  $InsP_3$  m<br>the postulated chemical messenger for excitation<br>traction coupling (400, 395). Interestingly, the abil different cells including skinned muscles fibers (see, how-<br>ever, ref. 274) led to the suggestion that  $\text{InsP}_3$  may be<br>the postulated chemical messenger for excitation-con-<br>traction coupling (400, 395). Interestingly, th different cells including skinned muscles fibers (see, how-<br>ever, ref. 274) led to the suggestion that  $\text{InsP}_3$  may be<br>the postulated chemical messenger for excitation-con-<br>traction coupling (400, 395). Interestingly, th ever, ref. 274) led to the suggestion that  $\text{InsP}_3$  may l<br>the postulated chemical messenger for excitation-co<br>traction coupling (400, 395). Interestingly, the ability<br>InsP<sub>3</sub> to release calcium from the endoplasmic retic the postulated chemical messenger for excitation-contraction coupling  $(400, 395)$ . Interestingly, the ability  $\text{InsP}_3$  to release calcium from the endoplasmic reticulur is unaffected by ruthenium red  $(25)$ , a very pot traction coupling (400, 395). Interestingly, the ability of  $\text{InsP}_3$  to release calcium from the endoplasmic reticulum is unaffected by ruthenium red (25), a very potent inhibitor of the  $\text{Ca}^{2+}$  release channels loca InsP<sub>3</sub> to release calcium from the endoplasmic reticulum<br>is unaffected by ruthenium red (25), a very potent inhib<br>itor of the Ca<sup>2+</sup> release channels localized in the junc<br>tional SR of both skeletal and cardiac muscle (1 is unaffected by ruthenium red (25), a very potent inhib-<br>itor of the Ca<sup>2+</sup> release channels localized in the junc-<br>tional SR of both skeletal and cardiac muscle (130, 307).<br>The hypothesis was tested by injection into in itor of the Ca<sup>2+</sup> release channels localized in the junctional SR of both skeletal and cardiac muscle (130, 307).<br>The hypothesis was tested by injection into intact skeletal muscle fibers of either  $\text{InsP}_3$  (36, 152) or tional SR of both skeletal and cardiac muscle (130, 307).<br>The hypothesis was tested by injection into intact skeletal muscle fibers of either  $\text{InsP}_3$  (36, 152) or heparin, an inhibitor of  $\text{InsP}_3$ -induced  $\text{Ca}^{2+}$ The hypothesis was tested by injection into intact skel-<br>etal muscle fibers of either  $\text{InsP}_3$  (36, 152) or heparin, an<br>inhibitor of  $\text{InsP}_3$ -induced  $\text{Ca}^{2+}$  release in smooth muscle<br>and nonmuscle cells (301). No co etal muscle fibers of either  $\text{InsP}_3$  (36, 152) or heparin, an inhibitor of  $\text{InsP}_3$ -induced  $\text{Ca}^{2+}$  release in smooth muscle and nonmuscle cells (301). No contraction was ever observed in an intact fiber, and there inhibitor of InsP<sub>3</sub>-induced Ca<sup>2+</sup> release in smooth mus<br>and nonmuscle cells (301). No contraction was e<br>observed in an intact fiber, and there was no rise<br>aequorin luminescence after injection of InsP<sub>3</sub>, when<br>injection and nonmuscle cells (301). No contraction was ever<br>observed in an intact fiber, and there was no rise in<br>aequorin luminescence after injection of  $InsP_3$ , whereas<br>injections of  $CaCl_2$  or caffeine produced obvious sarcom-<br> observed in an intact fiber, and there was no rise in a<br>equorin luminescence after injection of  $InsP_3$ , whereas<br>injections of  $CaCl_2$  or caffeine produced obvious sarcom-<br>ere shortening. High concentrations of heparin did aequorin luminescence after injection of InsP<sub>3</sub>, whereas<br>injections of CaCl<sub>2</sub> or caffeine produced obvious sarcom-<br>ere shortening. High concentrations of heparin did not<br>affect Ca<sup>2+</sup> release elicited by the normal acti injections of CaCl<sub>2</sub> or caffeine produced obvious sarcom-<br>ere shortening. High concentrations of heparin did not<br>affect Ca<sup>2+</sup> release elicited by the normal action potential<br>mechanism as monitored by both fura-2 and an affect  $Ca^{2+}$  release elicited by the normal action potential mechanism as monitored by both fura-2 and an intrinsic<br>birefringence signal. InsP<sub>3</sub>-induced releases of  $Ca^{2+}$  in<br>skinned skeletal muscle fibers which had b affect  $Ca^{2+}$  release elicited by the normal action potential mechanism as monitored by both fura-2 and an intrinsic birefringence signal. InsP<sub>3</sub>-induced releases of  $Ca^{2+}$  in skinned skeletal muscle fibers which had b mechanism as monitored by both fura-2 and an intrinsic<br>birefringence signal. Ins $P_3$ -induced releases of  $Ca^{2+}$  in<br>skinned skeletal muscle fibers which had been reported<br>previously by several investigators were explaine birefringence signal. Ins $P_3$ -induced releases of  $Ca^{2+}$ <br>skinned skeletal muscle fibers which had been report<br>previously by several investigators were explained<br>being induced by the depolarization of sealed-off<br>tubules skinned skeletal muscle fibers which had been report<br>previously by several investigators were explained<br>being induced by the depolarization of sealed-off<br>tubules (152). The results argue against a major phys<br>logical role previously by several investigators were ex<br>being induced by the depolarization of sea<br>tubules (152). The results argue against a ma<br>logical role of  $\text{InsP}_3$  as a chemical messenger<br>tion-contraction coupling in skeletal tubules (152). The results argue against a major physio-<br>logical role of  $\text{InsP}_3$  as a chemical messenger of excita-<br>tion-contraction coupling in skeletal muscle.<br>In the so-called mechanical hypothesis of Schneider<br>and C

In the so-called mechanical hypothesis of Schneider logical role of  $\text{InsP}_3$  as a chemical messenger of excitation-contraction coupling in skeletal muscle.<br>In the so-called mechanical hypothesis of Schneider<br>and Chandler (341), a voltage-dependent movement of<br>fixed electr tion-contraction coupling in skeletal muscle.<br>In the so-called mechanical hypothesis of Schneider<br>and Chandler (341), a voltage-dependent movement of<br>fixed electrical charges in the surface membrane provides<br>the means by w In the so-called mechanical hypothesis of Schneider<br>and Chandler (341), a voltage-dependent movement of<br>fixed electrical charges in the surface membrane provides<br>the means by which the potential across the wall of the<br>tubu and Chandler (341), a voltage-dependent movement of<br>fixed electrical charges in the surface membrane provides<br>the means by which the potential across the wall of the<br>tubular system is sensed by the junctional attachments<br>o fixed electrical charges in the surface membrane provides<br>the means by which the potential across the wall of the<br>tubular system is sensed by the junctional attachments<br>of the SR. In the extended model (78), the charge is<br> the means by which the potential across the wall of the tubular system is sensed by the junctional attachments of the SR. In the extended model (78), the charge is linked by a molecular entity to a calcium release channel tubular system is sensed by the junctional attachmen<br>of the SR. In the extended model (78), the charge<br>linked by a molecular entity to a calcium release chann<br>of the SR which thereby is mechanically opened (<br>closed, depend of the SR. In the extended model  $(78)$ , the charge is linked by a molecular entity to a calcium release channe of the SR which thereby is mechanically opened of closed, depending on the potential of the tubular membrane. linked by a molecular entity to a calcium release channel<br>of the SR which thereby is mechanically opened or<br>closed, depending on the potential of the tubular mem-<br>brane. The model is consistent with the physiological<br>resu of the SR which thereby is mechanically opened or closed, depending on the potential of the tubular membrane. The model is consistent with the physiological results that  $(a)$  depolarization of the tubular membrane can inc closed, depending on the potential of the tubular me<br>brane. The model is consistent with the physiolog<br>results that  $(a)$  depolarization of the tubular membra<br>can increase  $Ca^{2+}$  flux across the SR membrane, and<br>repolariz brane. The model is consistent with the physiological<br>results that (*a*) depolarization of the tubular membrane<br>can increase  $Ca^{2+}$  flux across the SR membrane, and (*b*)<br>repolarization can rapidly shut off  $Ca^{2+}$  relea can increase Ca<sup>2+</sup> flux across the SR membrane, and (b) repolarization can rapidly shut off Ca<sup>2+</sup> release. Compatible with the charge movement concept is the finding can increase  $Ca^{2+}$  flux across the SR membrane, and  $(b)$ <br>repolarization can rapidly shut off  $Ca^{2+}$  release. Compat-<br>ible with the charge movement concept is the finding<br>that the perchlorate anion at low concentrations repolarization can rapidly shut off  $Ca^{2+}$  release. Compatible with the charge movement concept is the finding that the perchlorate anion at low concentrations rather specifically improves excitation-contraction coupling ible with the charge movement concept is the finding<br>that the perchlorate anion at low concentrations rather<br>specifically improves excitation-contraction coupling of<br>frog skeletal muscle fibers by shifting the voltage de-<br> specifically improves excitation-contraction coupling of frog skeletal muscle fibers by shifting the voltage dependence of force activation towards more negative potentials parallel with the voltage dependence of intracelspecifically improves excitation-contraction coupling of<br>frog skeletal muscle fibers by shifting the voltage de-<br>pendence of force activation towards more negative po-<br>tentials parallel with the voltage dependence of intra frog skeletal muscle fibers by shifting the voltage d<br>pendence of force activation towards more negative p<br>tentials parallel with the voltage dependence of intract<br>lular charge movement (145, 246a). Likewise, the line<br>rela pendence of force activation towards more negative potentials parallel with the voltage dependence of intracel-<br>lular charge movement (145, 246a). Likewise, the linear<br>relation of the calcium release rate to the charge mov bentials paralier with the voltage dependence of intracen-<br>
lular charge movement (145, 246a). Likewise, the linear<br>
relation of the calcium release rate to the charge move-<br>
ment, which was observed in several investigati relation of the calcium release rate to the charge move-<br>ment, which was observed in several investigations (311a,<br>264, 332a, 61), points to a tight control of activation of<br>SR calcium release by intramembrane charge movem relation of the calcium release rate to the charge move-<br>ment, which was observed in several investigations (311a,<br>264, 332a, 61), points to a tight control of activation of<br>SR calcium release by intramembrane charge movem ment, which was observed in several investigations (311a, 264, 332a, 61), points to a tight control of activation of SR calcium release by intramembrane charge movement.<br>The hypothesis would be in accordance also with the 264, 332a, 61), points to a tight control of activation of SR calcium release by intramembrane charge movement.<br>The hypothesis would be in accordance also with the potential dependence, in both skeletal and mammalian heart SR calcium release by intramembrane charge movement.<br>The hypothesis would be in accordance also with the<br>potential dependence, in both skeletal and mammalian<br>heart muscle, of the calcium leakage from the junctional<br>SR at p The hypothesis would be in accordance also with the potential dependence, in both skeletal and mammalian heart muscle, of the calcium leakage from the junctional SR at potentials more negative than the threshold for contr potential dependence, in both skeletal and mammalian<br>heart muscle, of the calcium leakage from the junctional<br>SR at potentials more negative than the threshold for<br>contraction, where the rate of release is apparently<br>smal heart muscle, of the calcium leakage from the junctional SR at potentials more negative than the threshold for contraction, where the rate of release is apparently smaller than the rate of  $Ca^{2+}$  sequestration (see above

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CALCIUM MOBILIZATION AND CAF<br>has been found to be identical with the foot structure<br>between the junctional SR and the tubular membrane<br>(see following section IV D), the control of the opening CALCIUM MOBILIZATION AND CARD<br>has been found to be identical with the foot structure<br>between the junctional SR and the tubular membrane<br>39<br>state following section IV D), the control of the opening<br>state of the calcium rele has been found to be identical with the foot structue<br>between the junctional SR and the tubular membrar<br>(see following section IV D), the control of the openir<br>state of the calcium release channel by a conformation<br>change has been found to be identical with the foot structure loss<br>between the junctional SR and the tubular membrane 399<br>(see following section IV D), the control of the opening the<br>state of the calcium release channel by a con between the junctional SR and the tubular membrain (see following section IV D), the control of the opening state of the calcium release channel by a conformation change of a sarcolemmal membrane protein may not as remote (see following see<br>state of the calciu<br>change of a sarce<br>as remote as orig<br>dler et al. (78). *Change of a sarces*<br>*D. Ryanodine*<br>*D. Ryanodine*<br>The alkaloid

a result of its leakiness, lost its capability<br>a result of its leakiness, lost its capability<br>calcium load for the usual period of time.<br>te, as measured by the rate of loss of the eat,<br>it, is not diminished by  $Mg^{2+}$  (3 duer et al. (78).<br>D. Ryanodine<br>The alkaloid ryanodine has been found to alter the<br>function of skeletal and cardiac muscle in nanomolar<br>concentrations (187). This potent drug specifically inhib-D. Ryanodine<br>The alkaloid ryanodine has been found to alter the<br>function of skeletal and cardiac muscle in nanomolo<br>concentrations (187). This potent drug specifically inhibits<br>the early contraction component of cardiac mu The alkaloid ryanodine has been found to alter the my<br>function of skeletal and cardiac muscle in nanomolar can<br>concentrations (187). This potent drug specifically inhib-<br>its the early contraction component of cardiac muscl function of skeletal and cardiac muscle in nanomolar concentrations (187). This potent drug specifically inhibits the early contraction component of cardiac muscle (fig. 6), an effect that resembles that of increasing the its the early contraction component of cardiac muscle (fig. 6), an effect that resembles that of increasing the extracellular potassium concentration to 16 mmol/liter (fig. 5). This effect is documented in the contraction its the early contraction component of cardiac muscle (fig. 6), an effect that resembles that of increasing the from the extracellular potassium concentration to 16 mmol/liter rest of (fig. 5). This effect is documented i (fig. 6), an effect that resembles that of increasing the  $\frac{1}{10}$  restracellular potassium concentration to 16 mmol/liter (fig. 5). This effect is documented in the contraction retracings of a number of authors, althou extracellular potassium concentration to 16 mmol/liter (fig. 5). This effect is documented in the contraction tracings of a number of authors, although some of them did not especially mention it or described the effect as (fig. 5). This effect is documented in the contraction read-<br>tracings of a number of authors, although some of them showed did not especially mention it or described the effect as and<br>not being substantial (305, 394, 303, tracings of a number of authors, although some of them<br>did not especially mention it or described the effect as<br>an<br>not being substantial  $(305, 394, 303, 167, 377, 375, 207,$  dis<br> $268, 416, 26, 422, 248$ ). The effect has include increase in the extended in the view that, in mammalian cardiac different with the view that, in mammalian cardiac muscle, calcium release from the SR is indispensable for not being substantial  $(305, 394, 303, 167, 377, 375, 207, 0268, 416, 26, 422, 248)$ . The effect has been ascribed to a checrease in the extent of SR calcium release  $(374)$  which is consistent with the view that, in mamm 268, 416, 26, 422, 248). The effect has been ascribed to a decrease in the extent of SR calcium release (374) which is consistent with the view that, in mammalian cardiac muscle, calcium release from the SR is indispensabl decrease in the extent of SR calcium release (374) which state consistent with the view that, in mammalian cardiac frequencies. The muscle, calcium release from the SR is indispensable for van early contraction component. is consistent with the view that, in mammalian cardiac<br>muscle, calcium release from the SR is indispensable for<br>an early contraction component. A decrease of SR cal-<br>cium release might, in principle, be achieved by either muscle, calcium release from the SR is indispensable for ventricular muscle  $(355, 139, 149, 162, 160, 367)$ . That<br>an early contraction component. A decrease of SR cal-<br>cium leak from the SR results in a significant<br>cium an early contraction component. A decrease of SR calcium release might, in principle, be achieved by either of<br>two opposing mechanisms—by inhibition of calcium re-<br>lease from a filled store or by interference with the<br>clos cium release might, in principle, be achieved by either of two opposing mechanisms—by inhibition of calcium release from a filled store or by interference with the closing of the calcium release channels in the junctional two opposing mechanisms—by inhibition of calcium re-<br>lease from a filled store or by interference with the<br>closing of the calcium release channels in the junctional (3<br>SR. The latter would prevent the accumulation of callease from a filled store or by interference with the closing of the calcium release channels in the junctional SR. The latter would prevent the accumulation of calcium, so that there would be no calcium in the release sto closing of the calcium release channels in the junctional SR. The latter would prevent the accumulation of calcium, so that there would be no calcium in the release<br>store to be released. That the latter and not the former<br> cium, so that there would be no calcium in the release rat heart  $(178)$ .<br>store to be released. That the latter and not the former Calcium efflux from a heavy sarcotubular fraction of<br>mechanism is responsible for the loss cium, so that there would be no calcium in the release<br>store to be released. That the latter and not the former<br>mechanism is responsible for the loss of the early con-<br>traction component is evident from its dependence on<br>c store to be released. That the latter and not the former mechanism is responsible for the loss of the early contraction component is evident from its dependence on contraction frequency. The early component returns im-<br>med mechanism is responsible for the loss of the early con-<br>traction component is evident from its dependence on<br>contraction frequency. The early component returns im-<br>calcium release from a refilled<br>(fig. 6). This indicates t contraction frequency. The early component returns im-<br>mediately with a reduction of the stimulation interval<br>in red, an inhibitor of the calcium release channel, can be<br>(fig. 6). This indicates that calcium release from contraction frequency. The early component returns im-<br>mediately with a reduction of the stimulation interval<br>(fig. 6). This indicates that calcium release from a refilled bloc<br>store of the SR is not impaired by ryanodine; mediately with a reduction of the stimulation interval red (fig. 6). This indicates that calcium release from a refilled blestore of the SR is not impaired by ryanodine; rather the induction, as a result of its leakiness, store, as a result of its leakiness, lost its capability to in the "open state," so that the terminal cisternae remain<br>keep the calcium load for the usual period of time. The leaky to calcium (130). The inhibition constan store of the SR is not impaired by ryanodine; rather the store, as a result of its leakiness, lost its capability to keep the calcium load for the usual period of time. The leakage rate, as measured by the rate of loss of store, as a result of its leakiness, lost its capability to keep the calcium load for the usual period of time. The leakage rate, as measured by the rate of loss of the early component, is not diminished by  $Mg^{2+}$  (397) a result of its leakiness, lost is<br>a result of its leakiness, lost is<br>alcium load for the usual peri<br>te, as measured by the rate of<br>t, is not diminished by Mg<sup>2+</sup> (<br>a the effect of Mg<sup>2+</sup> on the pot



1 **nmot/I** Ryanodine

FIG. 6. Frequency-dependent effect of ryanodine on the early con-<br>traction component. Guinea pig papillary muscle in the presence of 3 traction component. Guinea pig papillary muscle in the early contraction component. Guinea pig papillary muscle in the presence of 3 mmol/liter of norepinephrine. Stimulation frequency, 0.2 Hz; test con-<br>traction after an FIG. 6. Frequency-dependent effect of ryanodine on the early contraction component. Guinea pig papillary muscle in the presence of 3  $\mu$ mol/liter of norepinephrine. Stimulation frequency, 0.2 Hz; test contraction after an

as remote as originally suggested in the model of Chan-<br>
to 12.4 mmol/liter intensified the response to ryanodine,<br>
thas been shown in suspensions of single rat cardiac<br>
The alkaloid ryanodine has been found to alter the<br> EXECT INCOURTED IN CONSIDER THE CONSIDER SOLUTION OF SURFERI (See section IV C and ref.<br>
1999) and is clear evidence that ryanodine does not affect<br>
the sarcolemmal voltage sensor but acts intracellularly EUIAC INOTROPIC MECHANISMS 203<br>
loss of the early component (see section IV C and ref.<br>
399) and is clear evidence that ryanodine does not affect<br>
the sarcolemmal voltage sensor but acts intracellularly<br>
at the junctional it was observed in early component (see section IV C and Tel.<br>399) and is clear evidence that ryanodine does not affect<br>the sarcolemmal voltage sensor but acts intracellularly<br>at the junctional SR. In accordance with these 399) and is clear evidence that ryanodine does not affect<br>the sarcolemmal voltage sensor but acts intracellularly<br>at the junctional SR. In accordance with these findings,<br>it was observed in early experiments on frog skelet the satotenmal voltage school out acts intractment<br>at the junctional SR. In accordance with these finding<br>it was observed in early experiments on frog skeleta<br>muscle (45) that an increase in potassium concentratio<br>to 12.4 it was observed in early experiments on frog skeletal to 12.4 mmol/liter intensified the response to ryanodine, muscle (45) that an increase in potassium concentration<br>to 12.4 mmol/liter intensified the response to ryanodine,<br>an effect which was antagonized by magnesium ions. And<br>it has been shown in suspensions of single rat cardi to 12.4 mmol/liter intensified the response to ryanodine,<br>an effect which was antagonized by magnesium ions. And<br>it has been shown in suspensions of single rat cardiac<br>myocytes by the fluorescent dye, quin-2, that ryanodi an enect which was antagonized by magnesiam fons. This it has been shown in suspensions of single rat cardiac myocytes by the fluorescent dye, quin-2, that ryanodine causes a slow discharge of  $Ca^{2+}$  from the SR into the

myocytes by the nuorescent tye, quin-2, that ryanodine<br>causes a slow discharge of  $Ca^{2+}$  from the SR into the<br>myoplasmic space (153).<br>The ryanodine-induced increase in calcium leakage<br>from the SR leads to an acceleration The ryanodine-induced increase in calcium leakage<br>from the SR leads to an acceleration of the decay during<br>rest of ventricular contractility which, accordingly,<br>reaches its rested state much earlier than normal as myoplasmic space (153).<br>The ryanodine-induced increase in calcium leakage<br>from the SR leads to an acceleration of the decay during<br>rest of ventricular contractility which, accordingly,<br>reaches its rested state much earlier The ryanodine-induced increase in calcium leakage<br>from the SR leads to an acceleration of the decay during<br>rest of ventricular contractility which, accordingly,<br>reaches its rested state much earlier than normal as<br>shown fo from the SR leads to an acceleration of the decay during<br>rest of ventricular contractility which, accordingly,<br>reaches its rested state much earlier than normal as<br>shown for papillary muscles of the rat  $(376)$ , rabbit  $($ rest of ventricular contracting which, accordingly,<br>reaches its rested state much earlier than normal as<br>shown for papillary muscles of the rat (376), rabbit (373),<br>and ferret (249). In atrial muscle, which is normally<br>di shown for papinary muscles of the rat (570), rabbit (570), and ferret (249). In atrial muscle, which is normally distinguished by a strong rested state contraction, low concentrations of ryanodine selectively reduce the s distinguished by a strong rested state contraction, low concentrations of ryanodine selectively reduce the strength of contraction at low frequencies, turning the frequency-force relationship into one resembling that of ve concentrations of ryanodine selectively reduce the strength of contraction at low frequencies, turning the frequency-force relationship into one resembling that of ventricular muscle (355, 139, 149, 162, 160, 367). That th strength of contraction at low frequencies, turning the<br>frequency-force relationship into one resembling that of<br>ventricular muscle (355, 139, 149, 162, 160, 367). That<br>the calcium leak from the SR results in a significant frequency-force relationship into one resembling that of ventricular muscle  $(355, 139, 149, 162, 160, 367)$ . That the calcium leak from the SR results in a significant increase in calcium efflux from the muscle has been ventricular muscle (355, 139, 149, 162, 160, 367). That<br>the calcium leak from the SR results in a significant<br>increase in calcium efflux from the muscle has been<br>observed in skeletal (29, 150) and smooth muscle (179)<br>and i the calcium leak from the SR results in a significant<br>increase in calcium efflux from the muscle has been<br>observed in skeletal (29, 150) and smooth muscle (179)<br>and in ventricular muscle of the dog (283) and rabbit<br>(27), a increase in calcium efflux from the muscle has been<br>observed in skeletal  $(29, 150)$  and smooth muscle  $(179)$ <br>and in ventricular muscle of the dog  $(283)$  and rabbit<br> $(27)$ , and in guinea-pig atria  $(136)$ . Ryanodine cau observed in skele<br>and in ventricula<br>(27), and in guine<br>depletion of a co<br>rat heart (178).<br>Calcium efflux d in ventricular muscle of the dog (283) and rabbit 7), and in guinea-pig atria (136). Ryanodine caused the pletion of a contraction-relevant calcium pool in the t heart (178).<br>Calcium efflux from a heavy sarcotubular frac

(27), and in guinea-pig atria (136). Ryanodine caused the depletion of a contraction-relevant calcium pool in the rat heart (178).<br>
Calcium efflux from a heavy sarcotubular fraction of skeletal muscle was stimulated by ry depletion of a contraction-relevant calcium pool in the<br>rat heart (178).<br>Calcium efflux from a heavy sarcotubular fraction of<br>skeletal muscle was stimulated by ryanodine, but that of<br>a light fraction was not (121). The enh rat heart (178).<br>
Calcium efflux from a heavy sarcotubular fraction of<br>
skeletal muscle was stimulated by ryanodine, but that of<br>
a light fraction was not (121). The enhancement of the<br>
calcium loading rate of terminal ci Calcium efflux from a heavy sarcotubular fraction of<br>skeletal muscle was stimulated by ryanodine, but that of<br>a light fraction was not (121). The enhancement of the<br>calcium loading rate of terminal cisternae by ruthenium<br>r skeletal muscle was stimulated by ryanodine, but that of<br>a light fraction was not (121). The enhancement of the<br>calcium loading rate of terminal cisternae by ruthenium<br>red, an inhibitor of the calcium release channel, can a light fraction was not (121). The enhancement of the calcium loading rate of terminal cisternae by ruthenium red, an inhibitor of the calcium release channel, can be blocked by the previous addition of ryanodine. This i calcium loading rate of terminal cisternae by ruthenium<br>red, an inhibitor of the calcium release channel, can be<br>blocked by the previous addition of ryanodine. This<br>indicates that the alkaloid locks the  $Ca^{2+}$  release ch red, an inhibitor of the calcium release channel, can be blocked by the previous addition of ryanodine. This indicates that the alkaloid locks the  $Ca^{2+}$  release channel in the "open state," so that the terminal cisterna blocked by the previous addition of ryanodine. This<br>indicates that the alkaloid locks the Ca<sup>2+</sup> release channel<br>in the "open state," so that the terminal cisternae remain<br>leaky to calcium (130). The inhibition constant i in the "open state," so that the terminal cisternae remain leaky to calcium (130). The inhibition constant is in the nanomolar range (20 to 180 nmol/liter; ref. 130) which corresponds to the dissociation constant of  $[^{3}H]$ ryano-<br>dine binding both in skeletal (130) and in cardia leaky to calcium (130). The inhibition constant is in the<br>nanomolar range (20 to 180 nmol/liter; ref. 130) which<br>corresponds to the dissociation constant of  $[{}^3H]$ ryano-<br>dine binding both in skeletal (130) and in cardia ranomolar range (20  $\omega$  100 mmol/mer, rer. 150/whicorresponds to the dissociation constant of  $[^{3}H]$ rya dine binding both in skeletal (130) and in cardiac must (307). Earlier studies had shown that the uptake of  $[^{r}$ ryanodine by rat atria exposed to nanomolar concentrations of the drug correlated with the effects on contraction (85). The binding studies localized the receptors on (307). Earlier studies had shown that the uptake of  $[^{3}H]$  ryanodine by rat atria exposed to nanomolar concentrations of the drug correlated with the effects on contraction (85). The binding studies localized the recept ryanodine by rat atria exposed to hanomolar concentra-<br>tions of the drug correlated with the effects on contrac-<br>tion (85). The binding studies localized the receptors on<br>the junctional and not on the longitudinal SR (130) tion (85). The binding studies localized the receptors on<br>the junctional and not on the longitudinal SR (130). The<br>ryanodine receptor has been purified from junctional<br>terminal cisternae of fast skeletal muscle SR and from the junctional and not on the longitudinal SR (130). The ryanodine receptor has been purified from junctional terminal cisternae of fast skeletal muscle SR and from cardiac SR (183, 183a). The affinity for the purified car ryanoame receptor has been purified from junctional<br>terminal cisternae of fast skeletal muscle SR and from<br>cardiac receptor was 4- to 5-fold higher than that of<br>skeletal muscle (183a). Electron microscopy of the puri-<br>fied cardiac SR (183, 183a). The affinity for the purified cardiac receptor was 4- to 5-fold higher than that of skeletal muscle (183a). Electron microscopy of the purified receptors showed square structures comparable in size skeletal muscle (183a). Electron microscopy of the puri-<br>fied receptors showed square structures comparable in<br>size and shape to the "feet" of junctional SR (336),<br>indicating that ryanodine binds directly to the foot struc size and shape to the "feet" of junctional SR (336).

204<br>"feet" of about 2. These findings suggest that the ryan<br>dine receptor and Ca<sup>2+</sup> release channel represent a fur R<br>
"feet" of about 2. These findings suggest that the ryano<br>
dine receptor and Ca<sup>2+</sup> release channel represent a func<br>
tional unit, the structural unit being the foot structur REITI<br>
"feet" of about 2. These findings suggest that the ryano-<br>
dine receptor and Ca<sup>2+</sup> release channel represent a func-<br>
tional unit, the structural unit being the foot structure<br>
which, in situ, is junctionally assoc "feet" of about 2. These findings suggest that the ryandine receptor and  $Ca^{2+}$  release channel represent a funtional unit, the structural unit being the foot structure which, in situ, is junctionally associated with the "feet" of about 2. These findings suggest that the ryano-<br>dine receptor and  $Ca^{2+}$  release channel represent a func-<br>tional unit, the structural unit being the foot structure<br>which, in situ, is junctionally associated wi dional unit, the structural unit being the foot structure fract<br>which, in situ, is junctionally associated with the trans-<br>prep<br>verse tubules (183). According to some studies (191, 192, long<br>347, 263, 278), the effect of r which, in situ, is junctionally associated with the trans-<br>werse tubules (183). According to some studies (191, 192, lon<br>347, 263, 278), the effect of ryanodine on the calcium unc<br>channels of isolated junctional SR is rev verse tubules (183). According to some studies (191, 192, 1847, 263, 278), the effect of ryanodine on the calcium unchannels of isolated junctional SR is reversed at ryanophine concentrations four orders of magnitude high 347, 263, 278), the effect of ryanodine on the calcium unchannels of isolated junctional SR is reversed at ryano-<br>dine concentrations four orders of magnitude higher (100 c:<br>to 300  $\mu$ mol/liter) than the dissociation con channels of isolated junctional SR is reversed at ryano-<br>dine concentrations four orders of magnitude higher (100 card<br>to 300  $\mu$ mol/liter) than the dissociation constant for strat<br>specific binding, and there it resemble dine concentrations four orders of magnitude higher (1 to 300  $\mu$ mol/liter) than the dissociation constant is<br>specific binding, and there it resembles the more speci<br>inhibitory effect of 0.08 to 0.5  $\mu$ mol/liter of ruth to 300  $\mu$ mol/liter) than the dissociation constans pecific binding, and there it resembles the more sp<br>inhibitory effect of 0.08 to 0.5  $\mu$ mol/liter of ruthered (347, 77, 263, 278). At high concentrations of ry<br>dine, t specific binding, and there it resembles the more specific<br>inhibitory effect of 0.08 to 0.5  $\mu$ mol/liter of ruthenium<br>red (347, 77, 263, 278). At high concentrations of ryano-<br>dine, the paradoxical effect of the drug on the minimal ory effect of 0.08 to 0.3  $\mu$ mol/liter of ruthermum<br>red (347, 77, 263, 278). At high concentrations of ryano-<br>dine, the paradoxical effect of the drug on ATP-depend-<br>ent calcium accumulation by isolated SR ve dine, the paradoxical effect of the drug on ATP-dependent calcium accumulation by isolated SR vesicles is determined in part by the experimental environment (235).<br>Ryanodine was found to be ineffective in cardiac mus-

des from summer to the drug of ATT-dependent calcium accumulation by isolated SR vesicles is de-<br>termined in part by the experimental environment (235). When Ryanodine was found to be ineffective in cardiac mus-<br>cles from rammed in part by the experimental environment (255<br>Ryanodine was found to be ineffective in cardiac muscles from summer toads, from fetal mammalian heart<br>(human, cat, rabbit), and from newborn kittens an<br>rabbits. The char be interestive in catual mus-<br>cles from summer toads, from fetal mammalian hearts r.<br>(human, cat, rabbit), and from newborn kittens and P<br>rabbits. The characteristic adult sensitivity to the alka-<br>cloid appears within a fe the transverse tubular system includes the transverse tubular system (human, cat, rabbit), and from newborn kittens and rabbits. The characteristic adult sensitivity to the alk loid appears within a few days after birth at (numan, cat, rabolt), and from hewborn kittens and<br>rabbits. The characteristic adult sensitivity to the alk<br>loid appears within a few days after birth at the san<br>time as the transverse tubular system (T-system) deve<br>ops (3 rabolis. The characteristic addit sensitivity to the all<br>loid appears within a few days after birth at the satime as the transverse tubular system (T-system) de<br>ops (303). Since, in accompanying studies of the ultructure time as the transverse tubular system (T-system) devel-<br>time as the transverse tubular system (T-system) devel-<br>ops (303). Since, in accompanying studies of the ultra-<br>structure by electron microscopy, an apparent evagina ops (303). Since, in accompanying studies of the ultra-<br>structure by electron microscopy, an apparent evagina-<br>tion of the sarcolemma at the level of the Z lines was<br>found, it was suggested that ryanodine acts in adult ops (303). Since, in accompanying studies of the ultra-<br>structure by electron microscopy, an apparent evagina-<br>tion of the sarcolemma at the level of the Z lines was<br>found, it was suggested that ryanodine acts in adult<br>mam structure by electron microscopy, an apparent evagire<br>tion of the sarcolemma at the level of the Z lines w<br>found, it was suggested that ryanodine acts in ad<br>mammalian heart muscle by dissociating the T tubui<br>from the sarco tion of the sarcolemma at the level of the Z lines was<br>found, it was suggested that ryanodine acts in adult to p<br>mammalian heart muscle by dissociating the T tubules dine<br>from the sarcoplasmic reticulum system and thus un the ultrastructure could not be reproduced in a later<br>from the sarcoplasmic reticulum system and thus uncou-<br>pling excitation from contraction (304). These effects on<br>the ultrastructure could not be reproduced in a later<br>s from the sarcoplasmic reticulum system and thus uncoupling excitation from contraction  $(304)$ . These effects on before the ultrastructure could not be reproduced in a later study in which ryanodine-treated muscles were f pung excitation non contraction (504). These enects on<br>the ultrastructure could not be reproduced in a later<br>study in which ryanodine-treated muscles were found in<br>electron micrographs to show normal T tubules and an<br>unalt electron micrographs to show normal 1 tubules and an<br>unaltered morphology of the couplings between the sar-<br>colemma and the SR (167, 148). The previously published<br>observations were explained as artifacts arising from<br>musc unattered morphology of the couplings between the sar-<br>colemma and the SR (167, 148). The previously published<br>observations were explained as artifacts arising from<br>muscle contracture during the fixation process (148).<br>Ne observations were explained as artifacts arising from<br>muscle contracture during the fixation process (148).<br>Nevertheless, the specific binding of ryanodine to and<br>actions on the foot structures of the calcium release<br>compa muscle contracture during the insation process (146).<br>Nevertheless, the specific binding of ryanodine to and<br>actions on the foot structures of the calcium release<br>compartments associated with the transverse tubules<br>might f separation. tions on the foot structures of the calcium release<br>mpartments associated with the transverse tubules<br>ight facilitate an artificial contracture-induced spatial<br>paration.<br>On the basis of experiments with bundles of myofibri

comparations associated with the transverse thouses<br>might facilitate an artificial contracture-induced spatial<br>separation.<br>On the basis of experiments with bundles of myofibrils<br>containing sarcoplasmic reticulum around eac exparation.<br>
The basis of experiments with bundles of myofibrils<br>
containing sarcoplasmic reticulum around each myofibril<br>
as obtained by microdissection of cardiac cells, it was<br>
postulated that ryanodine, instead of prom For the basis of experiments with bundles of myofibrils<br>
containing sarcoplasmic reticulum around each myofibril<br>
as obtained by microdissection of cardiac cells, it was<br>
postulated that ryanodine, instead of promoting ca On the basis of experiments with bundles of myofibrils<br>containing sarcoplasmic reticulum around each myofibril<br>as obtained by microdissection of cardiac cells, it was<br>postulated that ryanodine, instead of promoting calciu as obtained by microdissection of cardiac cens, it was<br>postulated that ryanodine, instead of promoting calcium<br>release, inhibits calcium release from the SR (117). It<br>was observed in these experiments that ryanodine in<br>mil traction traces of the bundles). From the SN (117). It is was observed in these experiments that ryanodine in millimolar concentrations did not uniformly influence difference induced calcium release (as judged from content millimolar concentrations did not uniformly influer<br>caffeine-induced calcium release (as judged from corraction traces of the bundles). From this is was deduced<br>that ryanodine does not decrease the calcium content<br>the SR a calculate calculum release (as judged from con-<br>traction traces of the bundles). From this is was deduced further<br>the SR and that, therefore, a ryanodine-induced depres-<br>sion of calcium release from the SR could not be the the SR and that, therefore, a ryanodine-induced depresion of calcium release from the SR could not be tonsequence of an impairment of calcium accumulatify the SR. However, whereas the ryanodine-sensitive calcium channels a the SR and that, therefore, a ryanodine-induced depres-<br>sion of calcium release from the SR could not be the IBMX<br>consequence of an impairment of calcium accumulation line)<br>by the SR. However, whereas the ryanodine-sensit sion of calcium release from the SK could not be the<br>consequence of an impairment of calcium accumulation<br>by the SR. However, whereas the ryanodine-sensitive<br>calcium channels are restricted to the junctional SR es<br>(130),

ER<br>found by various authors (270, 370) to reside not only in<br>the heavy (junctional) but also in the lighter vesicular ER<br>found by various authors (270, 370) to reside not only in<br>the heavy (junctional) but also in the lighter vesicular<br>fractions of the SR. Although the skinned cardiac cell ER<br>found by various authors (270, 370) to reside not only in<br>the heavy (junctional) but also in the lighter vesicular<br>fractions of the SR. Although the skinned cardiac cell<br>preparations seem to contain a considerable quant found by various authors (270, 370) to reside not only in<br>the heavy (junctional) but also in the lighter vesicular<br>fractions of the SR. Although the skinned cardiac cell<br>preparations seem to contain a considerable quantity lound by various authors  $(270, 570)$  to reside not only in<br>the heavy (junctional) but also in the lighter vesicular<br>fractions of the SR. Although the skinned cardiac cell<br>preparations seem to contain a considerable quant the heavy (junctional) but also in the lighter vesicular<br>fractions of the SR. Although the skinned cardiac cell<br>preparations seem to contain a considerable quantity of<br>longitudinal (free) SR surrounding the myofibrils, it fractions of the SR. Although the skinned cardiac cell<br>preparations seem to contain a considerable quantity of<br>longitudinal (free) SR surrounding the myofibrils, it is<br>uncertain how much junctional SR survives the skinning preparations seem to contain a considerable quantity<br>longitudinal (free) SR surrounding the myofibrils, it<br>uncertain how much junctional SR survives the skinni<br>procedure (116, 117). Therefore, whereas the skinn<br>cardiac cel strational strational SR surveys the skinning<br>uncertain how much junctional SR survives the skinning<br>procedure (116, 117). Therefore, whereas the skinned<br>cardiac cell preparation may be useful for the demon-<br>stration of ca uncertain now much junctional SN survives the skinning<br>procedure (116, 117). Therefore, whereas the skinned<br>cardiac cell preparation may be useful for the demon-<br>stration of caffeine-induced calcium release from the<br>longit procedure (110, 117). Therefore, whereas the skill cardiac cell preparation may be useful for the demonstration of caffeine-induced calcium release from the longitudinal parts of the SR, its usefulness for the studiof calc tionable. ration of caffeine-induced calcium release from the ngitudinal parts of the SR, its usefulness for the study calcium release from junctional release stores is ques-<br>nable.<br>In view of the highly specific effect of ryanodine

study in which ryanodine-treated muscles were found in<br>electron micrographs to show normal T tubules and an<br>unaltered morphology of the couplings between the sar-<br>colemma and the SR (167, 148). The previously published<br>ob the calcium release from junctional release stores is questionable.<br>In view of the highly specific effect of ryanodine on<br>the calcium channels of the junctional SR, one wonders<br>whether the alkaloid also affects the calcium or calcium release from junctional release stores is ques-<br>tionable.<br>In view of the highly specific effect of ryanodine on<br>the calcium channels of the junctional SR, one wonders<br>whether the alkaloid also affects the calciu In view of the highly specific effect of ryanodine on<br>the calcium channels of the junctional SR, one wonders<br>whether the alkaloid also affects the calcium channels of<br>the sarcolemma. In a careful study on the effect of<br>rya the calcium channels of the junctional SR, one wonders<br>whether the alkaloid also affects the calcium channels of<br>the sarcolemma. In a careful study on the effect of<br>ryanodine on the contractile performance of guinea pig<br>p whether the alkaloid also affects the calcium channels of<br>the sarcolemma. In a careful study on the effect of<br>ryanodine on the contractile performance of guinea pig<br>papillary muscles, it was found that, in a rather high<br>co the sarcolennia. In a careful study on the effect of<br>ryanodine on the contractile performance of guinea pig<br>papillary muscles, it was found that, in a rather high<br>concentration (2  $\mu$ mol/liter), the alkaloid exerts a bipapillary muscles, it was found that, in a rather high concentration (2  $\mu$ mol/liter), the alkaloid exerts a biphasic effect (148). Immediately after the addition of the substance, the contraction force declined as a res the loss of the early contraction component. However, after 4 min, the force of the remaining late component concentration  $(2 \mu \text{mol/mer})$ , the anxiold exerts a biphasic effect (148). Immediately after the addition of the substance, the contraction force declined as a result of the loss of the early contraction component. However phasic effect (148). Immediately after the addition of the<br>substance, the contraction force declined as a result of<br>the loss of the early contraction component. However,<br>after 4 min, the force of the remaining late compone substance, the contraction force decimed as a result<br>the loss of the early contraction component. Howev<br>after 4 min, the force of the remaining late compone<br>began to increase, with a continuous increase of the ti<br>to peak f the foss of the early contraction component. However,<br>after 4 min, the force of the remaining late component<br>began to increase, with a continuous increase of the time<br>to peak force until, 50 min after the addition of ryano after 4 min, the force of the remaining late component began to increase, with a continuous increase of the tim<br>to peak force until, 50 min after the addition of ryand<br>dine, the force that developed in the late component c began w increase, with a continuous increase of the time<br>to peak force until, 50 min after the addition of ryano-<br>dine, the force that developed in the late component of<br>contraction was equal to that of the early component been made by others on cardiac muscle of the cat and contraction was equal to that of the early component before addition of the drug. Similar observations have been made by others on cardiac muscle of the cat and dog (281 contraction was equal to that of the early component<br>before addition of the drug. Similar observations have<br>been made by others on cardiac muscle of the cat and<br>dog (281, 377, 207). The transmembrane action potential<br>was been made by others on cardiac muscle of the cat and been made by others on cardiac muscle of the cat and<br>dog (281, 377, 207). The transmembrane action potential<br>was found to be prolonged (14); the "slow" potential at<br>24 mmol/liter of K<sup>+</sup> was also prolonged, and its veloci dog (281, 377, 207). The transmembrane action potential<br>was found to be prolonged (14); the "slow" potential at<br>24 mmol/liter of  $K^+$  was also prolonged, and its velocity<br>of depolarization was slightly increased (148, 33 was round to be prolonged (14); the "slow" potential at  $24 \text{ mmol/liter}$  of  $K^+$  was also prolonged, and its velocity of depolarization was slightly increased (148, 339). A prolongation of the calcium current was also obtain or depolarization was slightly increased (148, 339). A prolongation of the calcium current was also obtained in rat ventricular muscle cells (267). However, in cesium-<br>dialyzed guinea pig ventricular myocytes the amplitud prolongation of the calcium current was also obtained<br>rat ventricular muscle cells  $(267)$ . However, in cesiu<br>dialyzed guinea pig ventricular myocytes the amplitu<br>time course, and voltage dependence of  $I_{Ca}$  were a<br>affec rat ventricular muscle cells (207). However, in cesium-<br>dialyzed guinea pig ventricular myocytes the amplitude,<br>time course, and voltage dependence of  $I_{Ca}$  were not<br>affected by ryanodine (290). This indicates that ryano time course, and voltage dependence of  $I_{Ca}$  were not affected by ryanodine (290). This indicates that ryano-<br>dine has no direct influence on the sarcolemmal calcium time course, and voltage dependence of  $L_{Ca}$  were not affected by ryanodine (290). This indicates that ryano-<br>dine has no direct influence on the sarcolemmal calcium<br>channel and that the observed prolongation of the calchannel and that the observed prolongation of the calcium current (with the effect on the late contraction peak) is probably the consequence of the lack of an early increase in cytosolic calcium concentration and its influ enannel and that the observed prolongation of<br>cium current (with the effect on the late con<br>peak) is probably the consequence of the lack of<br>increase in cytosolic calcium concentration and i<br>ence on the ionic conductance o **peak**) is probably the consequence of the lack of an early<br>increase in cytosolic calcium concentration and its influ-<br>ence on the ionic conductance of the sarcolemma.<br>*E. Caffeine*<br>Caffeine has, besides its inhibiting act crease in cytosolic calcium concentration and its in<br>ce on the ionic conductance of the sarcolemma.<br>Caffeine has, besides its inhibiting action on phosphoterase (section III C 3), a special effect on the Sl

ence on the ionic conductance of the sarcolemma.<br>
E. Caffeine<br>
Caffeine has, besides its inhibiting action on phospho-<br>
diesterase (section III C 3), a special effect on the SR of<br>
skeletal and cardiac muscle which is inde E. Caffeine<br>Caffeine has, besides its inhibiting action on phospho-<br>diesterase (section III C 3), a special effect on the SR of<br>skeletal and cardiac muscle which is independent of and<br>functionally antagonistic to that of c Caffeine has, besides its inhibiting action on phospho-<br>diesterase (section III C 3), a special effect on the SR of<br>skeletal and cardiac muscle which is independent of and<br>functionally antagonistic to that of cyclic AMP. Carreine has, besides its inhibiting action on phospho-<br>diesterase (section III C 3), a special effect on the SR of<br>skeletal and cardiac muscle which is independent of and<br>functionally antagonistic to that of cyclic AMP. F difference (section III C 3), a special effect on the SK of<br>skeletal and cardiac muscle which is independent of and<br>functionally antagonistic to that of cyclic AMP. From<br>the standpoint of the positive inotropic action of a Skeletal and cardiac muscle which is independent of<br>functionally antagonistic to that of cyclic AMP. F<br>the standpoint of the positive inotropic action of a<br>(selectively acting) phosphodiesterase inhibitor<br>IBMX; this second Innetionally antagonistic to that of cyclic AMP. From<br>the standpoint of the positive inotropic action of a pure<br>(selectively acting) phosphodiesterase inhibitor like<br>IBMX; this second action of caffeine (and of theophyl-<br>l the standpoint of the positive inotropic action of a<br>(selectively acting) phosphodiesterase inhibitor<br>IBMX; this second action of caffeine (and of theor<br>line) is an unsought side effect which occurs in<br>millimolar concentra (selectively acting) phosphodiesterase inhibitor like<br>IBMX; this second action of caffeine (and of theophyl-<br>line) is an unsought side effect which occurs in the<br>millimolar concentration range, whereas the phosphodi-<br>ester

**a**spet

CALCIUM MOBILIZATION AND CARDIAC INOTROPIC MECHANISMS<br>Studies on the effects of caffeine on ATPase activity, the observation that the supprealcium transport (404), and calcium accumulation of traction component of an intac CALCIUM MOBILIZATION AND CARD<br>Studies on the effects of caffeine on ATPase activity, the<br>calcium transport (404), and calcium accumulation of the SR isolated from skeletal muscle (406, 199) suggest by CALCIUM MOBILIZATION AND CA<br>Studies on the effects of caffeine on ATPase activity,<br>calcium transport (404), and calcium accumulation of<br>the SR isolated from skeletal muscle (406, 199) suggest<br>that caffeine acts by increasi Studies on the effects of caffeine on ATPase activity, the calcium transport (404), and calcium accumulation of trease. The SR isolated from skeletal muscle (406, 199) suggest by that caffeine acts by increasing the permea Studies on the effects of caffeine on ATPase activity, the calcium transport  $(404)$ , and calcium accumulation of the SR isolated from skeletal muscle  $(406, 199)$  suggest behat caffeine acts by increasing the permeabilit calcium transport  $(404)$ , and calcium accumulation of the SR isolated from skeletal muscle  $(406, 199)$  suggest be that caffeine acts by increasing the permeability of the sSR membrane to calcium  $(199)$ . The increased l the SR isolated from skeletal muscle (406, 199) suggest by<br>that caffeine acts by increasing the permeability of the<br>SR membrane to calcium (199). The increased leakage from<br>of calcium from the SR is modulated by the relati that caffeine acts by increasing the permeability of the s-<br>SR membrane to calcium (199). The increased leakage five of calcium from the SR is modulated by the relative b-<br>internal and external calcium concentrations (198 SR membrane to calcium (199). The increased leakage fro<br>of calcium from the SR is modulated by the relative by<br>internal and external calcium concentrations (198). The<br>entire surface of the SR must be involved, since speci internal and external calcium concentrations (198). The The entire surface of the SR must be involved, since specific state of caffeine-sensitive Ca<sup>2+</sup> gates have been found not only the SI in the heavy (junctional) SR, caffeine-sensitive  $Ca^{2+}$  gates have been found not only<br>in the heavy (junctional) SR, but also in the lighter<br>vesicular fractions of the free or longitudinal SR<br>(270, 370). The effects of caffeine on ATPase activity and

in the heavy (junctional) SR, but also in the lighter tivesicular fractions of the free or longitudinal SR p (270, 370). fither free studied in SR vesicles from cardiac nuscle of guinea pigs (284), rats (284), and rabbits vesicular fractions of the free or longitudinal SR<br>(270, 370).<br>The effects of caffeine on ATPase activity and calcium<br>uptake have been studied in SR vesicles from cardiac<br>muscle of guinea pigs (284), rats (284), and rabbit (270, 370). Fig. 16<br>
The effects of caffeine on ATPase activity and calcium ent in<br>
uptake have been studied in SR vesicles from cardiac no rel<br>
muscle of guinea pigs (284), rats (284), and rabbits (35). state<br>
In all spe The effects of caffeine on ATPase activity and calcium<br>uptake have been studied in SR vesicles from cardiac<br>muscle of guinea pigs (284), rats (284), and rabbits (35).<br>In all species it was found that caffeine impaired calc uptake have been studied in SR vesicles from card<br>muscle of guinea pigs  $(284)$ , rats  $(284)$ , and rabbits  $(3)$ <br>In all species it was found that caffeine impaired calci<br>accumulation by isolated SR vesicles, but paradoxic muscle of guinea pigs (284), rats (284), and rabbits (35).<br>In all species it was found that caffeine impaired calcium<br>accumulation by isolated SR vesicles, but paradoxically<br>it could increase the rate constant for calcium In all species it was found that caffeine impaired calcium is accumulation by isolated SR vesicles, but paradoxically lest it could increase the rate constant for calcium accumulation and the  $Ca^{2+}$ -activated ATPase acti accumulation by isolated SR vesicles, but paradoxically leaft to culd increase the rate constant for calcium accumulation and the  $Ca^{2+}$ -activated ATPase activity (35). It ulambibited calcium accumulation to a greater ex it could increase the rate constant for calcium accunduction and the Ca<sup>2+</sup>-activated ATPase activity (35).<br>inhibited calcium accumulation to a greater extent whexternal (cytosolic) calcium concentration was low, a<br>to a sm lation and the  $Ca^{2+}$ -activated ATPase activity (35). It<br>inhibited calcium accumulation to a greater extent when<br>external (cytosolic) calcium concentration was low, and<br>to a smaller extent if the internal free calcium co immoted caffelin accumulation to a greater extent when most<br>external (cytosolic) calcium concentration was low, and tract<br>to a smaller extent if the internal free calcium concen-<br>tration of the SR was kept low by oxalate. to a smaller extent if the internal free calcium concentration of the SR was kept low by oxalate. These findings (imply that caffeine increases the passive efflux of calcium the SR vesicles when the outward gradient is hig tration of the SR was kept low by oxalate. These findings (46)<br>imply that caffeine increases the passive efflux of calcium thro<br>from the SR vesicles when the outward gradient is high by c<br>and thus that caffeine also acts i imply that caffeine increases the passive efflux of calcium the from the SR vesicles when the outward gradient is high by and thus that caffeine also acts in mammalian cardiac calcium (35). Functional evidence for an incr from the SR vesicles when the outward gradient is high b and thus that caffeine also acts in mammalian cardiac comuscle by making the SR membrane more permeable to is calcium (35). Functional evidence for an increased rate and thus that caffeine also acts in mammalian cardiac muscle by making the SR membrane more permeable to calcium (35). Functional evidence for an increased rate of release of activator calcium from the SR was obtained in i muscle by making the SR membrane more permeable to<br>calcium (35). Functional evidence for an increased rate<br>of release of activator calcium from the SR was obtained<br>in intact ventricular muscle preparations of various (<br>mam calcium (35). Functional evidence for an increased range of release of activator calcium from the SR was obtain<br>in intact ventricular muscle preparations of vario-<br>mammalian species (81) and in skinned canine cardi<br>Purkinj of release of activator calcium from the SR was obtained a<br>in intact ventricular muscle preparations of various (2<br>mammalian species (81) and in skinned canine cardiac la<br>Purkinje cells (115). The effect resembles that of in intact ventricular muscle preparations of various  $(296)$ .<br>mammalian species (81) and in skinned canine cardiac lation<br>Purkinje cells (115). The effect resembles that of ryano-<br>dine (see section IV D) in that it leads mammalian species (81) and in skinned canine cardiac<br>Purkinje cells (115). The effect resembles that of ryano-<br>dine (see section IV D) in that it leads to an increase of<br>the spontaneous rate of calcium leakage from the SR<br> dine (see section IV D) in that it leads to an increase of caffeine consists predominantly of an increase in calcium<br>the spontaneous rate of calcium leakage from the SR influx through the sarcolemma (205, 288).<br>with an acc dine (see section IV D) in that it leads to an increase of<br>the spontaneous rate of calcium leakage from the SR<br>with an accompanying reduction of the calcium content<br>of the release compartments and, consequently, to a<br>dimin the spontaneous rate of calcium leakage from the SR in with an accompanying reduction of the calcium content of the release compartments and, consequently, to a the diminution or total suppression of the early contraction with an accompanying reduction of the calcium content<br>of the release compartments and, consequently, to a<br>diminution or total suppression of the early contraction<br>component (40, 157, 218, 46). For the increased loss of va of the release compartments and, consequently, to a diminution or total suppression of the early contraction component (40, 157, 218, 46). For the increased loss of calcium from the release compartments of the SR, it is a diminution or total suppression of the early contraction<br>component (40, 157, 218, 46). For the increased loss of<br>calcium from the release compartments of the SR, it is<br>apparently unimportant whether calcium leaks (as unde component (40, 157, 218, 46). For the increased loss of valuation from the release compartments of the SR, it is cively apparently unimportant whether calcium leaks (as under op the influence of ryanodine) through the spe calcium from the release compartments of the SR, it is c<br>apparently unimportant whether calcium leaks (as under of<br>the influence of ryanodine) through the specific  $Ca^{2+}$  la<br>release channels at the foot structures connec apparently unimportant whether calcium leaks (as under or<br>the influence of ryanodine) through the specific  $Ca^{2+}$ <br>release channels at the foot structures connecting the b<br>junctional SR with the sarcolemma or through spec the influence of ryanodine) through the specific  $Ca^{2+}$ <br>release channels at the foot structures connecting the<br>junctional SR with the sarcolemma or through specific<br>caffeine-sensitive  $Ca^{2+}$  gates distributed over the e release channels at the foot structures connecting the junctional SR with the sarcolemma or through specific caffeine-sensitive Ca<sup>2+</sup> gates distributed over the entire SR. However, this difference becomes noticeable if, u SR. However, this difference becomes noticeable if, under high calcium loading conditions, spontaneous mechanical oscillations occur in unstimulated cardiac muscle preparations. The frequency of these oscillations, which a SR. However, this difference becomes noticeable if, un-<br>der high calcium loading conditions, spontaneous me-<br>chanical oscillations occur in unstimulated cardiac mus-<br>guinea<br>cle preparations. The frequency of these oscillat der high calcium loading conditions, spontaneous mechanical oscillations occur in unstimulated cardiac mus-<br>cle preparations. The frequency of these oscillations,<br>which are caused by spontaneous calcium release from<br>the SR cle preparations occur in unstimulated cafuat mus-<br>cle preparations. The frequency of these oscillations,<br>which are caused by spontaneous calcium release from<br>the SR (section IV B), is decreased by ryanodine, whereas<br>it is which are caused by spontaneous calcium release from and<br>the SR (section IV B), is decreased by ryanodine, whereas lari<br>it is increased by caffeine (230; see section IV B 3). The the<br>increased frequency of spontaneous cycl the SR (section IV B), is decreased by ryanodine, where it is increased by caffeine (230; see section IV B 3).<br>
increased frequency of spontaneous cyclic contractions found, in skinned guinea pig cardiac fibers, to prevent it is increased by caffeine (230; see section IV B 3). The the m<br>increased frequency of spontaneous cyclic contractions The a<br>was found, in skinned guinea pig cardiac fibers, to be lowest<br>prevented by procaine (209). This increased frequency of spontaneous cyclic contractions The<br>was found, in skinned guinea pig cardiac fibers, to be low<br>prevented by procaine (209). This points to procaine-<br>material entagonism at the caffeine-sensitive calc

the observation that the suppression of the early contraction component of an intact kitten papillary muscle the component of an intact kitten papillary contraction component of an intact kitten papillary muscle<br>by caffeine was antagonized by procaine (40). The rever-BUAC INOTROPIC MECHANISMS 20<br>the observation that the suppression of the early contraction component of an intact kitten papillary musc<br>by caffeine was antagonized by procaine (40). The rever-<br>sal by procaine of the caffei the observation that the suppression of the early contraction component of an intact kitten papillary muscle by caffeine was antagonized by procaine (40). The reversal by procaine of the caffeine-induced release of calcium traction component of an in<br>by caffeine was antagonized<br>sal by procaine of the caffeir<br>from the SR of skeletal mus<br>by Weber and Herz (406).<br>The action of caffeine an sal by procaine of the caffeine-induced release of calcium<br>from the SR of skeletal muscle had been reported earlier<br>by Weber and Herz (406).<br>The action of caffeine and theophylline under rested from the SR of skeletal muscle had been reported earlier

caffeine-sensitive Ca<sup>2+</sup> gates have been found not only the SR. The action consists of a late-appearing contrac-<br>in the heavy (junctional) SR, but also in the lighter tion peak (fig. 5 of ref. 40; 24) which resembles tha state conditions is virtually uninfluenced by an effect on by Weber and Herz (406).<br>The action of caffeine and theophylline under rested<br>state conditions is virtually uninfluenced by an effect on<br>the SR. The action consists of a late-appearing contrac-<br>tion peak (fig. 5 of ref. 40 The action of caffeine and theophylline under rested<br>state conditions is virtually uninfluenced by an effect on<br>the SR. The action consists of a late-appearing contrac-<br>tion peak (fig. 5 of ref. 40; 24) which resembles tha state conditions is virtually diminuenced by an ent<br>the SR. The action consists of a late-appearing co<br>tion peak (fig. 5 of ref. 40; 24) which resemble<br>produced by catecholamines in all respects (345; se<br>fig. 1a) and prob the SR. The action consists of a late-appearing contraction peak (fig. 5 of ref. 40; 24) which resembles that produced by catecholamines in all respects (345; see also fig. 1*a*) and probably results from a cyclic AMP-dep produced by catecholamines in all respects (345; see also fig. 1a) and probably results from a cyclic AMP-dependent increase in  $I_{Ca}$  into a cardiac cell whose SR contains no releasable calcium (see section III A). The l produced by catedronamines in an respects (340, see also<br>fig. 1a) and probably results from a cyclic AMP-depend-<br>ent increase in  $I_{Ca}$  into a cardiac cell whose SR contains<br>no releasable calcium (see section III A). The ig. 1*u*) and probably results from a cyclic AWP-dependent increase in  $I_{Cs}$  into a cardiac cell whose SR contains<br>no releasable calcium (see section III A). The late rested<br>state contraction under the influence of norep no releasable calcium (see section III A). The late rested<br>state contraction under the influence of norepinephrine<br>leakage from the SR becomes noticeable by the delay in<br>contraction development if the muscle is stimulated is strengthened by carieme (40). The increased carrier<br>leakage from the SR becomes noticeable by the delay is<br>contraction development if the muscle is stimulated reg<br>ularly at relatively low frequencies (40). The effect is traction development if the muscle is stimulated regularly at relatively low frequencies (40). The effect is most obvious if caffeine acts on a two component contraction in the presence of norepinephrine: it eliminates the contraction development if the muscle is stimulated regularly at relatively low frequencies (40). The effect if most obvious if caffeine acts on a two component contraction in the presence of norepinephrine: it eliminate t diarity at relatively low frequencies (40). The effect is<br>most obvious if caffeine acts on a two component con-<br>traction in the presence of norepinephrine: it eliminates<br>the early and strengthens the late contraction compo most obvious in carieme acts on a two component con-<br>traction in the presence of norepinephrine: it eliminates<br>the early and strengthens the late contraction component<br>(46). Activity-dependent inotropic effects which opera (46). Activity-dependent inotropic effects which operate<br>
through increased calcium loading of the SR are inhibited<br>
by caffeine, such as post-extrasystolic potentiation in the<br>
cat heart (157), the progressive increase in through increased carrum loading of the SK are immoted<br>by caffeine, such as post-extrasystolic potentiation in the<br>cat heart (157), the progressive increase in the mechan-<br>ical responses to successive depolarizing pulses u cat heart (157), the progressive increase in the mecical responses to successive depolarizing pulses u<br>voltage clamp, and the increase in peak force that fol<br>a period of depolarization in the dog papillary mu<br>(296). Likewi lation responses to successive depotatizing pulses under<br>voltage clamp, and the increase in peak force that follows<br>a period of depolarization in the dog papillary muscle<br>(296). Likewise, in dog ventricular muscle, post-st a period of depolarization in the dog papillary muscle<br>
(296). Likewise, in dog ventricular muscle, post-stimu-<br>
lation potentiation is inhibited by theophylline (110).<br>
Understandably, in frog ventricular muscle, the act (296). Likewise, in dog ventricular muscle, lation potentiation is inhibited by theophy. Understandably, in frog ventricular muscle, it caffeine consists predominantly of an increasinflux through the sarcolemma (205, 288) As in the case of ryanodical by the case in cation of<br>ffeine consists predominantly of an increase in calcium<br>flux through the sarcolemma (205, 288).<br>As in the case of ryanodine, the effect of caffeine on<br>e early contracti caffeine consists predominantly of an increase in calcium

caffeine consists predominantly of an increase in calcium<br>influx through the sarcolemma (205, 288).<br>As in the case of ryanodine, the effect of caffeine c<br>the early contraction component can, at least to a gree<br>extent, be o influx through the sarcolemma (205, 288).<br>
As in the case of ryanodine, the effect of caffeine on<br>
the early contraction component can, at least to a great<br>
extent, be overcome by decreasing the contraction inter-<br>
val (40 As in the case of ryandume, the effect of calience of<br>the early contraction component can, at least to a great<br>extent, be overcome by decreasing the contraction inter-<br>val (40) and thus shortening the time available for ca val (40) and thus shortening the time available for calcium leakage from the SR. Under such conditions, theophylline increases force of contraction of dog ventricuval (40) and thus shottening the time available for car-<br>cium leakage from the SR. Under such conditions, the-<br>ophylline increases force of contraction of dog ventricu-<br>lar muscle at low concentrations (0.1 to 0.6 mmol/lit ophylline increases force of contraction of dog ventric<br>lar muscle at low concentrations (0.1 to 0.6 mmol/lite<br>by increasing the rate of force development, but with<br>higher concentrations (1 to 20 mmol/liter), a furth<br>incre ity, to a prolongation of the time to peak force is due, at unchanged contraction velocity, to a prolongation of the time to peak force (37). A similar action of theophylline had been observed in the guinea pig papillary higher concentrations (1 to 20 mmol/liter), a further increase of force is due, at unchanged contraction velocity, to a prolongation of the time to peak force (37). A similar action of theophylline had been observed in the Increase of force is due, at unchanged contraction velocity, to a prolongation of the time to peak force (37). A similar action of theophylline had been observed in the guinea pig papillary muscle (218).<br>Together with the

and Endoh (37) recorded the light signals of intracellu-<br>larly applied aequorin which disclosed the influence of<br>the methylxanthine on the cytosolic calcium transients. guinea pig papillary muscle (218).<br>Together with the isometric contraction curves, Blink<br>and Endoh (37) recorded the light signals of intracellu<br>larly applied aequorin which disclosed the influence of<br>the methylxanthine on Together with the isometric contraction curves, Blinks<br>and Endoh (37) recorded the light signals of intracellu-<br>larly applied aequorin which disclosed the influence of<br>the methylxanthine on the cytosolic calcium transients and Endon (57) recorded the fight signals of intracend-<br>larly applied aequorin which disclosed the influence of<br>the methylxanthine on the cytosolic calcium transients.<br>The amplitude of the calcium transient increased at t mary applied aequorm which disclosed the influence of<br>the methylxanthine on the cytosolic calcium transients.<br>The amplitude of the calcium transient increased at the<br>lowest inotropically effective concentrations (0.1 to 0. lowest inotropically effective concentrations (0.1 to 0.3 mmol/liter), but it decreased at higher concentrations.<br>At concentrations above 1 mmol/liter, the amplitude of the aequorin signal was below the control level, and

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206<br>continued to fall as the drug concentration was increased. laid<br>Concomitantly with the decline of its amplitude there res REITER<br>Continued to fall as the drug concentration was increased. La<br>Concomitantly with the decline of its amplitude there<br>was a progressive prolongation of the aequorin signal be REFI<br>continued to fall as the drug concentration was increased.<br>Concomitantly with the decline of its amplitude there<br>was a progressive prolongation of the aequorin signal<br>until a second light peak became distinguishable w until a second to fall as the drug concentration was increased. In Concomitantly with the decline of its amplitude there requass a progressive prolongation of the aequorin signal beatill a second light peak became distingu continued to fall as the drug concentration was increased.<br>Concomitantly with the decline of its amplitude there<br>was a progressive prolongation of the aequorin signal<br>until a second light peak became distinguishable which<br> Concomitantly with the decline of its amplitude there rewas a progressive prolongation of the aequorin signal until a second light peak became distinguishable which meas finally higher than the remnant of the early contro was a progressive prolongation of the aequorin signal<br>until a second light peak became distinguishable which<br>was finally higher than the remnant of the early control<br>signal. The second peak of the calcium transient started until a second light peak became distinguishable which<br>was finally higher than the remnant of the early control<br>signal. The second peak of the calcium transient started<br>about 100 ms later, and then declined with a half-tim signal. The second peak of the calcium transient started<br>about 100 ms after stimulation of the muscle, culminated<br>about 50 ms later, and then declined with a half-time<br>considerably longer than in the control record. The ef about 100 ms after stimulation of the muscle, culminated<br>about 50 ms later, and then declined with a half-time<br>considerably longer than in the control record. The ef-<br>fects of the low concentrations of the drug were though about 50 ms later, and then declined with a half-tim<br>considerably longer than in the control record. The e<br>fects of the low concentrations of the drug were though<br>by the authors to result from an elevation of cytoplasm<br>cyc considerably longer than in the control record. The effects of the low concentrations of the drug were thought<br>by the authors to result from an elevation of cytoplasmic<br>cyclic AMP concentration due to the inhibition of ph fects of the low concentrations of the drug were thought the authors to result from an elevation of cytoplase cyclic AMP concentration due to the inhibition of photolesterase, whereas they regarded the effects higher conce by the authors to result from an elevation of cytoplasmic cyclic AMP concentration due to the inhibition of phos-<br>phodiesterase, whereas they regarded the effects of<br>higher concentrations on the calcium transient as refle cyclic AMP concentration due to the inhibition of phos-<br>phodiesterase, whereas they regarded the effects of<br>higher concentrations on the calcium transient as reflect-<br>ing the action of theophylline on the SR (37). Indeed, higher concentrations on the calcium transient as reflect-<br>ing the action of theophylline on the SR (37). Indeed, it<br>seems very likely that the concentration-dependent de-<br>crease of an early aequorin light signal reflects ing the action of theophylline on the SR (37). Indeed, it<br>seems very likely that the concentration-dependent de-<br>crease of an early aequorin light signal reflects the pro-<br>gressive reduction of the content of activator cal seems very likely that the concentration-dependent decrease of Na<sup>+</sup> (316). From such sarcolem-<br>crease of an early aequorin light signal reflects the pro-<br>gressive reduction of the content of activator calcium in partiall crease of an early aequorin light signal reflects the progressive reduction of the content of activator calcium in pathe release compartments of the SR caused by the drug-<br>induced increase of the rate of calcium leakage from the  $\mu$ m<br>SR. This brings the muscle functionally int the release compartments of the SR caused by the drug-<br>induced increase of the rate of calcium leakage from the  $\mu$ m<br>SR. This brings the muscle functionally into the situa-<br>invition of the rested state (section III A), i induced increase of the rate of calcium leakage from the  $\mu$ mol/<br>SR. This brings the muscle functionally into the situa-<br>involved into of the rested state (section III A), in spite of the specif<br>relatively high contracti SK. This brings the muscle functionally into the situation of the rested state (section III A), in spite of the speakively high contraction frequency. Consistent with 0.3 the reduction of the early part of the cytosolic c relatively high contraction frequency. Consistent with 0.3  $\mu$ mol/liter; ref. 72; see section VI). However, the<br>the reduction of the early part of the cytosolic calcium<br>transient is the observation of a concentration-dep the reduction of the early part of the cytosolic calcium<br>transient is the observation of a concentration-depend-<br>ent increase in the duration of the transmembrane action<br>potentials produced by caffeine in guinea pig and k transient is the observation of a concentration-depend-<br>ent increase in the duration of the transmembrane action<br>potentials produced by caffeine in guinea pig and kitten<br>cardiac muscle (89, 86). This is presumably because ent increase in the duration of the transmembrane action<br>potentials produced by caffeine in guinea pig and kitt<br>cardiac muscle (89, 86). This is presumably because the<br>stimulating effect of the initial intracellular calciu potentials produced by caffeine in guindicardiac muscle (89, 86). This is presured stimulating effect of the initial intuitansient on the potassium conducta lemma is reduced (see section II C). As in rested state contracti rdiac muscle (89, 86). This is presumably because the commulating effect of the initial intracellular calcium variations under the sarcomma is reduced (see section II C).<br>As in rested state contractions under the influenc stimulating effect of the initial intracellular calcius<br>transient on the potassium conductance of the sarce<br>lemma is reduced (see section II C).<br>As in rested state contractions under the influence<br>catecholamines, the meth

transient on the potassium conductance of the sarcollemma is reduced (see section II C).<br>As in rested state contractions under the influence of method<br>animes, the methylxanthine-dependent elevation of cyclic AMP will incr biomagnet is reduced (see section II C).<br>
As in rested state contractions under the influence of  $\frac{m}{\text{catecholamines}}$ , the methylxanthine-dependent elevation of cyclic AMP will increase  $I_{Ca}$ . In the light of the biochemical As in rested state contractions under the influence of catecholamines, the methylxanthine-dependent elevation of cyclic AMP will increase  $I_{Cs}$ . In the light of biochemical reports of an increased rate constant of calciu cate cholamines, the methylxanthine-dependent elevation of cyclic AMP will increase  $I_{Ca}$ . In the light of the biochemical reports of an increased rate constant of the calcium accumulation into the SR (see above and ref. biochemical reports of an increased rate constant of calcium accumulation into the SR (see above and ref. 35), there is no reason to assume that the inflowing calcium is not taken up by the SR before it is released after s calcium accumulation into the SR (see above and 35), there is no reason to assume that the inflow<br>calcium is not taken up by the SR before it is relea<br>after some delay into the cytosol, giving rise to a p<br>nounced late calc 35), there is no reason to assume that the inflow calcium is not taken up by the SR before it is released after some delay into the cytosol, giving rise to a p nounced late calcium transient and a prolonged contration. Whe calcium is not taken up by the SR before it is released outward or inward depending on the direction and mag-<br>after some delay into the cytosol, giving rise to a pro-<br>nounced late calcium transient and a prolonged contrac nounced late calcium transient and a prolonged contraction. Whether calcium is released only through voltage-<br>dependent gates or whether calcium leakage through<br>caffeine-sensitive gates is also involved in the course of<br>th on. Whether calcium is released only through voltage-<br>pendent gates or whether calcium leakage through<br>ffeine-sensitive gates is also involved in the course of<br>e calcium transient is not clear.<br>The same pattern of effects

dependent gates or whether calcium leakage through<br>caffeine-sensitive gates is also involved in the course of<br>the calcium transient is not clear.<br>The same pattern of effects of theophylline and caf-<br>feine on intracellular caffeine-sensitive gates is also involved in the course of<br>the calcium transient is not clear.<br>The same pattern of effects of theophylline and caf-<br>feine on intracellular calcium transient and contraction<br>was observed in was observed in cat papillary muscles (9, 273, 41), and compatible results have been obtained with rat ventric-<br>ular muscle (216) and canine Purkinje fibers (158). The The same pattern of effects of theophylline and caf-<br>feine on intracellular calcium transient and contraction<br>was observed in cat papillary muscles  $(9, 273, 41)$ , and<br>compatible results have been obtained with rat ventri feine on intracellular calcium transient and contraction<br>was observed in cat papillary muscles  $(9, 273, 41)$ , and<br>compatible results have been obtained with rat ventric-<br>ular muscle  $(216)$  and canine Purkinje fibers  $(1$ was observed in cat papillary muscles  $(9, 273, 41)$ , and<br>compatible results have been obtained with rat ventric-<br>ular muscle  $(216)$  and canine Purkinje fibers  $(158)$ . The<br>precise relative importance for the overall eff compatible results have been obtained with rat ventric-<br>ular muscle (216) and canine Purkinje fibers (158). The<br>precise relative importance for the overall effects of the<br>methylxanthines of an increased calcium sensitivit ular muscle (216) and canine Purkinje fibers (158). The precise relative importance for the overall effects of the methylxanthines of an increased calcium sensitivity of (the myofilaments as observed in skinned cardiac mu precise relative importance for the overall effective imethylxanthines of an increased calcium set<br>the myofilaments as observed in skinned card<br>preparations (411) or in voltage-clamped she<br>Purkinje fibers (104) remains to methylxanthines of an increased calcium sensitivity of<br>the myofilaments as observed in skinned cardiac muscle<br>preparations (411) or in voltage-clamped sheep cardiac<br>Purkinje fibers (104) remains to be elucidated.<br>V. Sodium

## *A. Cakium Extrusion*

ultimately to be extruded again in order to maintain the

ER<br>large concentration gradient which is necessary for its<br>regulatory function. Part of this uphill movement has ER<br>large concentration gradient which is necessary for its<br>regulatory function. Part of this uphill movement has<br>been found to depend on extracellular sodium in heart<br>muscle (330) as in nerve (33) and attributed to exchang large concentration gradient which is necessary for its regulatory function. Part of this uphill movement has been found to depend on extracellular sodium in heart muscle (330) as in nerve (33) and attributed to exchange d diffusion in which calcium efflux is completed to exchange diffusion in which calcium efflux is coupled to sodium entry. In this sodium-calcium exchange the energy for extruding calcium is provided by the downhill movement been found to depend on extracellular sodium in heart<br>muscle (330) as in nerve (33) and attributed to exchange<br>diffusion in which calcium efflux is coupled to sodium<br>entry. In this sodium-calcium exchange the energy for<br>ex muscle (330) as in nerve (33) and attributed to exchibility diffusion in which calcium efflux is coupled to sodentry. In this sodium-calcium exchange the energy extruding calcium is provided by the downhill moven of sodium diffusion in which calcium efflux is coupled to sodium<br>entry. In this sodium-calcium exchange the energy for<br>extruding calcium is provided by the downhill movement<br>of sodium. Consistent with a bidirectional carrier-me-<br>dia entry. In this sodium-calcium exchange the energy for extruding calcium is provided by the downhill movement<br>of sodium. Consistent with a bidirectional carrier-me-<br>diated sodium-calcium exchange system is a calcium<br>influx extruding calcium is provided by the downhill movement<br>of sodium. Consistent with a bidirectional carrier-me-<br>diated sodium-calcium exchange system is a calcium<br>influx component that depends on [Na]; (15, 143). The<br>activit of sodium. Consistent with a bidirectional carrier-me-<br>diated sodium-calcium exchange system is a calcium<br>influx component that depends on  $[Na]_i$  (15, 143). The<br>activity of this transport system has been demonstrated<br>in diated sodium-calcium exchange system is a calcium<br>influx component that depends on  $[Na]_i$  (15, 143). The<br>activity of this transport system has been demonstrated<br>in a preparation of cardiac sarcolemmal vesicles in which<br> influx component that depends on  $[Na]_i$  (15, 143). The activity of this transport system has been demonstrated in a preparation of cardiac sarcolemmal vesicles in which transmembrane  $Ca^{2+}$  movements in either direction activity of this transport system has been demonstrain a preparation of cardiac sarcolemmal vesicles in which transmembrane  $Ca^{2+}$  movements in either direct could be induced by generating oppositely directed contration in a preparation of cardiac sarcolemmal vesicles in which<br>transmembrane  $Ca^{2+}$  movements in either direction<br>could be induced by generating oppositely directed con-<br>centration gradients of Na<sup>+</sup> (316). From such sarcolem transmembrane  $Ca^{2+}$  movements in either direction<br>could be induced by generating oppositely directed con-<br>centration gradients of Na<sup>+</sup> (316). From such sarcolem-<br>mal vesicles, the sodium-calcium exchanger has been<br>part could be induced by generating oppositely directed concentration gradients of Na<sup>+</sup> (316). From such sarcolem-<br>mal vesicles, the sodium-calcium exchanger has been<br>partially purified and identified as a glycoprotein (151). centration gradients of Na<sup>+</sup> (316). From such sarcolem-<br>mal vesicles, the sodium-calcium exchanger has been<br>partially purified and identified as a glycoprotein (151).<br>The affinity of the exchanger for Ca<sup>2+</sup> (apparent  $K$ mal vesicles, the sodium-calcium exchanger has been<br>partially purified and identified as a glycoprotein (151).<br>The affinity of the exchanger for  $Ca^{2+}$  (apparent  $K_m$  1.5<br> $\mu$ mol/liter; ref. 73) is lower than that of ano partially purified and identified as a glycoprotein (151).<br>
The affinity of the exchanger for  $Ca^{2+}$  (apparent  $K_m$  1.5<br>  $\mu$ mol/liter; ref. 73) is lower than that of another system<br>
involved in the extrusion of  $Ca^{2+}$   $\mu$ mol/liter; ref. 73) is lower than that of another system mvolved in the extrasion of<br>specific Ca<sup>2+</sup>-pumping ATPas<br>0.3  $\mu$ mol/liter; ref. 72; see a<br>maximal velocity of Ca<sup>2+</sup> pum<br>(17) to 30 times (73) as high.<br>The stoichiometry of the Na ecific Ca<sup>2+</sup>-pumping ATPase of the sarcolemma  $(K_m)$ <br>3  $\mu$ mol/liter; ref. 72; see section VI). However, the<br>aximal velocity of Ca<sup>2+</sup> pumping by the exchanger is 5<br>7) to 30 times (73) as high.<br>The stoichiometry of the Na

after some delay into the cytosol, giving rise to a pro-<br>nitude of the electrochemical gradients for Na<sup>+</sup> and Ca<sup>2+</sup>,<br>nounced late calcium transient and a prolonged contrac-<br>tion. Whether calcium is released only through V. Sodium-Calcium Exchange<br>
V. Sodium-Calcium Exchange<br>
Calcium Extrusion<br>
Calcium entering the cell during rest or activity has<br>
Calcium entering the cell during rest or activity has<br>
Calcium entering the cell during res could be matted by generating oppositely one of the calculation gradients of Na<sup>+</sup> (316). From such sare<br>clemental velocities, the sodium-calcium exchanger has been<br>partially purified and identified as a glycoprotein (151 0.3  $\mu$ mol/liter; ref. 72; see section VI). However, the<br>maximal velocity of Ca<sup>2+</sup> pumping by the exchanger is 5<br>(17) to 30 times (73) as high.<br>The stoichiometry of the Na-Ca exchange determined<br>by Pitts (308) from meas maximal velocity of  $Ca^{2+}$  pumping by the exchanger is 5<br>(17) to 30 times (73) as high.<br>The stoichiometry of the Na-Ca exchange determined<br>by Pitts (308) from measurements of tracer fluxes in<br>cardiac sarcolemmal vesicles The stoichiometry of the Na-Ca exchange determin<br>by Pitts (308) from measurements of tracer fluxes<br>cardiac sarcolemmal vesicles was  $3$  Na<sup>+</sup> to  $1$  Ca<sup>2+</sup>. Simil<br>values have been obtained by other authors with sarc<br>lemma The stoichiometry of the Na-Ca exchange determine<br>by Pitts (308) from measurements of tracer fluxes is<br>cardiac sarcolemmal vesicles was  $3$  Na<sup>+</sup> to  $1$  Ca<sup>2+</sup>. Simila<br>values have been obtained by other authors with sarce by Pitts (308) from measurements of tracer fluxes in cardiac sarcolemmal vesicles was  $3 \text{ Na}^+$  to  $1 \text{ Ca}^{2+}$ . Similar values have been obtained by other authors with sarcolemmal vesicles (315), frog atrial tissue (176 cartuate sartoiemmal vesicies was 3 Na to 1 Ca. Similar<br>values have been obtained by other authors with sarco-<br>lemmal vesicles (315), frog atrial tissue (176, 82), mam-<br>malian cardiac muscle (348, 80, 59), and squid axons lemmal vesicles (315), frog atrial tissue (176, 82), mammalian cardiac muscle (348, 80, 59), and squid axone<br>(34). A stoichiometry of more than  $2 \text{ Na}^+$  per  $\text{Ca}^{2+}$  implies<br>that the Na-Ca exchange must be electrogen (34). A stoichiometry of more than  $2 \text{ Na}^+$  per  $\text{Ca}^{2+}$  implies that the Na-Ca exchange must be electrogenic. Indeed, the operation of the exchanger in cardiac sarcolemmal vesicles has been shown to generate an elec (34). A stoichiometry of more than  $2 \text{ Na}^+$  per  $\text{Ca}^{2+}$  implies<br>that the Na-Ca exchange must be electrogenic. Indeed,<br>the operation of the exchanger in cardiac sarcolemmal<br>vesicles has been shown to generate an elec that the Na-Ca exchange must be electrogenic. Indeed<br>the operation of the exchanger in cardiac sarcolemma<br>vesicles has been shown to generate an electric curren<br>(317, 73). Since the Na-Ca exchange can move Ca eithe<br>outwar the operation of the exchanger in cardiac sarcolemmal<br>vesicles has been shown to generate an electric current<br>(317, 73). Since the Na-Ca exchange can move Ca either<br>outward or inward depending on the direction and mag-<br>ni vesicles has been shown to generate an electric curre (317, 73). Since the Na-Ca exchange can move Ca eith outward or inward depending on the direction and ma mitude of the electrochemical gradients for Na<sup>+</sup> and Ca<sup>3</sup> bo (317, 73). Since the Na-Ca exchange can move Ca either outward or inward depending on the direction and magnitude of the electrochemical gradients for Na<sup>+</sup> and Ca<sup>2+</sup>, both inward and outward carrier currents can be gene nitude of the electrochemical gradients for Na<sup>+</sup> and Ca<sup>2+</sup>, nitude of the electrochemical gradients for Na<sup>+</sup> and Ca<sup>2+</sup>,<br>both inward and outward carrier currents can be gener-<br>ated during cardiac action potentials (276). However, the<br>actual reversal potential of the carrier curre both inward and outward carrier currents can be generated during cardiac action potentials (276). However, the actual reversal potential of the carrier current is rapidly displaced toward positive values when  $[Ca]$ ; rises ated during cardiac action potentials (276). However, the actual reversal potential of the carrier current is rapidly displaced toward positive values when [Ca]<sub>i</sub> rises during the action potential as a result of calcium r actual reversal potential of the carrier current is rapidly<br>displaced toward positive values when [Ca], rises during<br>the action potential as a result of calcium release from<br>the SR (291, 102, 292, 140). The Na-Ca exchange displaced toward positive values when [Ca], rises during<br>the action potential as a result of calcium release from<br>the SR (291, 102, 292, 140). The Na-Ca exchange process<br>then should carry inward current (i.e., Na moving in the action potential as a result of calcium release from<br>the SR (291, 102, 292, 140). The Na-Ca exchange process<br>then should carry inward current (i.e., Na moving in-<br>ward) during part of the action potential, even at posi the SR (291, 102, 292, 140). The Na-Ca exchange process<br>then should carry inward current (i.e., Na moving in-<br>ward) during part of the action potential, even at positive<br>membrane voltage. Actually, an inward plateau curre then should carry inward current (i.e., Na moving in-<br>ward) during part of the action potential, even at positive<br>membrane voltage. Actually, an inward plateau current<br>that activates more slowly than the inward Ca current ward) during part of the action potential, even at positive<br>membrane voltage. Actually, an inward plateau current<br>that activates more slowly than the inward Ca current<br> $(I_{C_a})$  and contributes to the second inward current that activates more slowly than the inward placeau current ( $I_{ci}$ ) and contributes to the second inward current ( $I_{si}$ ) has been found in work on single cells (268, 291, 125). Unlike  $I_{Ca}$  this slower current is not im ( $I_{C_a}$ ) and contributes to the second inward current ( $I_{ii}$ )<br>has been found in work on single cells (268, 291, 125).<br>Unlike  $I_{C_a}$  this slower current is not immediately inhib-<br>ited by Cd ions, and the suggestion has has been found in work on single cens (200, 251, 125).<br>Unlike  $I_{Ca}$  this slower current is not immediately inhibited by Cd ions, and the suggestion has been made that<br>it is a Na-Ca exchange current  $(I_{NaCa})$ . This current tions IV B 4 and IV A). Since during a normal twitch the intracellular calcium may rise to values even greater the intracellular calcium may rise to values even greater

surprising that a similar current is activated during normal electrical activity and contributes to the slower phase CALCIUM MOBILIZATION AND CARD<br>than that occurring during aftercontractions, it is not<br>surprising that a similar current is activated during nor-<br>mal electrical activity and contributes to the slower phase<br>of  $I_{ai}$ , corres than that occurring during aftercontractions, it is not<br>surprising that a similar current is activated during nor-<br>mal electrical activity and contributes to the slower phase<br>of  $I_{ai}$ , corresponding to a net outward flow than that occurring during aftercontractions, it is not<br>surprising that a similar current is activated during nor-<br>mal electrical activity and contributes to the slower phase<br>of  $I_{ai}$ , corresponding to a net outward flow surprising that a similar current is activated during nor-<br>mal electrical activity and contributes to the slower phase<br>of  $I_{ai}$ , corresponding to a net outward flow of calcium<br>from the cell. Thereby the Na-Ca exchange mec mal electrical activity and contributes to the slower phase<br>of I<sub>si</sub>, corresponding to a net outward flow of calcium<br>from the cell. Thereby the Na-Ca exchange mechanism<br>can contribute both to electrical activity and to the from the cell. Thereby the Na-Ca exchange mechanism<br>can contribute both to electrical activity and to the<br>maintenance of calcium balance during rhythmic activity<br>of the heart (292; see also section VI B).<br>B. Calcium Uptak

of the heart (292; see also section VI B).<br> *B. Calcium Uptake*<br>
Ca uptake by the exchanger will take place if the intenance of calcium balance during rhythmic activity<br>the heart (292; see also section VI B).<br>Calcium Uptake<br>Ca uptake by the exchanger will take place if the<br>ectrochemical gradient for Na is reduced, especially if of the heart (292; see also section VI B).<br>
B. Calcium Uptake<br>
Ca uptake by the exchanger will take place if the<br>
electrochemical gradient for Na is reduced, especially if<br>
the Ca gradient is not reduced as during the intr B. Calcium Uptake<br>Ca uptake by the exchanger will take place if the<br>electrochemical gradient for Na is reduced, especially if<br>the Ca gradient is not reduced as during the intracellular<br>Ca transient after Ca release from th B. Calcium Uptake<br>Ca uptake by the exchanger will take place if the<br>electrochemical gradient for Na is reduced, especially if<br>the Ca gradient is not reduced as during the intracellular<br>Ca transient after Ca release from th Ca uptake by the exchanger will take place if the<br>electrochemical gradient for Na is reduced, especially if<br>the Ca gradient is not reduced as during the intracellular<br>Ca transient after Ca release from the SR (see above,<br>s the Ca gradient is not reduced as during the intracellular<br>Ca transient after Ca release from the SR (see above,<br>section V A). Therefore, the interval between the con-<br>tractions will be favorable for Ca uptake through the<br> the Ca gradient is not reduced as during the intracellular Ca transient after Ca release from the SR (see above, section V A). Therefore, the interval between the contractions will be favorable for Ca uptake through the e Ca transient after Ca release from the SR (see above,<br>section V A). Therefore, the interval between the con-<br>tractions will be favorable for Ca uptake through the<br>exchanger in the case of an increased intracellular so-<br>di section V A). Therefore, the interval between the contractions will be favorable for Ca uptake through the exchanger in the case of an increased intracellular so-<br>dium-activity,  $a_{\text{Na}}^i$ . Lipp and Pott (243) observed, tractions will be favorable for Ca uptake through the exchanger in the case of an increased intracellular so-<br>dium activity,  $a_{Na}^i$ . Lipp and Pott (243) observed, in<br>isolated cardiac cells,  $I_{NaCa}$  in the outward dire exenanger in the case of an increased intracentual so-<br>dium activity,  $a_{N_a}^i$ . Lipp and Pott (243) observed, in<br>isolated cardiac cells,  $I_{N_aC_a}$  in the outward direction dur-<br>ing rest at a holding potential of  $-50$  mV isolated cardiac cells,  $I_{Naca}$  in the outward direction during rest at a holding potential of -50 mV, indicating a<br>net Ca<sup>2+</sup> influx. The concentration of intracellular so-<br>dium was kept constant at 20 mmol/liter and th ing rest at a holding potential of -50 mV, indicating a<br>net  $Ca^{2+}$  influx. The concentration of intracellular so-<br>dium was kept constant at 20 mmol/liter and that of<br> $Ca^{2+}$  at 50 nmol/liter; the calculated reversal pote net Ca<sup>2+</sup> influx. The concentration of intracellular so-<br>dium was kept constant at 20 mmol/liter and that of Ca.<br>Ca<sub>i</sub><sup>2+</sup> at 50 nmol/liter; the calculated reversal potential, mn<br>E<sub>NaCa</sub>, under these conditions was -86 m dium was kept constant at 20 mmol/liter and that of  $Ca_i^{2+}$  at 50 nmol/liter; the calculated reversal potential,  $E_{NaCa}$ , under these conditions was  $-86$  mV. Ca uptake by the exchanger opposes the spontaneous Ca leak fr  $Ca_i^{2+}$  at 50 nmol/liter; the calculated reversal potential, mmol<br>E<sub>NaCa</sub>, under these conditions was -86 mV. Ca uptake by to 1:<br>the exchanger opposes the spontaneous Ca leak from the mmo<br>SR and leads to an increase in s  $E_{\text{NaCa}}$ , under these conditions was  $-86$  mV. Ca uptake<br>the exchanger opposes the spontaneous Ca leak from<br>SR and leads to an increase in stored Ca, to a grea<br>amount of Ca released during depolarization, and to<br>increas the exchanger opposes the spontaneous Ca leak from the  $\text{SR}$  and leads to an increase in stored Ca, to a greater amount of Ca released during depolarization, and to an increased rate of force development of the early co SR and leads to an increase in stored Ca, to a greater<br>amount of Ca released during depolarization, and to an<br>increased rate of force development of the early contrac-<br>tion component (see section III A). The importance of<br> amount of Ca released during depolarization, and to an increased rate of force development of the early contraction component (see section III A). The importance of inot the reduction of both the concentration (chemical) tion component (see section III A). The importance of inotropic effects of a number of these toxins have been<br>the reduction of both the concentration (chemical) gra-<br>dient and the electrical gradient of Na is illustrated the reduction of both the concentration (chemical) gradient and the electrical gradient of Na is illustrated in fig. 7 which shows the inotropic effectiveness of changes in  $a_{Na}^i$  at different resting membrane potential dient and the electrical gradient of Na is illustrated<br>fig. 7 which shows the inotropic effectiveness of chan<br>in  $a_{Na}^i$  at different resting membrane potentials (96). T<br>increase in  $a_{Na}^i$  was obtained through Na pump fig. 7 which shows the inotropic effectiveness of changes<br>in  $a_{N_a}^i$  at different resting membrane potentials (96). The<br>increase in  $a_{N_a}^i$  was obtained through Na pump inhibition<br>by ouabain. The inotropic effect in r in  $a_{Na}^i$  at different resting membrane potentials (96). The<br>increase in  $a_{Na}^i$  was obtained through Na pump inhibition<br>by ouabain. The inotropic effect in rested state contrac-<br>tions produced at comparable values of increase in  $a_{Na}^{i}$  was obtained through Na pump inhibition<br>by ouabain. The inotropic effect in rested state contractions<br>produced at comparable values of  $a_{Na}^{i}$  was increased<br>by a factor of approximately ten after t by ouabain. The inotropic effect in rested state contrac-<br>tions produced at comparable values of  $a_{Na}^2$  was increased<br>by a factor of approximately ten after the cell membrane<br> $32$ <br>depolarized from  $-102$  V to  $-65$  mV w tions produced at comparable values of  $a_{Na}^{i}$  was increased by a factor of approximately ten after the cell membrane 33<br>depolarized from  $-102$  V to  $-65$  mV with the increase of  $10$ <br>K from 2.4 to 12 mmol/liter. While by a factor of approximately ten after the cell membrane  $32$ <br>depolarized from  $-102$  V to  $-65$  mV with the increase of  $10$ <br>K from 2.4 to 12 mmol/liter. While Na influx and the itic<br>counter-current Ca efflux are reduced depolarized from  $-102 \times 10 - 66$  mV with the increase of low<br>K from 2.4 to 12 mmol/liter. While Na influx and the itive<br>counter-current Ca efflux are reduced with decreases of lula<br>the resting membrane potential, the oppo counter-current Ca efflux are reduced with decreases of the resting membrane potential, the opposite fluxes (Nefflux-Ca influx) are stimulated. With the alterations of flux ratios, more intracellular Ca becomes available i the resting membrane potential, the opposite fluxes (Na  $\frac{1}{2}$  influx) are stimulated. With the alterations of flux ratios, more intracellular Ca becomes available in the release sites of the SR for the subsequent cont efflux-Ca influx) are stimulated. With the alterations of flux ratios, more intracellular Ca becomes available in the release sites of the SR for the subsequent contraction. The dependence of the inotropic effectiveness o flux ratios, more intracellular Ca becomes available in the release sites of the SR for the subsequent contraction The dependence of the inotropic effectiveness of the intracellular sodium activity on the membrane potenti The dependence of the inotropic effectiveness of the intracellular sodium activity on the membrane potential in is unlikely to be influenced by  $\text{Na}^+/H^+$  exchange across reveardiac muscle membranes, since this is elect intracellular sodium activity on the membrane potential<br>is unlikely to be influenced by  $Na^+/H^+$  exchange across<br>cardiac muscle membranes, since this is electroneutral  $C(90)$ . During hyperpolarization (2.4 mmol of K/lite is unlikely to be influenced by  $\text{Na}^+/H^+$  exchange across revicardiac muscle membranes, since this is electroneutral  $\text{Ca}^2$ <br>(90). During hyperpolarization (2.4 mmol of K/liter), Ca ref.<br>influx via Na-Ca exchange is cardiac muscle membranes, since this is ele<br>(90). During hyperpolarization (2.4 mmol of H<br>influx via Na-Ca exchange is presumably smal<br>in extracellular Ca, therefore, was quite ine<br>contrast to the situation at high K (fig. 0). During hyperpolarization (2.4 mmol of K/liter), Ca ref.<br>flux via Na-Ca exchange is presumably small. A change (71 extracellular Ca, therefore, was quite ineffective in lem<br>ntrast to the situation at high K (fig. 7).

influx via Na-Ca exchange is presumably small. A change (71<br>in extracellular Ca, therefore, was quite ineffective in len<br>contrast to the situation at high K (fig. 7).  $\mu$ m<br>An increase of intracellular sodium concentratio in extracellular Ca, therefore, was quite ineffective<br>contrast to the situation at high K (fig. 7).<br>An increase of intracellular sodium concentration c:<br>be achieved not only by inhibiting the sodium pump wi<br>cardioactive st contrast to the situation at high K (fig. 7).<br>
An increase of intracellular sodium concentration can<br>
be achieved not only by inhibiting the sodium pump with<br>
cardioactive steroids or by reducing extracellular potas-<br>
siu An increase of intracellular sodium concentration can<br>be achieved not only by inhibiting the sodium pump with<br>cardioactive steroids or by reducing extracellular potas-<br>sium concentration (106), but also through an increase



FIG. 7. Dependence of the inotropic effectiveness of  $a_{N_a}^1$  on K and<br>Ca. Values below the dashed line were obtained in the presence of 2.4<br>mmol/liter of K and 0.3  $\mu$ mol/liter of ouabain; values above correspond<br>to 12 as the medical control of the value after the value after the values above correspond to 12.0 mmol/liter of K, 3  $\mu$ mol/liter of ouabain, and 1.2 (O) or 3.2 mmol/liter of Ca (<sup>®</sup>). *Ordinates*, force of test contractions scale. Adapted: Ordinates, force of test contractions every 16 min as the percentage of the value after the initial equilibration period at 1-Hz stimulation frequency, log scale; *abscissae*,  $a_{N_a}$  in mmol/liter, log sca

1-Hz sumulation frequency, log scale; abscissae,  $a_{i_4}$  in mmol/liter, i<br>scale. Adapted from Ebner et al. (96). Bars, SE.<br>inotropic effects of a number of these toxins have bee<br>analyzed: ceveratrum alkaloids (veratrine, reflects of a number of these toxins have been<br>inotropic effects of a number of these toxins have been<br>analyzed: ceveratrum alkaloids (veratrine, ref. 174; ver-<br>atridine, ref. 170; germitrine, ref. 171); batrachotoxin,<br>ref inotropic effects of a number of these toxins have been<br>analyzed: ceveratrum alkaloids (veratrine, ref. 174; ver-<br>atridine, ref. 170; germitrine, ref. 171); batrachotoxin,<br>ref. 172; aconitine, ref. 169; the grayanotoxins ( analyzed: ceveratrum alkaloids (veratrine, ref. 174<br>atridine, ref. 170; germitrine, ref. 171); batracho<br>ref. 172; aconitine, ref. 169; the grayanotoxins (2,<br>and certain polypeptide animal toxins (314). Th<br>dence in support entrical in the solution of the interest are coupled to the increase of the increase of  $\frac{1}{2}$  and  $\frac{1}{2$ has been compiled in a series of reviews (314). The evidence in support of the theory that the sodium-dependent inotropic effects are coupled to the increase in a<sub>Na</sub> has been compiled in a series of reviews (325, 234, 32 and certain polypeptice animal toxins (314). The evidence in support of the theory that the sodium-dependent inotropic effects are coupled to the increase in  $a_{Na}$  has been compiled in a series of reviews (325, 234, 32, dence in support of the theory that the sodium-dependent inotropic effects are coupled to the increase in  $a_N^i$  has been compiled in a series of reviews (325, 234, 32, 1 321, 166). It has been found recently that stimula has been compiled in a series of reviews  $(325, 234, 32, 1, 321, 166)$ . It has been found recently that stimulation of low-affinity cardiac muscarinic receptors produces a positive inotropic effect parallel to an increase 321, 166). It has been found recently the<br>low-affinity cardiac muscarinic receptors<br>itive inotropic effect parallel to an incredular Na<sup>+</sup> activity (221, 222) and leading<br>intracellular Ca<sup>2+</sup> concentration (223).<br>NH<sub>E</sub> Se low-affinity cardiac muscarinic receptors produces a positive inotropic effect parallel to an increase of intracel-<br>lular Na<sup>+</sup> activity (221, 222) and leading to a rise of free<br>intracellular Ca<sup>2+</sup> concentration (223).<br>V

# *A. Ca2-Transport ATPase of the Sarcolemma*

tracellular Ca<sup>2+</sup> concentration (223).<br>
VI. The Sarcolemmal Calcium Pump<br>  $Ca^{2+}$ -Transport ATPase of the Sarcolemma<br>
A plasma membrane-localized Ca<sup>2+</sup> transport system<br>
heart muscle mediates an active efflux of Ca<sup>2+</sup> **VI. The Sarcolemmal Calcium Pump**<br>A.  $Ca^{2+}$ -Transport ATPase of the Sarcolemma<br>A plasma membrane-localized  $Ca^{2+}$  transport system<br>in heart muscle mediates an active efflux of  $Ca^{2+}$  (for<br>reviews, see refs. 371 and 30 A.  $Ca^{2+}$ -Transport ATPase of the Sarcolemma<br>
A plasma membrane-localized  $Ca^{2+}$  transport system<br>
in heart muscle mediates an active efflux of  $Ca^{2+}$  (for<br>
reviews, see refs. 371 and 306). This ATP-dependen<br>  $Ca^{2+}$ -p A plasma membrane-localized  $Ca^{2+}$  transport system<br>in heart muscle mediates an active efflux of  $Ca^{2+}$  (for<br>reviews, see refs. 371 and 306). This ATP-dependent<br> $Ca^{2+}$ -pumping system (like that of the red cell membrane in heart muscle mediates an active efflux of  $Ca^{2+}$  (for<br>reviews, see refs. 371 and 306). This ATP-dependent<br> $Ca^{2+}$ -pumping system (like that of the red cell membrane,<br>ref. 340) requires the presence of  $Mg^{2+}$  in the reviews, see refs. 371 and 306). This ATP-dependent  $Ca^{2+}$ -pumping system (like that of the red cell membrane, ref. 340) requires the presence of  $Mg^{2+}$  in the medium (71). The  $Ca^{2+}$  transport ATPase of dog heart sar Ca<sup>--</sup>-pumping system (like that of the red cell memorane,<br>ref. 340) requires the presence of  $Mg^{2+}$  in the medium<br>(71). The Ca<sup>2+</sup> transport ATPase of dog heart sarco-<br>lemma possesses an apparent  $K_m$  (Ca<sup>2+</sup>) of 0.3 t (71). The Ca<sup>2+</sup> transport ATPase of dog heart sarco-<br>lemma possesses an apparent  $K_m$  (Ca<sup>2+</sup>) of 0.3 to 1.0<br> $\mu$ mol/liter when saturated with the activator calmodulin<br>(72, 232, 229). Its depletion results in the transit lemma possesses an apparent  $K_m$  ( $Ca^{2+}$ ) of 0.3 to 1.0  $\mu$ mol/liter when saturated with the activator calmodulin (72, 232, 229). Its depletion results in the transition of the Ca<sup>2+</sup>-pumping ATPase to a low Ca<sup>2+</sup> affi  $\mu$ mol/liter when saturated with the activator calmodulin (72, 232, 229). Its depletion results in the transition of the Ca<sup>2+</sup>-pumping ATPase to a low Ca<sup>2+</sup> affinity state  $(K_m \sim 20 \ \mu m o l/liter$ ; ref. 74). The catalytic sub the Ca<sup>2+</sup>-pumping ATPase to a low Ca<sup>2+</sup> affinity state  $(K_m \sim 20 \text{ }\mu\text{mol/liter}$ ; ref. 74). The catalytic subunit of the cyclic AMP-dependent protein kinase stimulates the Ca<sup>2+</sup>-ATPase, primarily by increasing its affinity

**a**spet

**a**spet



To evaluate the effectiveness of the sarcolemmal cal-<br>cium pump in reducing cellular calcium in the resting B. Relation to the Calcium Pump of the Sarcoplasmic or<br>Reticulum in Ventricular and Atrial Muscle gr<br>To evaluate the effectiveness of the sarcolemmal cal-<br>cium pump in reducing cellular calcium in the resting re<br>muscle, so Reticulum in Ventricular and Atrial Muscle<br>To evaluate the effectiveness of the sarcolemmal cal-<br>cium pump in reducing cellular calcium in the resting<br>muscle, some quantitative aspects should be considered<br>in relation to To evaluate the enectiveness of the sarcolemmal calcium pump in reducing cellular calcium in the resting remuscle, some quantitative aspects should be considered prior in relation to the Ca<sup>2+</sup>-ATPase of the SR which comp in relation to the Ca<sup>2+</sup>-ATPase of the SR which competes<br>with the sarcolemmal calcium pump for Ca<sup>2+</sup> leaking into<br>the cytoplasm from both the SR and the extracellular<br>space. In contrast to that of the sarcolemma, the Ca in relation to the Ca<sup>2+</sup>-ATPase of the SR which competes<br>with the sarcolemmal calcium pump for Ca<sup>2+</sup> leaking into<br>the cytoplasm from both the SR and the extracellular<br>space. In contrast to that of the sarcolemma, the Ca with the sarcolemmal calcium pump for  $Ca^{2+}$  leaking into<br>the cytoplasm from both the SR and the extracellular<br>space. In contrast to that of the sarcolemma, the  $Ca^{2+}$ <br>pump protein of canine cardiac SR constitutes 35 to the cytoplasm from both the SR and the extracellular space. In contrast to that of the sarcolemma, the Ca<sup>2+</sup> or pump protein of canine cardiac SR constitutes 35 to 40% of the total SR protein (75). In reconstituted vesic space. In contrast to that of the sarcolemma, the  $Ca^{2+}$ <br>pump protein of canine cardiac SR constitutes 35 to 40%<br>of the total SR protein (75). In reconstituted vesicles<br>(182), it is half-maximally activated at 0.5  $\mu$ mo pump protein of canine cardiac SR constitutes 35 to 40%<br>of the total SR protein (75). In reconstituted vesicles<br>(182), it is half-maximally activated at 0.5  $\mu$ mol/liter of<br>Ca<sup>2+</sup>, a value quite similar to that reported of the total SR protein (75). In reconstituted vesicles rat (182), it is half-maximally activated at 0.5  $\mu$ mol/liter of the Ca<sup>2+</sup>, a value quite similar to that reported for the sarcolemmal pump in situ. The amount of (182), it is half-maximally activated at 0.5  $\mu$ mol/liter of the Ca<sup>2+</sup>, a value quite similar to that reported for the sarcelemmal pump in situ. The amount of available Ca<sup>2+</sup> Unultimately achieved in cardiac muscle at  $Ca^{2+}$ , a value quite similar to that reported for the sar-<br>colemmal pump in situ. The amount of available  $Ca^{2+}$ <br>ultimately achieved in cardiac muscle at rest will then<br>depend on the quantitative relation between the t lemmal pump in situ. The amount of available  $Ca^{2+}$ <br>timately achieved in cardiac muscle at rest will then<br>pend on the quantitative relation between the two<br>mpeting  $Ca^{2+}$  ATPases in the cell.<br>The existing stereometric m

The existing stereometric measurements show (table section III A), appear without delay after stimulation,<br>2) that there are great differences in the volume fractions they are presumably activated by calcium previously<br>and depend on the quantitative relation between the two<br>depend on the quantitative relation between the two<br>competing Ca<sup>2+</sup> ATPases in the cell.<br>The existing stereometric measurements show (table<br>2) that there are great diffe

ER<br>animal species but also between ventricular and atrial<br>tissues of the same species. As has been pointed out by ER<br>animal species but also between ventricular and atrial<br>tissues of the same species. As has been pointed out by<br>Sommer and Johnson (364), the SR is remarkably prom-ER<br>animal species but also between ventricular and atr<br>tissues of the same species. As has been pointed out<br>Sommer and Johnson (364), the SR is remarkably pro<br>inent in atrial fibers. The relation of total SR volume animal species but also between ventricular and atrial tissues of the same species. As has been pointed out by Sommer and Johnson (364), the SR is remarkably prominent in atrial fibers. The relation of total SR volume to t tissues of the same species. As has been pointed out b Sommer and Johnson (364), the SR is remarkably prom<br>inent in atrial fibers. The relation of total SR volume the myofibril fraction is considerably higher in the atri<br>t commer and bomison (504), the Srt is remarkably prom-<br>inent in atrial fibers. The relation of total SR volume to<br>the myofibril fraction is considerably higher in the atria<br>than in the ventricles. This is in contrast to the inent in atrial fibers. The relation of total SR volume to<br>the myofibril fraction is considerably higher in the atria<br>than in the ventricles. This is in contrast to the mito-<br>chondrial volume fraction which amounts, in mou the myofibril fraction is considerably higher in the atrival than in the ventricles. This is in contrast to the mit chondrial volume fraction which amounts, in mountatria, to only one-half that of the ventricle (50). Thigh chan in the ventrices. This is in contrast to the inflo-<br>chondrial volume fraction which amounts, in mouse<br>atria, to only one-half that of the ventricle (50). The<br>higher volume fraction of the SR in atrial muscle corre-<br>s enondrial volume fraction which amounts, in mouse<br>atria, to only one-half that of the ventricle (50). The<br>higher volume fraction of the SR in atrial muscle corre-<br>sponds to the finding that the total calcium content of<br>the atria, to only one-half that of the ventricle (50). The higher volume fraction of the SR in atrial muscle corresponds to the finding that the total calcium content of the atria of all species studied (guinea pig, rat, and higher volume fraction of the SR in atrial muscle corre-<br>sponds to the finding that the total calcium content of<br>the atria of all species studied (guinea pig, rat, and cat)<br>is significantly higher than that of the ventric sponds to the finding that the total calcium content of<br>the atria of all species studied (guinea pig, rat, and cat)<br>is significantly higher than that of the ventricles (138).<br>When  $[Ca^{2+}]_o$  is increased, the cellular cal the atria of an species studied (guinea pig, rat, and cat)<br>is significantly higher than that of the ventricles (138).<br>When  $[Ca^{2+}]_o$  is increased, the cellular calcium content<br>of atrial muscle varies in proportion to  $[Ca$ Solutionally inglef than that of the ventities (156<br>When  $[Ca^{2+}]_o$  is increased, the cellular calcium conter<br>of atrial muscle varies in proportion to  $[Ca^{2+}]_o$ , whereather<br>that of ventricular muscle remains fairly const when  $[\text{Ca}]_0$  is increased, the central reactum content<br>of atrial muscle varies in proportion to  $[\text{Ca}^{2+}]_0$ , whereas<br>that of ventricular muscle remains fairly constant (138).<br>This indicates that the SR in the atria ef of atrial muscle varies in proportion to  $[Ca^{2+}]_0$ , whereas<br>that of ventricular muscle remains fairly constant (138).<br>This indicates that the SR in the atria effectively com-<br>petes in calcium sequestration with the sarco that of ventricular muscle remains fairly constant (138).<br>This indicates that the SR in the atria effectively com-<br>petes in calcium sequestration with the sarcolemmal Ca<sup>2+</sup><br>pump. The higher SR fraction with a greater loa This indicates that the Srt in the atria enectively competes in calcium sequestration with the sarcolemmal  $Ca^{2+}$  pump. The higher SR fraction with a greater loading capacity for calcium is apparently essential for the s pump. The higher SR fraction with a greater loading capacity for calcium is apparently essential for the special function of the atria whose contractions precede the onset of ventricular contractions. This is achieved by g capacity for calcium is apparently essential for the special function of the atria whose contractions precede the onset of ventricular contractions. This is achieved by greater velocities and briefer durations of atrial m cial function of the atria whose contractions precede the<br>onset of ventricular contractions. This is achieved by<br>greater velocities and briefer durations of atrial muscle<br>contractions (54, 217, 386) for which a greater cal onset of ventricular contractions. This is achieved by<br>greater velocities and briefer durations of atrial muscle<br>contractions (54, 217, 386) for which a greater calcium<br>release and uptake capacity of the SR seem to be a<br>p greater velocities and briefer durations of atrial muscle contractions (54, 217, 386) for which a greater calcium release and uptake capacity of the SR seem to be a prerequisite. The inequality of their cellular calcium co contractions (54, 217, 386) for which a greater calcium<br>release and uptake capacity of the SR seem to be a<br>prerequisite. The inequality of their cellular calcium<br>content is probably responsible for other functional dif-<br>fe release and uptake capacity of the SR seem to be a<br>prerequisite. The inequality of their cellular calcium<br>content is probably responsible for other functional dif-<br>ferences between the two kinds of cardiac muscle, such<br>as prerequisite. The inequality of their cellular calciu<br>content is probably responsible for other functional d<br>ferences between the two kinds of cardiac muscle, su<br>as the duration of the action potential and the magnitu<br>of r content is probably responsible for other functional differences between the two kinds of cardiac muscle, such as the duration of the action potential and the magnitude of rested-state contractions. Consistent with the imp ferences between the two kinds of cardiac muscle, such as the duration of the action potential and the magnitude of rested-state contractions. Consistent with the importance of intracellular calcium for the short plateau d as the duration of the action potential and the magnitude<br>of rested-state contractions. Consistent with the impor-<br>tance of intracellular calcium for the short plateau du-<br>ration of the atrial action potential is the demon tance of intracellular calcium for the short plateau duration of the atrial action potential is the demonstration that, in Ca-poor solutions, the atrial action potential becomes quite similar to that of a ventricular fiber that, in Ca-poor solutions, the atrial action potential becomes quite similar to that of a ventricular fiber (165).<br>Unlike cardiac ventricles of most species, mammalian atria are distinguished by strong rested state contra ration of the atrial action potential is the demonstration<br>that, in Ca-poor solutions, the atrial action potential<br>becomes quite similar to that of a ventricular fiber (165).<br>Unlike cardiac ventricles of most species, mamm that, in Ca-poor solutions, the atrial action potential<br>becomes quite similar to that of a ventricular fiber (165).<br>Unlike cardiac ventricles of most species, mammalian<br>atria are distinguished by strong rested state contra becomes quite similar to that of a ventricular fiber (165).<br>Unlike cardiac ventricles of most species, mammalian<br>atria are distinguished by strong rested state contractions<br>(225, 213). Since these contractions, in contrast Unlike cardiac ventricles of most species, mammalia<br>atria are distinguished by strong rested state contraction<br>(225, 213). Since these contractions, in contrast to th<br>late appearing rested state contractions of ventricles atria are distinguished by strong rested state contractions<br>(225, 213). Since these contractions, in contrast to the<br>late appearing rested state contractions of ventricles (see<br>section III A), appear without delay after st late appearing rested state contractions of ventricles (see

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TABLE 2 Stereology of cardiac cell components								
	Mouse*			Rat. left	<b>Lizzard</b>		Frog <sub>‡</sub>	
	Right atrium	Left atrium	Left ventricle	ventriclet	Atrium	Ventricle	Atrium	Ventricle
SR volume (total %)	1.76	1.73	0.88\$	3.5	1.22	$0.69$ \$	0.56	0.38
SR surface area $(\mu m^2/\mu m^3$ cell)	1.687	1.576	$0.896$ §	1.22	0.914	0.503\$	0.459	$0.277$ §
Plasmalemma $Surface + T system$ Plasmalemma $(\mu m^2/\mu m^3$ cell)	0.694	0.747	0.667	0.39	1.254	1.143	1.319	1.193
Myofibrils (%)	52.56	52.95	54.32	47.6	41.14	50.05\$	42.38	46.15

 $\dagger$  Ref. 299.<br> $\dagger$  Ref. 48.<br>§ Difference significant from atrium  $(P < 0.05)$ .

CALCIUM MOBILIZATION AND CART<br>The calcium content of the atrial SR will probably not<br>completely uninfluenced by calcium leakage during CALCIUM MOBILIZATION AND CARDI<br>The calcium content of the atrial SR will probably not<br>long rest periods. But the remaining calcium content is wi CALCIUM MOBILIZATION AND CARDI<br>The calcium content of the atrial SR will probably not<br>13<br>the completely uninfluenced by calcium leakage during hig<br>tong rest periods. But the remaining calcium content is wivery likely restr The calcium content of the atrial SR will probably not 13<br>be completely uninfluenced by calcium leakage during hig<br>long rest periods. But the remaining calcium content is wit<br>very likely restricted to the release compartme be completely uninfluenced by calcium leakage during hilong rest periods. But the remaining calcium content is wivery likely restricted to the release compartments of the Tijunctional SR, whereas the larger parts of the SR long rest periods. But the remaining calcium content<br>very likely restricted to the release compartments of t<br>junctional SR, whereas the larger parts of the SR (fr<br>or longitudinal SR) probably contain relatively litt<br>calciu very likely restricted to the release compartments of the junctional SR, whereas the larger parts of the SR (free<br>or longitudinal SR) probably contain relatively little<br>calcium. This may be deduced from the general experijunctional SR, whereas the larger parts of the SR (free ce<br>or longitudinal SR) probably contain relatively little un<br>calcium. This may be deduced from the general experi-<br>litence that the strong, early appearing, rested st or longitudinal SR) probably contain relatively little ured calcium. This may be deduced from the general experi-<br>litence that the strong, early appearing, rested state con-<br>traction is, at a higher stimulation frequency, calcium. This may be deduced from the general experience that the strong, early appearing, rested state contraction is, at a higher stimulation frequency, followed by contractions which rapidly (in 1 to 3 beats) decline in ence that the strong, early appearing, rested state con-<br>traction is, at a higher stimulation frequency, followed ul<br>by contractions which rapidly (in 1 to 3 beats) decline in pi<br>strength, before the force of contraction g traction is, at a higher stimulation frequency, followed ulter by contractions which rapidly (in 1 to 3 beats) decline in pig strength, before the force of contraction gradually in-<br>creases again until its frequency-depend by contractions which rapidly (in 1 to 3 beats) decline<br>strength, before the force of contraction gradually<br>creases again until its frequency-dependent steady st<br>is reached (225, 38; for review, see ref. 213). The ra<br>loss strength, before the force of contraction gradually in-<br>creases again until its frequency-dependent steady state<br>is reached (225, 38; for review, see ref. 213). The rapid<br> $t$  loss of contractile strength after the rested creases again until its frequency-dependent steady state<br>is reached (225, 38; for review, see ref. 213). The rapid<br>loss of contractile strength after the rested state contrac-<br>tions has been described by Blinks and Koch-W is reached (225, 38; for review, see ref. 213). The rapid loss of contractile strength after the rested state contractions has been described by Blinks and Koch-Weser (38 as a consequence of the predominance of a large neg loss of contractile strength after the rested state contrac-<br>tions has been described by Blinks and Koch-Weser (38) lations<br>as a consequence of the predominance of a large negative ular<br>inotropic effect of activation (NIEA tions has been described by Blinks and Koch-Weser (38) lat as a consequence of the predominance of a large negative ultimotropic effect of activation (NIEA) over a small positive inotropic effect of activation (PIEA). Acco as a consequence of the predominance of a large negative uniotropic effect of activation (NIEA) over a small positive inotropic effect of activation (PIEA). According to athese authors, the steady-state force of contractio inotropic effect of activation (NIEA) over a small positive inotropic effect of activation (PIEA). According to after these authors, the steady-state force of contraction is latite determined by the cumulation of these two tive inotropic effect of activation (PIEA). According<br>these authors, the steady-state force of contraction<br>determined by the cumulation of these two oppos<br>effects, of which the small PIEA disappears slowly, a<br>the larger NI tion. termined by the cumulation of these two opposing<br>fects, of which the small PIEA disappears slowly, and<br>e larger NIEA disappears rapidly after each contrac-<br>n.<br>An explanation for the rapid decline of the contractile<br>rength

effects, of which the small PIEA disappears slowly, and<br>the larger NIEA disappears rapidly after each contraction.<br>An explanation for the rapid decline of the contractile<br>strength after the rested stated contraction (and t An explanation for the rapid decline of the contractile<br>strength after the rested stated contraction (and thereby<br>for NIEA) would be a calcium extrusion from the cell<br>through the sarcolemma via Na-Ca exchange. If a con-<br>th tion.<br>
An explanation for the rapid decline of the contractile<br>
strength after the rested stated contraction (and thereby<br>
for NIEA) would be a calcium extrusion from the cell<br>
through the sarcolemma via Na-Ca exchange. I An explanation for the rapid decline of the contractile<br>strength after the rested stated contraction (and thereby<br>for NIEA) would be a calcium extrusion from the cell<br>through the sarcolemma via Na-Ca exchange. If a con-<br>s strength after the rested stated contraction (and thereby<br>for NIEA) would be a calcium extrusion from the cell<br>through the sarcolemma via Na-Ca exchange. If a con-<br>siderable part of the amount of  $Ca^{2+}$  released in the<br>r for NIEA) would be a calcium extrusion from the cell<br>through the sarcolemma via Na-Ca exchange. If a con-<br>siderable part of the amount of  $Ca^{2+}$  released in the<br>rested state contraction is indeed extruded during the<br>calc through the sarcolemma via Na-Ca exchange. If a considerable part of the amount of  $Ca^{2+}$  released in the rested state contraction is indeed extruded during the calcium transient (see section V A), the remaining part of siderable part of the amount of  $Ca^{2+}$  released in the rested state contraction is indeed extruded during the calcium transient (see section V A), the remaining part of the released calcium may not suffice to refill an e rested state contraction is indeed extruded during the<br>calcium transient (see section V A), the remaining part<br>of the released calcium may not suffice to refill an empty<br>has<br>accoplasmic reticulum with a great uptake capac of the released calcium may not suffice to refill an empty<br>sarcoplasmic reticulum with a great uptake capacity.<br>Activator calcium would then become available again<br>only according to the slowly cumulating activity-depend-<br> of the released calcium may not suffice to refill an empty<br>sarcoplasmic reticulum with a great uptake capacity.<br>Activator calcium would then become available again<br>only according to the slowly cumulating activity-depend-<br> sarcoplasmic reticulum with a great uptake capacity.<br>Activator calcium would then become available again<br>only according to the slowly cumulating activity-depend-<br>ent Ca<sup>2+</sup> uptake from the extracellular space (PIEA).<br>Evid Activator calcium would then become available again<br>only according to the slowly cumulating activity-depend-<br>ent Ca<sup>2+</sup> uptake from the extracellular space (PIEA).<br>Evidence in support of the idea that Ca<sup>2+</sup> extrusion<br>thr only according to the slowly cumulating activity-dependent  $Ca^{2+}$  uptake from the extracellular space (PIEA).<br>Evidence in support of the idea that  $Ca^{2+}$  extrusion through Na-Ca exchange is partly responsible for the lo ent Ca<sup>2+</sup> uptake from the extracellular space (PIEA).<br>Evidence in support of the idea that Ca<sup>2+</sup> extrusion<br>through Na-Ca exchange is partly responsible for the<br>loss in contractile strength was obtained in experiments<br>wi through Na-Ca exchange is partly responsible for the loss in contractile strength was obtained in experiments with guinea pig papillary muscles in magnesium-free solution (399a). These muscles have a distinct atrium-like f through Na-Ca exchange is partly responsible for the<br>loss in contractile strength was obtained in experiments<br>with guinea pig papillary muscles in magnesium-free<br>solution (399a). These muscles have a distinct atrium-<br>like solution (399a). These muscles have a distinct atrium-<br>like frequency-force relationship with strong rested state<br>contractions (see below). The duration of the transmem-<br>brane action potential accompanying the rested state with guinea pig papillary muscles in magnesium-free<br>solution (399a). These muscles have a distinct atrium-<br>like frequency-force relationship with strong rested state<br>contractions (see below). The duration of the transmensolution (399a). These muscles have a distinct atrium-<br>like frequency-force relationship with strong rested state AMP (contractions (see below). The duration of the transmem-<br>brane action potential accompanying the rested like frequency-force relationship with strong rested state<br>contractions (see below). The duration of the transmem-<br>brane action potential accompanying the rested state<br>contraction was longer than that of the following low contractions (see below). The duration of the transmembrane action potential accompanying the rested state radio<br>contraction was longer than that of the following low actrength contractions. The difference became more mor brane action potential accompanying the rested state<br>contraction was longer than that of the following low<br>strength contractions. The difference became more<br>prominent  $(25\% \text{ at } 60\% \text{ repolarization of the action})$ <br>potential,  $n = 4$ ) after t contraction was longer than that of the following low<br>strength contractions. The difference became more m<br>prominent (25% at 60% repolarization of the action<br>potential,  $n = 4$ ) after the sarcolemmal calcium channels<br>had be strength contractions. The difference became more major mechanism for calcium transport through the sar-<br>prominent (25% at 60% repolarization of the action<br>potential,  $n = 4$ ) after the sarcolemmal calcium channels<br>had bee potential,  $n = 4$ ) after the sarcolemmal calcium channels potential,  $n = 4$ ) after the sarcolemmal calcium channels Na-<br>had been inhibited with 1  $\mu$ mol/liter of nifedipine. These grace<br>results are interpreted to show that the second inward incr<br>current  $(I_{ai})$  responsible for t had been inhibited with 1  $\mu$ mol/liter of nifedipine. These gresults are interpreted to show that the second inward in current  $(I_{ai})$  responsible for the action potential plateau v during the strong rested state contract results are interpreted to<br>current  $(I_{ai})$  responsible for<br>during the strong rested s<br>a great extent by  $I_{NaCa}$ ,<br>through Na-Ca exchange.<br>A notable exception to Frent  $(I_{ai})$  responsible for the action potential plateau<br>ring the strong rested state contraction was carried to<br>great extent by  $I_{NaCe}$ , indicating calcium extrusion<br>rough Na-Ca exchange.<br>A notable exception to the usua during the strong rested state contraction was carried to<br>a great extent by  $I_{Nac,a}$ , indicating calcium extrusion po<br>through Na-Ca exchange.<br>A notable exception to the usual frequency-force rela-<br>tionship of mammalian ve

a great extent by  $I_{\text{NaCa}}$ , indicating calcium extrusion<br>through Na-Ca exchange.<br>A notable exception to the usual frequency-force rela-<br>tionship of mammalian ventricular muscle is that of the<br>rat, which shows strong res

CALCIUM MOBILIZATION AND CARDIAC INOTROPIC MECHANISMS 209<br> **CALCIUM MOBILIZATION AND CARDIAC INCRETE:**<br> **CALCIUM FOR A FORM** This may be causally related to an exceptionally be completely uninfluenced by calcium leakage during high SR volume fraction in the rat ventricle (table 2) long rest periods. But the remaining calcium content is with a consequent high intracellular calcium activity, ve high SR volume fraction in the rat ventricle (table 2) FINAC INOTROPIC MECHANISMS 209<br>133). This may be causally related to an exceptionally<br>high SR volume fraction in the rat ventricle (table 2)<br>with a consequent high intracellular calcium activity. EXECUTE INCOTROPIC MECHANISMS 209<br>133). This may be causally related to an exceptionally<br>high SR volume fraction in the rat ventricle (table 2)<br>with a consequent high intracellular calcium activity.<br>The reported values of 133). This may be causally related to an exceptionally high SR volume fraction in the rat ventricle (table 2) with a consequent high intracellular calcium activity. The reported values of the intracellular free  $Ca^{2+}$  co 133). This may be causally related to an exceptional<br>high SR volume fraction in the rat ventricle (table with a consequent high intracellular calcium activit<br>The reported values of the intracellular free  $Ca^{2+}$  concentra high SR volume fraction in the rat ventricle (table 2) with a consequent high intracellular calcium activity.<br>The reported values of the intracellular free Ca<sup>2+</sup> concentration in resting rat ventricular myocytes, as meas with a consequent high intracellular calcium activity.<br>The reported values of the intracellular free  $Ca^{2+}$  concentration in resting rat ventricular myocytes, as measured with the fluorescent  $Ca^{2+}$  indicator quin-2 (in The reported values of the intracellular free Ca<sup>2+</sup> contration in resting rat ventricular myocytes, as me ured with the fluorescent Ca<sup>2+</sup> indicator quin-2 (in nm liter: 121  $\pm$  11, ref. 93; 137.1  $\pm$  2.6, ref. 310; 18 centration in resting rat ventricular myocytes, as measured with the fluorescent  $Ca^{2+}$  indicator quin-2 (in nmol/<br>liter: 121  $\pm$  11, ref. 93; 137.1  $\pm$  2.6, ref. 310; 181  $\pm$  18,<br>ref. 349), are considerably higher th ured with the fluorescent Ca<sup>2+</sup> indicator quin-2 (in nmol/<br>liter: 121  $\pm$  11, ref. 93; 137.1  $\pm$  2.6, ref. 310; 181  $\pm$  18,<br>ref. 349), are considerably higher than those in ventric-<br>ular myocytes of the cat (57  $\pm$  4 liter: 121  $\pm$  11, ref. 93; 137.1  $\pm$  2.6, ref. 310; 181  $\pm$  18, ref. 349), are considerably higher than those in ventric-<br>ular myocytes of the cat (57  $\pm$  4, ref. 93) and the guinea<br>pig (99.9  $\pm$  10, ref. 310). Acco ref. 349), are considerably higher than those in ventr<br>ular myocytes of the cat  $(57 \pm 4, \text{ref. } 93)$  and the guin<br>pig  $(99.9 \pm 10, \text{ref. } 310)$ . Accordingly, the magnitude<br>the rested state contraction of the rat ventricle ular myocytes of the cat  $(57 \pm 4, \text{ref. } 93)$  and the guinea<br>pig  $(99.9 \pm 10, \text{ref. } 310)$ . Accordingly, the magnitude of<br>the rested state contraction of the rat ventricle declines<br>when  $[Ca]<sub>o</sub>$  is reduced, and at low pig (99.9  $\pm$  10, ref. 310). Accordingly, the magnitude<br>the rested state contraction of the rat ventricle declin<br>when [Ca]<sub>o</sub> is reduced, and at low Ca<sup>2+</sup> concentration<br>the rat myocardium has properties similar to those the rested state contraction of the rat ventricle decline when  $[Ca]_o$  is reduced, and at low  $Ca^{2+}$  concentratio the rat myocardium has properties similar to those other species with respect to inotropic effects of stin when  $[Ca]_o$  is reduced, and at low  $Ca^{2+}$  concentrations,<br>the rat myocardium has properties similar to those of<br>other species with respect to inotropic effects of stimu-<br>lation (133). The reverse is seen with guinea pig the rat myocardium has properties similar to those of other species with respect to inotropic effects of stimulation (133). The reverse is seen with guinea pig ventricular muscles kept in magnesium-free solutions. They dev other species with respect to inotropic effects of stimulation (133). The reverse is seen with guinea pig ventricular muscles kept in magnesium-free solutions. They develop strong rested state contractions without a delay lation (133). The reverse is seen with guinea pig ventricular muscles kept in magnesium-free solutions. They develop strong rested state contractions without a delay after stimulation and an atrium-like frequency-force rel ular muscles kept in magnesium-free solutions. They<br>develop strong rested state contractions without a delay<br>after stimulation and an atrium-like frequency-force re-<br>lationship (398), probably as a result of an unfavorable develop strong rested state contractions without a delay<br>after stimulation and an atrium-like frequency-force re-<br>lationship (398), probably as a result of an unfavorable<br>shift in the relation between sarcolemmal calcium p Not an ecritain-incertial<br>robably as a result<br>between sarcolem<br>vii. Conclusions<br>focused on the ift in the relation between sarcolemmal calcium pump<br>pacity and passive calcium leak into the cell.<br>  $VII.$  Conclusions<br>
The review has focused on the central role of an<br>tracellular calcium store, the sarcoplasmic reticulu

capacity and passive calcium leak into the cell.<br>
VII. Conclusions<br>
The review has focused on the central role of an<br>
intracellular calcium store, the sarcoplasmic reticulum,<br>
in the regulation of mammalian cardiac contrac VII. Conclusions<br>The review has focused on the central role of an<br>intracellular calcium store, the sarcoplasmic reticulum,<br>in the regulation of mammalian cardiac contraction. It<br>is the amount of calcium released from the S VII. Conclusions<br>The review has focused on the central role of an<br>intracellular calcium store, the sarcoplasmic reticulum,<br>in the regulation of mammalian cardiac contraction. It<br>is the amount of calcium released from the S The review has focused on the central role of an<br>intracellular calcium store, the sarcoplasmic reticulum,<br>in the regulation of mammalian cardiac contraction. It<br>is the amount of calcium released from the SR after<br>depolariz intracellular calcium store, the sarcoplasmic reticulum,<br>in the regulation of mammalian cardiac contraction. It<br>is the amount of calcium released from the SR after<br>depolarization which determines the degree of activation<br>o in the regulation of mammalian cardiac contraction. It<br>is the amount of calcium released from the SR after<br>depolarization which determines the degree of activation<br>of the contractile apparatus. The property of leaking<br>calc is the amount of calcium released from the SR after<br>depolarization which determines the degree of activation<br>of the contractile apparatus. The property of leaking<br>calcium at a considerable rate during rest makes the<br>calciu depolarization which determines the degree of activation<br>of the contractile apparatus. The property of leaking<br>calcium at a considerable rate during rest makes the<br>calcium content of the SR extremely labile. On the other<br>h of the contractile apparatus. The property of leaking<br>calcium at a considerable rate during rest makes the<br>calcium content of the SR extremely labile. On the other<br>hand, the ability of the SR to accumulate calcium leads<br>t calcium at a considerable rate during rest makes<br>calcium content of the SR extremely labile. On the ot<br>hand, the ability of the SR to accumulate calcium le<br>to the refilling of its stores to an extent that depends<br>the amoun calcium content of the SR extremely labile. On the other<br>hand, the ability of the SR to accumulate calcium leads<br>to the refilling of its stores to an extent that depends on<br>the amount of calcium made available from the ext hand, the ability of the SR to accumulate calcium leads to the refilling of its stores to an extent that depends on the amount of calcium made available from the extracel-lular space. This offers the common mechanistic bas ways. e amount of calcium made available from the extracelar space. This offers the common mechanistic basis<br>r a variety of inotropic agents that act in quite different<br>ys.<br>According to our present knowledge, calcium enters<br>e ce

the common mechanistic based of the common mechanistic based for a variety of inotropic agents that act in quite different ways.<br>According to our present knowledge, calcium ent<br>the cell mainly during depolarization through for a variety of inotropic agents that act in quite different<br>ways.<br>According to our present knowledge, calcium enters<br>the cell mainly during depolarization through voltage-<br>dependent channels whose functional availability ways.<br>
According to our present knowledge, calcium enters<br>
the cell mainly during depolarization through voltage-<br>
dependent channels whose functional availability is reg-<br>
ulated by cyclic AMP. Since the cellular content According to our present knowledge, calcium enters<br>the cell mainly during depolarization through voltage-<br>dependent channels whose functional availability is reg-<br>ulated by cyclic AMP. Since the cellular content of cyclic<br> the cell mainly during depolarization through voltage-<br>dependent channels whose functional availability is reg-<br>ulated by cyclic AMP. Since the cellular content of cyclic<br>AMP depends on a series of enzymatic steps, initiat dependent channels whose functional availability is regulated by cyclic AMP. Since the cellular content of cyclic AMP depends on a series of enzymatic steps, initiated by receptor stimulation and ending in cyclic AMP degra ulated by cyclic AMP. Since the cellular content of cyclic<br>AMP depends on a series of enzymatic steps, initiated<br>by receptor stimulation and ending in cyclic AMP deg-<br>radation, an increase in cellular calcium uptake may b AMP depends on a series of enzymatic steps, initiated<br>by receptor stimulation and ending in cyclic AMP deg-<br>radation, an increase in cellular calcium uptake may be<br>achieved by interventions that act on any of them. A<br>major by receptor stimulation and ending in cyclic AMP degradation, an increase in cellular calcium uptake may be achieved by interventions that act on any of them. A major mechanism for calcium transport through the sarcolemma radation, an increase in cellular calcium uptake may leachieved by interventions that act on any of them.<br>major mechanism for calcium transport through the sa<br>colemma in both directions consists of an electrochemic<br>Na-Ca e achieved by interventions that act on any of them. A major mechanism for calcium transport through the sar-<br>colemma in both directions consists of an electrogenic<br>Na-Ca exchange which depends on the electrochemical<br>gradien major mechanism for calcium transport through the sar-<br>colemma in both directions consists of an electrogenic<br>Na-Ca exchange which depends on the electrochemical<br>gradient for Na. A reduction of this gradient leads to<br>incre colemma in both directions consists of an electrogenic<br>Na-Ca exchange which depends on the electrochemical<br>gradient for Na. A reduction of this gradient leads to<br>increased Ca uptake by the exchanger. Therefore, a great<br>var Na-Ca exchange which depends on the electrochemical<br>gradient for Na. A reduction of this gradient leads to<br>increased Ca uptake by the exchanger. Therefore, a great<br>variety of agents causing, in one way or another, an<br>incre gradient for Na. A reduct<br>increased Ca uptake by the<br>variety of agents causing<br>increase in intracellular<br>positive inotropic effects.<br>While we believe we un creased Ca uptake by the exchanger. Therefore, a grea<br>riety of agents causing, in one way or another, an<br>crease in intracellular sodium activity will produc<br>sitive inotropic effects.<br>While we believe we understand, more or

variety of agents causing, in one way or another, an increase in intracellular sodium activity will produce positive inotropic effects.<br>While we believe we understand, more or less thoroughly, the mechanisms responsible fo increase in intracellular sodium activity will produce<br>positive inotropic effects.<br>While we believe we understand, more or less thor-<br>oughly, the mechanisms responsible for an increase in<br>cellular calcium uptake, we know, positive inotropic effects.<br>While we believe we understand, more or less thor-<br>oughly, the mechanisms responsible for an increase in<br>cellular calcium uptake, we know, at present, relatively<br>little about possible pharmacolo

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210 REITER<br>binding modulator proteins and their quantitative con-<br>tributions to inotropic effects on cardiac muscle. 210<br>binding modulator proteins and their quantitative<br>tributions to inotropic effects on cardiac muscle.<br>Acknowledgements I am indebted to Drs. John B. Blinks.

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