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# VOL. 40, No. 3<br>Delayed Afterdepolarizations in Heart Muscle:<br>Delayed Afterdepolarizations in Heart Muscle:<br>Mechanisms and Relevance\*<sup>,</sup> † Eisty for Pharmacology and Experimental Therapeutics<br> **Afterdepolarizations in Heart Mu**<br> **Mechanisms and Relevance\***, †<br>
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CRAIG T. JANUARY AND HARRY A. FOZZARD‡



### I. Introduction

I. Introduction<br>THE CELLULAR MECHANISMS that cause cardiac ar-<br>ythmias are of immense importance and are the object I. Introduction<br>THE CELLULAR MECHANISMS that cause cardiac ar-<br>rhythmias are of immense importance and are the object<br>of intense investigation. One mechanism postulated to I. Introduction dep<br>
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rathythmias are of immense importance and are the object<br>
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cause cardiac arrhythmias, and possibly THE CELLULAR MECHANISMS that cause cardiac arrhythmias are of immense importance and are the object of intense investigation. One mechanism postulated to cause cardiac arrhythmias, and possibly conduction disturbances, is THE CELLULAR MECHANISMS that cause cardiac arriversing and the object<br>of intense investigation. One mechanism postulated to<br>cause cardiac arrhythmias, and possibly conduction dis-<br>turbances, is delayed afterdepolarization rhythmias are of immense importance and are the object<br>of intense investigation. One mechanism postulated to<br>cause cardiac arrhythmias, and possibly conduction dis-<br>turbances, is delayed afterdepolarizations (also called<br> of intense investigation. One mechanism postulated to cause cardiac arrhythmias, and possibly conduction disturbances, is delayed afterdepolarizations (also called late afterdepolarizations, oscillatory afterpotentials, o cause cardiac arrhythmias, and possibly conduction disturbances, is delayed afterdepolarizations (also called late afterdepolarizations, oscillatory afterpotentials, or transient depolarizations). These depolarizations ar turbances, is delayed afterdepolarizations (also called late afterdepolarizations, oscillatory afterpotentials, or action<br>transient depolarizations). These depolarizations are in-<br>duced by  $Ca^{2+}$  overload of the cardiac late afterdepolarizations, oscillatory afterpotentials,<br>transient depolarizations). These depolarizations are i<br>duced by  $Ca^{2+}$  overload of the cardiac cell. In the la<br>decade, several review articles have been published transient depolarizations). These depolarizations are in-<br>duced by  $Ca^{2+}$  overload of the cardiac cell. In the last<br>decade, several review articles have been published on<br>the subjects of delayed afterdepolarizations and duced by  $Ca^{2+}$  overload of the cardiac cell. In the last decade, several review articles have been published on the subjects of delayed afterdepolarizations and of mechanisms of arrhythmias (16, 28, 86). The purpose of decade, several review articles have been published on<br>the subjects of delayed afterdepolarizations and of mech-<br>anisms of arrhythmias (16, 28, 86). The purpose of this<br>review is to summarize recent experimental evidence<br> the subjects of delayed afterdepolarizations and of mech-<br>anisms of arrhythmias (16, 28, 86). The purpose of this<br>review is to summarize recent experimental evidence<br>pertinent to the mechanisms responsible for delayed<br>aft anisms of arrhythmias (16, 28, 86). The<br>review is to summarize recent experim<br>pertinent to the mechanisms responsi<br>afterdepolarizations and their relation<br>gain insight into their clinical relevance. rtinent to the mechanisms responsible for<br>erdepolarizations and their relation to Ca<sup>2+</sup>,<br>in insight into their clinical relevance.<br>**II. Induction of Delayed Afterdepolarizations** afterdepolarizations and their relation to  $Ca^{2+}$ , and to<br>gain insight into their clinical relevance.<br>II. Induction of Delayed Afterdepolarizations<br>Delayed afterdepolarizations are oscillations of mem-

II. Induction of Delayed Afterdepolarizations  $\frac{c}{s}$ <br>Delayed afterdepolarizations are oscillations of membrane voltage that occur after complete repolarization of  $\frac{c}{c}$  the cardiac action potential. Hence, they are II. Induction of Delayed Afterdepolarizations<br>Delayed afterdepolarizations are oscillations of men<br>brane voltage that occur after complete repolarization<br>the cardiac action potential. Hence, they are initiate<br>during electr

branc voltage share occur and recompled repondization of the cardiac action potential. Hence, they are initiated during electrical and mechanical diastole. Delayed after-<br>
\* This article is the second of a series of articl <sup>\*</sup> This article is the second of a series of articles arising from program on Vistas in Pharmacology presented at a joint meeting of the American Society for Pharmacology and Experimental Therapeutiand the American Chemic This article is the second of a series of articles ansing from a<br>program on Vistas in Pharmacology presented at a joint meeting of the<br>August 18-22, 1985, in Boston. The program entitled, "The Role of<br>Calcium in Cardiac Fu American Society for Pharmacology and Experimental Therapeutics (the and the American Chemical Society Division of Medicinal Chemistry, dengthe and prepared to Otto Krayer. The material has been updated by the authors and acknowledged. material has been updated by the authors and prepared for publication<br>with the assistance of John R. Blinks whose participation is gratefully<br>acknowledged.<br>
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on the cast water of some as shalls whose paradepation is gravitally<br>
the comported by National Heart, Lung, and Blood Institute grants<br>
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South Maryland Ave. South Maryland HL 31322.<br> **HL 20592 and HL 31322.**<br> **Address reprint requests to: Harry 4**<br> **Department of Medicine (Cardiology), The South Maryland Ave., Chicago, IL 60637.** 

 $220$ <br>
The channel versus exchange pump current  $120$ <br>  $221$ <br>  $\frac{1}{224}$ <br>
depolarizations are a type of triggered activity. They do<br>
not occur spontaneously in unstimulated preparations;<br>
rather, their induction requires depolarizations are a type of triggered activity. They d<br>not occur spontaneously in unstimulated preparations<br>rather, their induction requires an initiating or triggerin depolarizations are a type of triggered activity. They do<br>not occur spontaneously in unstimulated preparations;<br>rather, their induction requires an initiating or triggering<br>event such as one or more action potentials. The depolarizations are a type of triggered activity. They not occur spontaneously in unstimulated preparation rather, their induction requires an initiating or triggerievent such as one or more action potentials. The amplitud depolarizations are a type of triggered activity. They do<br>not occur spontaneously in unstimulated preparations;<br>rather, their induction requires an initiating or triggering<br>event such as one or more action potentials. The not occur spontaneously in unstimulated preparations;<br>rather, their induction requires an initiating or triggering<br>event such as one or more action potentials. The ampli-<br>tude of a delayed afterdepolarization can be subthr rather, their induction requires an initiating or triggering<br>event such as one or more action potentials. The ampli-<br>tude of a delayed afterdepolarization can be subthreshold<br>(i.e., not reaching threshold voltage and initi event such as one or more action potentials. The amplitude of a delayed afterdepolarization can be subthreshold (i.e., not reaching threshold voltage and initiating an action potential), or a delayed afterdepolarization ca tude of a delayed afterdepolarization can be subthreshold<br>(i.e., not reaching threshold voltage and initiating an<br>action potential), or a delayed afterdepolarization can<br>reach threshold voltage and result in an action pote (i.e., not reaching threshold voltage and initiating and action potential), or a delayed afterdepolarization can reach threshold voltage and result in an action potential. When threshold is achieved repetitively, sustained **review).** The produced repetitively, sustained<br>the can be produced under certain experimental<br>method is in several cardiac cell types (see ref. 86 for<br>view).<br>The prototypical experimental method used to induce<br>layed afterdepolarizat

and insight into their clinical relevance.<br> **EXECUTE:** The same preparations and under similar experimental<br>
II. Induction of Delayed Afterdepolarizations<br>
Delayed afterdepolarizations are oscillations of mem-<br>
brane volt rhythms can be produced under certain experimental<br>conditions in several cardiac cell types (see ref. 86 for<br>review).<br>The prototypical experimental method used to induce<br>delayed afterdepolarizations is to expose cardiac ti conditions in several cardiac cell types (see ref. 86 for<br>review).<br>The prototypical experimental method used to induce<br>delayed afterdepolarizations is to expose cardiac tissue<br>to higher concentrations of cardiac glycosides noticly in the prototypical experimental method used to induce<br>delayed afterdepolarizations is to expose cardiac tissue<br>to higher concentrations of cardiac glycosides. This is<br>not a property of a particular cardiac glycosi The prototypical experimental method used to induc<br>delayed afterdepolarizations is to expose cardiac tissue<br>to higher concentrations of cardiac glycosides. This is<br>not a property of a particular cardiac glycoside, since is delayed afterdepolarizations is to expose cardiac tissue<br>to higher concentrations of cardiac glycosides. This is<br>not a property of a particular cardiac glycoside, since in<br>the same preparations and under similar experiment to higher concentrations of cardiac glycosides. This not a property of a particular cardiac glycoside, since the same preparations and under similar experiment conditions several cardiac glycosides have been shown induce d not a property of a particular cartuac grycoside, since in<br>the same preparations and under similar experimental<br>conditions several cardiac glycosides have been shown to<br>induce delayed afterdepolarizations (39). Cardiac gly conditions several cardiac glycosides have been shown to<br>induce delayed afterdepolarizations (39). Cardiac glyco-<br>sides are known to inhibit the Na-K exchange pump,<br>causing the intracellular Na<sup>+</sup> activity to rise (18, 51 induce delayed afterdepolarizations (39). Cardiac glycosides are known to inhibit the Na-K exchange pump, causing the intracellular Na<sup>+</sup> activity to rise (18, 51, 83). Through the Na-Ca exchange mechanism this results in sides are known to inhibit the Na-K exchange pump,<br>causing the intracellular Na<sup>+</sup> activity to rise (18, 51, 83).<br>Through the Na-Ca exchange mechanism this results in<br>a rise in intracellular Ca<sup>2+</sup> and the development of causing the intracellular Na<sup>+</sup> activity to rise (18, 51, 83).<br>Through the Na-Ca exchange mechanism this results in<br>a rise in intracellular Ca<sup>2+</sup> and the development of ten-<br>sion (51, 74). Consistent with a role for intr Through the Na-Ca exchange mechanism this results in<br>a rise in intracellular  $Ca^{2+}$  and the development of ten-<br>sion (51, 74). Consistent with a role for intracellular  $Ca^{2+}$ <br>in delayed afterdepolarizations, a transient a rise in intracellular  $Ca^{2+}$  and the development o<br>sion (51, 74). Consistent with a role for intracellula<br>in delayed afterdepolarizations, a transient contra<br>(the aftercontraction) can be recorded concomitant<br>delayed a sion (51, 74). Consistent with a role for intracellular Ca<sup>-1</sup><br>in delayed afterdepolarizations, a transient contraction<br>(the aftercontraction) can be recorded concomitant with<br>delayed afterdepolarizations. Delayed afterde (the aftercontraction) can be recorded concomitant with delayed afterdepolarizations. Delayed afterdepolarizations in cardiac cells have been attributed to  $Ca^{2+}$  overload, which can then result in a damped oscillatory r delayed alterdepolarizations. Delayed alterdepolarizations in cardiac cells have been attributed to  $Ca^{2+}$  over-<br>load, which can then result in a damped oscillatory<br>release of  $Ca^{2+}$  from internal stores. In agreement w load, which can then result in a damped oscillate release of  $Ca^{2+}$  from internal stores. In agreement w this hypothesis, several other interventions that raintracellular  $Ca^{2+}$  by different mechanisms also have been sho release of  $Ca^{2+}$  from internal stores. In agreement withis hypothesis, several other interventions that raintracellular  $Ca^{2+}$  by different mechanisms also have been shown to enhance development of delayed afterd polar this hypothesis, several other interventions that raise<br>intracellular  $Ca^{2+}$  by different mechanisms also have<br>been shown to enhance development of delayed afterde-<br>polarizations or the underlying transient inward trans220 **JANUARY AND**<br>clude lowering or removing  $[K]_0$ ,<sup>5</sup> lowering  $[Na]_0$ , raising (4<br>[Ca]<sub>0</sub>, and exposing the tissue to catecholamines. cu 220<br>  $\begin{aligned}\n\text{clude lowering or removing } [\mathbf{K}]_0, \text{'s lowering } [\mathbf{Na}]\n\text{[Cal]}_0, \text{ and exposing the tissue to catcholamin}\n\end{aligned}$  **III. A Transient Inward Current Causes** JANUARY ANI<br>
lude lowering or removing  $[K]_0$ ,<sup>\$</sup> lowering  $[Na]_0$ , raising<br>
Ca $]_0$ , and exposing the tissue to cate cholamines.<br>
III. A Transient Inward Current Causes Delayed<br>
After depolarizations and Is Induced by

## Nowering or removing  $[K]_0$ ,<sup>5</sup> lowering  $[Na]_0$ , raising<br>and exposing the tissue to cate cholamines.<br>A **Transient Inward Current Causes Delayed**<br>A **fterdepolarizations and Is Induced by**<br>Intracellular Ca<sup>2+</sup> [Ca]<sub>0</sub>, and exposing the tissue to catecholamines.<br>III. A Transient Inward Current Causes Delayed<br>Afterdepolarizations and Is Induced by<br>Intracellular Ca<sup>2+</sup>

**Single cells (60, 62), a transient inward current Causes Delayed**<br> **Afterdepolarizations and Is Induced by**<br> **In voltage-clamped cardiac preparations (40, 50) and**<br>
single cells (60, 62), a transient inward current ( $i_{\$ **Arterdepolarizations and Is Induced by**<br> **In voltage-clamped cardiac preparations (40, 50) an**<br>
single cells (60, 62), a transient inward current ( $i_{TI}$ ) has<br>
been associated with delayed afterdepolarizations. Sev-<br>
era In voltage-clamped cardiac preparations (40, 50) and<br>single cells (60, 62), a transient inward current  $(i_{\text{TI}})$  has<br>been associated with delayed afterdepolarizations. Sev-<br>eral lines of evidence suggest that  $i_{\text{TI}}$  i In voltage-clamped cardiac preparations (40, 50) and<br>single cells (60, 62), a transient inward current  $(i_{TI})$  has<br>been associated with delayed afterdepolarizations. Sev-<br>eral lines of evidence suggest that  $i_{TI}$  is the c single cells (60, 62), a transient inward current  $(i_{\text{TI}})$  has<br>been associated with delayed afterdepolarizations. Sev-<br>eral lines of evidence suggest that  $i_{\text{TI}}$  is the current that<br>underlies delayed afterdepolarizat been associated with delayed afterdepolarizations. S<br>eral lines of evidence suggest that  $i_{TI}$  is the current t<br>underlies delayed afterdepolarizations and that it<br>closely linked to a rise in intracellular Ca<sup>2+</sup>. (a) 7<br>a eral lines of evidence suggest that  $i_{TI}$  is the current<br>underlies delayed afterdepolarizations and that<br>closely linked to a rise in intracellular  $Ca^{2+}$ . (*a*)<br>appearance of  $i_{TI}$  coincides temporally with the dev<br>men underlies delayed afterdepolarizations and that it is<br>closely linked to a rise in intracellular  $Ca^{2+}$ . (a) The<br>appearance of  $i_{TI}$  coincides temporally with the develop-<br>ment of delayed afterdepolarizations and afterco closely linked to a rise in intracellular  $Ca^{2+}$ . (a) The<br>appearance of  $i_{TI}$  coincides temporally with the develop-<br>ment of delayed afterdepolarizations and aftercontrac-<br>tions following exposure to cardiac glycosides, appearance of  $i_{TI}$  coincides temporally with the develop-<br>ment of delayed afterdepolarizations and aftercontrac-<br>tions following exposure to cardiac glycosides, and they<br>all appear at similar concentrations. (b) The dep ment of delayed afterdepolarizations and aftercontractions following exposure to cardiac glycosides, and they all appear at similar concentrations. (b) The dependence of delayed afterdepolarizations and  $i_{\text{TI}}$  on frequ tions following exposure to cardiac glycosides, and they<br>all appear at similar concentrations. (b) The dependence<br>of delayed afterdepolarizations and  $i_{\text{TI}}$  on frequency of<br>stimulation is similar (50, 81). (c)  $Ca^{2+}$  all appear at similar concentrations. (b) The dependence<br>of delayed afterdepolarizations and  $i_{TI}$  on frequency of<br>stimulation is similar (50, 81). (c)  $Ca^{2+}$  overload of heart<br>cells results in increased spontaneous mem of delayed afterdepolarizations and  $i_{\text{TI}}$  on frequency of stimulation is similar (50, 81). (c)  $Ca^{2+}$  overload of heart cells results in increased spontaneous membrane voltage or current (recorded under voltage clamp stimulation is similar (50, 81). (c)  $Ca^{2+}$  overload of heart<br>cells results in increased spontaneous membrane voltage<br>or current (recorded under voltage clamp conditions)<br>moise. Power spectral analysis has shown that the cells results in increased spontaneous membrane voltage<br>or current (recorded under voltage clamp conditions)<br>noise. Power spectral analysis has shown that the fre-<br>quency distribution contained within these voltage or<br>curr noise. Power spectral analysis has shown that the frequency distribution contained within these voltage or<br>current signals is similar  $(42, 60)$ , and that evoking  $\frac{1}{11}$  the<br>results in additional power that contains t quency distribution contained within these voltage or current signals is similar  $(42, 60)$ , and that evoking i<sub>TI</sub> results in additional power that contains the same frequency distribution  $(42)$ . A similar relationship current signals is similar  $(42, 60)$ , and that evoking i<sub>TI</sub><br>results in additional power that contains the same fre-<br>quency distribution  $(42)$ . A similar relationship has been<br>shown between the frequency spectra of spon results in additional power that contains the same frequency distribution (42). A similar relationship has been shown between the frequency spectra of spontaneous membrane current noise and tension fluctuations (42; ur se quency distribution (42). A similar relationship has been<br>shown between the frequency spectra of spontaneous<br>membrane current noise and tension fluctuations (42;<br>see also ref. 10). These and other studies (41) showed<br>that shown between the frequency spectra of spontaneous<br>membrane current noise and tension fluctuations (42; und<br>see also ref. 10). These and other studies (41) showed<br>that changes in contractile force lagged behind changes<br>in membrane current noise and tension fluctuations (42;<br>see also ref. 10). These and other studies (41) showed<br>that changes in contractile force lagged behind changes<br>in membrane current in a voltage-dependent manner by<br>40 t see also ref. 10). These and other studies (41) showed<br>that changes in contractile force lagged behind changes<br>in membrane current in a voltage-dependent manner by<br>40 to 140 ms. (d) An intracellular  $Ca^{2+}$  transient has<br> that changes in contractile force lagged behind change<br>in membrane current in a voltage-dependent manner b<br>40 to 140 ms. (*d*) An intracellular  $Ca^{2+}$  transient ha<br>been associated with delayed afterdepolarizations (84<br>( in membrane current in a voltage-dependent manner by<br>40 to 140 ms. (d) An intracellular  $Ca^{2+}$  transient has<br>been associated with delayed afterdepolarizations (84).<br>(e) Intracellular injection of  $Ca^{2+}$  elicits delayed 40 to 140 ms. (d) An intracellular  $Ca^{2+}$  trablem associated with delayed afterdepolarization (e) Intracellular injection of  $Ca^{2+}$  elicits delapolarizations (60). (f) Modification of in $Ca^{2+}$  by the injection of ethyl been associated with delayed afterdepolarizations (84).<br>
(e) Intracellular injection of Ca<sup>2+</sup> elicits delayed after-<br>
depolarizations (60). (f) Modification of intracellular<br>
Ca<sup>2+</sup> by the injection of ethyleneglycol-bis (e) Intracellular injection of Ca<sup>2+</sup> elicits delayed after-<br>depolarizations (60). (f) Modification of intracellular<br>Ca<sup>2+</sup> by the injection of ethyleneglycol-bis( $\beta$ -aminoeth-<br>ylether)-N,N'-tetraacetic acid (EGTA) into depolarizations (60). (*f*) Modification of intracellu Ca<sup>2+</sup> by the injection of ethyleneglycol-bis( $\beta$ -aminoe ylether)-N,N'-tetraacetic acid (EGTA) into cells, or the application of caffeine, suppresses both delayed te Ca<sup>2+</sup> by the injection of ethyleneglycol-bis( $\beta$ -aminoeth-<br>ylether)-N,N'-tetraacetic acid (EGTA) into cells, or by<br>the application of caffeine, suppresses both delayed af-<br>terdepolarizations and  $i_{\text{TI}}$  (60; see also ylether)-N,N'-tetraacetic acid (EGTA) into cells, or by<br>the application of caffeine, suppresses both delayed af-<br>terdepolarizations and  $i_{TI}$  (60; see also ref. 42). Ryano-<br>dine, which blocks  $Ca^{2+}$  release from the sar the application of caffeine, suppresses both delayed at<br>terdepolarizations and  $i_{TI}$  (60; see also ref. 42). Ryano<br>dine, which blocks  $Ca^{2+}$  release from the sarcoplasmi<br>reticulum (SR), has been shown to suppress delaye terdepolarizations and  $i_{TI}$  (60; see also ref. 42). Ryano-<br>dine, which blocks  $Ca^{2+}$  release from the sarcoplasmic<br>reticulum (SR), has been shown to suppress delayed<br>afterdepolarizations or  $i_{TI}$  and the associated  $Ca$ dine, which blocks  $Ca^{2+}$  release from the sarcoplasmic the reticulum (SR), has been shown to suppress delayed necter-<br>afterdepolarizations or  $i_{TI}$  and the associated  $Ca^{2+}$  transient (59, 76, 79). Recently, it was sh reticulum (SR), has been shown to suppress delayed networks after<br>depolarizations or  $i_{TI}$  and the associated Ca<sup>2+</sup> tran-<br>sient (59, 76, 79). Recently, it was shown that, when 1,2-<br>methods (2-aminophenoxy)ethane-N,N,N', afterdepolarizations or  $i_{TI}$  and the associated Ca<sup>2+</sup><br>sient (59, 76, 79). Recently, it was shown that, whe<br>bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic<br>(BAPTA), a potent chelator of Ca<sup>2+</sup>, was diffused<br>cardiac tiss sient (59, 76, 79). Recently, it was shown that, when 1,2-<br>bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid age<br>(BAPTA), a potent chelator of  $Ca^{2+}$ , was diffused into spocardiac tissue, it also abolished delayed aft bis(2-aminophenoxy)ethano(BAPTA), a potent chelato<br>cardiac tissue, it also abolis<br>tions, the associated oscillat<br>the aftercontraction (59).<br>IV Calcium Release cardiac tissue, it also abolished delayed afterdepolarizations, the associated oscillation in intracellular  $Ca^{2+}$ , and the aftercontraction (59).<br>IV. Calcium Release by the Sarcoplasmic

### Reticulum

The SR of striated muscle is the major storage site for<br>  $\frac{1}{2}$  The SR of striated muscle is the major storage site for<br>  $\frac{1}{2}$  Ca<sup>2+</sup> that is released to produce normal contraction contraction IV. Calcium Release by the Sarcoplasmic<br>Reticulum<br>The SR of striated muscle is the major storage site for<br>the Ca<sup>2+</sup> that is released to produce normal contraction<br>§ Abbreviations used are: [K]<sub>0</sub>, [Na]<sub>0</sub>, and [Ca]<sub>0</sub>, e The SR of striated muscle is the major storage site for<br>e Ca<sup>2+</sup> that is released to produce normal contraction<br>§ Abbreviations used are: [K]<sub>0</sub>, [Na]<sub>0</sub>, and [Ca]<sub>0</sub>, extracellular K, Na,<br>d Ca concentrations, respectively

[Ca]<sub>0</sub>, and exposing the tissue to catecholamines. current. Ca<sup>2+</sup> for contraction is then released by the SR,<br> **III. A Transient Inward Current Causes Delayed** and it diffuses to the myofibrils. Binding to troponin C<br> (44). First, the action potential activates a small  $Ca^{2+}$  current.  $Ca^{2+}$  for contraction is then released by the SR, FOZZARD<br>(44). First, the action potential activates a small  $Ca^{2+}$ <br>current.  $Ca^{2+}$  for contraction is then released by the SR,<br>and it diffuses to the myofibrils. Binding to troponin C and it diffuses to the myofibrils. Binding to translation is the myofibrils. Binding to troponin C initiates cell shortening or force development through (44). First, the action potential activates a small  $Ca^{2+}$  current.  $Ca^{2+}$  for contraction is then released by the SR, and it diffuses to the myofibrils. Binding to troponin C initiates cell shortening or force developm (44). First, the action potential activates a small  $Ca^{2+}$ <br>current.  $Ca^{2+}$  for contraction is then released by the SR,<br>and it diffuses to the myofibrils. Binding to troponin C<br>initiates cell shortening or force developm current.  $Ca^{2+}$  for contraction is then released by the SI<br>and it diffuses to the myofibrils. Binding to troponin<br>initiates cell shortening or force development throug<br>interaction of actin and myosin filaments. The relea and it diffuses to the myofibrils. Binding to troponinitiates cell shortening or force development throutinteraction of actin and myosin filaments. The relea  $Ca^{2+}$  is then pumped back into the SR by an A<sup>7</sup> dependent  $Ca$ tion. teraction of actin and myosin filaments. The released  $a^{2+}$  is then pumped back into the SR by an ATP-<br>pendent  $Ca^{2+}$  pump and stored for the next contrac-<br>on.<br>The  $Ca^{2+}$  uptake phase of SR function has been well<br>udie

 $Ca^{2+}$  is then pumped back into the SR by an ATP-<br>dependent  $Ca^{2+}$  pump and stored for the next contrac-<br>tion.<br>The  $Ca^{2+}$  uptake phase of SR function has been well<br>studied. The primary amino acid sequence of the  $Ca^{2+}$ dependent  $Ca^{2+}$  pump and stored for the next control tion.<br>The  $Ca^{2+}$  uptake phase of SR function has been vestudied. The primary amino acid sequence of the C pump has been determined, and much of its 3-dimensional str tion.<br>
The Ca<sup>2+</sup> uptake phase of SR function has been well<br>
studied. The primary amino acid sequence of the Ca<sup>2+</sup><br>
pump has been determined, and much of its 3-dimen-<br>
sional structure deduced. However, the Ca<sup>2+</sup> releas The Ca<sup>2+</sup> uptake phase of SR function has been well studied. The primary amino acid sequence of the Ca<sup>2+</sup> pump has been determined, and much of its 3-dimensional structure deduced. However, the Ca<sup>2+</sup> release phase of S studied. The primary amino acid sequence of the  $Ca^{2+}$ <br>pump has been determined, and much of its 3-dimen-<br>sional structure deduced. However, the  $Ca^{2+}$  release<br>phase of SR function is less well understood. The major<br>hyp pump has been determined, and much of its 3-dimensional structure deduced. However, the  $Ca^{2+}$  release phase of SR function is less well understood. The major hypothesis to explain  $Ca^{2+}$  release from cardiac SR is that sional structure deduced. However, the Ca<sup>2+</sup> release<br>phase of SR function is less well understood. The major<br>hypothesis to explain Ca<sup>2+</sup> release from cardiac SR is<br>that release is triggered by an increase in cytoplasmic phase of SR function is less well understood. The major<br>hypothesis to explain  $Ca^{2+}$  release from cardiac SR is<br>that release is triggered by an increase in cytoplasmic<br> $Ca^{2+}$  (25-27; see also ref. 4). According to this hypothesis to explain  $Ca^{2+}$  release from cardiac SR is<br>that release is triggered by an increase in cytoplasmic<br> $Ca^{2+}$  (25–27; see also ref. 4). According to this concept,<br>transsarcolemmal  $Ca^{2+}$  current increases  $Ca^{2$ that release is triggered by an increase in cytoplasmic  $Ca^{2+}$  (25-27; see also ref. 4). According to this concept, transsarcolemmal  $Ca^{2+}$  current increases  $Ca^{2+}$  in the vicinity of the SR, causing it to release its  $Ca^{2+}$  (25-27; see also ref. 4). According to this concept,<br>transsarcolemmal  $Ca^{2+}$  current increases  $Ca^{2+}$  in the<br>vicinity of the SR, causing it to release its store. With<br>an action potential as trigger, release of S transsarcolemmal Ca<sup>2+</sup> current increases Ca<sup>2+</sup> in the vicinity of the SR, causing it to release its store. With an action potential as trigger, release of SR-stored Ca<sup>2+</sup> under normal conditions is complete and is suff vicinity of the SR, causing it to release its store. With<br>an action potential as trigger, release of SR-stored Ca<sup>2+</sup><br>under normal conditions is complete and is sufficient for<br>a contraction that is 10 to 20% of maximum. A an action potential as trigger, release of SR-stored  $Ca^{2+}$ <br>under normal conditions is complete and is sufficient for<br>a contraction that is 10 to 20% of maximum. Additional<br> $Ca^{2+}$  loading of the cell, and consequently o under normal conditions is complete and is sufficient for<br>a contraction that is 10 to 20% of maximum. Additional<br>Ca<sup>2+</sup> loading of the cell, and consequently of the SR, can<br>therefore result in a 5- to 10-fold increase in a contraction that is 10 to 20% of maximum. Additional  $Ca^{2+}$  loading of the cell, and consequently of the SR, can therefore result in a 5- to 10-fold increase in contraction strength. Partial release of  $Ca^{2+}$  stored i  $Ca^{2+}$  loading of the cell, and consequently of the SR, can<br>therefore result in a 5- to 10-fold increase in contraction<br>strength. Partial release of  $Ca^{2+}$  stored in the SR can be<br>obtained experimentally, and this may o therefore result in a 5- to 10-fold increase in contraction<br>strength. Partial release of  $Ca^{2+}$  stored in the SR can be<br>obtained experimentally, and this may occur naturally<br>under unusual circumstances. The mechanism of strength. Partial release of  $Ca^{2+}$  stored in the SR can be obtained experimentally, and this may occur naturally under unusual circumstances. The mechanism of  $Ca^{2+}$ -triggered release is not well understood, but there obtained experimentally, and this may occurred under unusual circumstances. The mechanitriggered release is not well understood, because the SR of cardiac muscular Ca<sup>2+</sup> channels that are gated by Ca<sup>2+</sup> (72). The cytopl der unusual circumstances. The mechanism of  $Ca^{2+}$ -<br>ggered release is not well understood, but there is<br>cent evidence that the SR of cardiac muscle contains<br> $a^{2+}$  channels that are gated by  $Ca^{2+}$  (72).<br>The cytoplasmi

triggered release is not well understood, but there is<br>recent evidence that the SR of cardiac muscle contains<br> $Ca^{2+}$  channels that are gated by  $Ca^{2+}$  (72).<br>The cytoplasmic  $Ca^{2+}$  level itself is established by a<br>compl recent evidence that the SR of cardiac muscle contains  $Ca^{2+}$  channels that are gated by  $Ca^{2+}$  (72).<br>The cytoplasmic  $Ca^{2+}$  level itself is established by a complex interaction between sarcolemmal influx through  $Ca^{2+$  $Ca^{2+}$  channels that are gated by  $Ca^{2+}$  (72).<br>The cytoplasmic  $Ca^{2+}$  level itself is established by a complex interaction between sarcolemmal influx through  $Ca^{2+}$  channels and perhaps Na-Ca exchange, efflux through The cytoplasmic  $Ca^{2+}$  level itself is established by a complex interaction between sarcolemmal influx through  $Ca^{2+}$  channels and perhaps Na-Ca exchange, efflux through Na-Ca exchange and the sarcolemmal  $Ca^{2+}$  pump, complex interaction between sarcolemmal influx through  $Ca^{2+}$  channels and perhaps Na-Ca exchange, efflux through Na-Ca exchange and the sarcolemmal  $Ca^{2+}$  pump, intracellular sequestration in the SR and perhaps in orga  $Ca^{2+}$  channels and perhaps Na-Ca exchange, efflux<br>through Na-Ca exchange and the sarcolemmal  $Ca^{2+}$ <br>pump, intracellular sequestration in the SR and perhaps<br>in organelles such as mitochondria, and binding to tro-<br>ponin through Na-Ca exchange and the sarcolemmal  $Ca^{2+}$ <br>pump, intracellular sequestration in the SR and perhaps<br>in organelles such as mitochondria, and binding to tro-<br>ponin C and perhaps to other cytoplasmic molecules.<br>When t in organelles such as mitochondria, and binding to tro-<br>ponin C and perhaps to other cytoplasmic molecules.<br>When the resting myocardial cell is overloaded with  $Ca^{2+}$ ,<br>the SR cannot maintain its increased store, and spon in organelles such as mitochondria, and binding to tro-<br>ponin C and perhaps to other cytoplasmic molecules.<br>When the resting myocardial cell is overloaded with  $Ca^{2+}$ ,<br>the SR cannot maintain its increased store, and spon ponin C and perhaps to other cytoplasmic molecules.<br>When the resting myocardial cell is overloaded with Ca<sup>2+</sup>,<br>the SR cannot maintain its increased store, and sponta-<br>neous release can be seen, even in quiescent cells (1, 49, 85). Spontaneous fluctuations can then occur in the membrane potential, the membrane current under volt-<br>age clamp, and contractions (42). The relation between the SR cannot maintain its increased store, and spontaneous release can be seen, even in quiescent cells  $(1, 23, 49, 85)$ . Spontaneous fluctuations can then occur in the membrane potential, the membrane current under vol neous release can be seen, even in quiescent cells  $(1, 23, 49, 85)$ . Spontaneous fluctuations can then occur in the membrane potential, the membrane current under voltage clamp, and contractions  $(42)$ . The relation betw 49, 85). Spontaneous fluctuations can then occur in the membrane potential, the membrane current under voltage clamp, and contractions (42). The relation between spontaneous or cyclical  $Ca^{2+}$  release and the  $Ca^{2+}$  tra membrane potential, the membrane current under volt-<br>age clamp, and contractions (42). The relation between<br>spontaneous or cyclical  $Ca^{2+}$  release and the  $Ca^{2+}$  tran-<br>sient producing the afterdepolarization is proposed age clamp, and contractions (42). The relation between<br>spontaneous or cyclical Ca<sup>2+</sup> release and the Ca<sup>2+</sup> tran-<br>sient producing the afterdepolarization is proposed to be<br>the following. If the cell is stimulated to have spontaneous or cyclical  $Ca^{2+}$  release and the  $Ca^{2+}$  transient producing the afterdepolarization is proposed to be the following. If the cell is stimulated to have action potentials and contractions, the SR releases it sient producing the afterdepolarization is proposed to be<br>the following. If the cell is stimulated to have action<br>potentials and contractions, the SR releases its  $Ca^{2+}$ <br>synchronously, and it reaccumulates  $Ca^{2+}$  in a s the following. If the cell is stimulated to have action<br>potentials and contractions, the SR releases its  $Ca^{2+}$ <br>synchronously, and it reaccumulates  $Ca^{2+}$  in a similarly potentials and contractions, the SR releases its  $Ca^{2+}$ <br>synchronously, and it reaccumulates  $Ca^{2+}$  in a similarly<br>synchronous fashion. When overfilled with  $Ca^{2+}$ , the SR<br>can then spontaneously release  $Ca^{2+}$  again. T synchronously, and it reaccumulates  $Ca^{2+}$  in a similarly<br>synchronous fashion. When overfilled with  $Ca^{2+}$ , the SR<br>can then spontaneously release  $Ca^{2+}$  again. This spon-<br>taneous release and reaccumulation may occur fo can then spontaneously release  $Ca^{2+}$  again. This spontaneous release and reaccumulation may occur for 2 or 3 cycles, until  $Ca^{2+}$  reassumes steady-state conditions or release becomes asynchronous. The rise in  $Ca^{2+}$  t taneous release and reaccumulation may occur for  $2$  or  $3$ cycles, until Ca<sup>2+</sup> reassumes steady-state conditions or release becomes asynchronous. The rise in Ca<sup>2+</sup> tempo-<br>rally correlates with the aftercontraction that character-<br>izes the Ca<sup>2+</sup>-overloaded state (66, 84).<br>The m cles, until Ca<sup>2+</sup> reassumes steady-state conditions or lease becomes asynchronous. The rise in Ca<sup>2+</sup> tempo-<br>lly correlates with the aftercontraction that character-<br>s the Ca<sup>2+</sup>-overloaded state (66, 84).<br>The mechanism release becomes asynchronous. The rise in  $Ca^{2+}$  temporally correlates with the aftercontraction that character-<br>izes the  $Ca^{2+}$ -overloaded state (66, 84).<br>The mechanism of this spontaneous release in  $Ca^{2+}$ -<br>overloade



PHARMACOLOGICAL REVIEW

The SR of striated muscle is the major storage site for<br>the  $Ca^{2+}$  that is released to produce normal contraction<br>§ Abbreviations used are:  $[K]_0$ ,  $[Na]_0$ , and  $[Ca]_0$ , extracellular K, Na,<br>and Ca concentrations, respec the Ca<sup>2+</sup> that is released to produce normal contraction<br>§ Abbreviations used are: [K]<sub>0</sub>, [Na]<sub>0</sub>, and [Ca]<sub>0</sub>, extracellular K, Na,<br>and Ca concentrations, respectively;  $i_{\text{Tr}}$ , transient inward current;<br>EGTA, ethylen § Abbreviations used are:  $[K]_0$ ,  $[Na]_0$ , and  $[Ca]_0$ , extracellular K, Na, and Ca concentrations, respectively;  $i_{\text{TI}}$ , transient inward current; EGTA, ethyleneglycol-bis( $\beta$ -aminoethylether)-N,N'-tetraacetic acid; aminophenoxy associated. The expectively, and Canconductations, respectively,  $i_{\text{H}}$ , transient inward current expectively is the experiment of the experiment of the experiment of the experiment of the saminophenoxy)eth xlammonium; TRIS, Terycourive, Tris, Trischensen, TRIS, Tris(hydroxymethyletheninophenoxy)ethane-N,N,N',N'-tetraacetic<br>saminophenoxy)ethane-N,N,N',N'-tetraacetic<br>ylammonium; TRIS, Tris(hydroxymethyl)am

DELAYED AFTERDEPOLARI<br>"breakdown" of the membrane, backward transport<br>through the Ca<sup>2+</sup> pump, or opening of the SR Ca<sup>2+</sup> **DELAYED AFTERDEPOLARIZ.**<br>
"breakdown" of the membrane, backward transport<br>
through the  $Ca^{2+}$  pump, or opening of the SR  $Ca^{2+}$ <br>
channels. The most likely mechanism would seem to be "breakdown" of the membrane, backward transport ity<br>through the Ca<sup>2+</sup> pump, or opening of the SR Ca<sup>2+</sup> age<br>channels. The most likely mechanism would seem to be on<br>opening of SR Ca<sup>2+</sup> channels. It also has been shown ne "breakdown" of the membrane, backward transport ithrough the Ca<sup>2+</sup> pump, or opening of the SR Ca<sup>2+</sup> a channels. The most likely mechanism would seem to be opening of SR Ca<sup>2+</sup> channels. It also has been shown rethat inc through the Ca<sup>2+</sup> pump, or opening of the SR Ca<sup>2+</sup> age channels. The most likely mechanism would seem to be or opening of SR Ca<sup>2+</sup> channels. It also has been shown nethat increasing cytoplasmic Ca<sup>2+</sup> in "skinned" card channels. The most likely mechanism would seem to be opening of SR  $Ca^{2+}$  channels. It also has been shown that increasing cytoplasmic  $Ca^{2+}$  in "skinned" cardiac cells (25) can produce cyclical  $Ca^{2+}$  release from SR. opening of SR  $Ca^{2+}$  channels. It also has been shown that increasing cytoplasmic  $Ca^{2+}$  in "skinned" cardiac (cells (25) can produce cyclical  $Ca^{2+}$  release from SR. The increase of spontaneous release and reaccumulat that increasing cytoplasmic  $Ca^{2+}$  in "skinned" cardiac (2<br>cells (25) can produce cyclical  $Ca^{2+}$  release from SR. The<br>presence of spontaneous release and reaccumulation that by<br>can be seen in isolated SR or in skinned cells (25) can produce cyclical  $Ca^{2+}$  release from SR. The interest presence of spontaneous release and reaccumulation that can be seen in isolated SR or in skinned cells is evidence that sarcolemmal current is not requ presence of spontaneous release and reaccumulation that b:<br>
can be seen in isolated SR or in skinned cells is evidence<br>
that sarcolemmal current is not required to trigger the<br>
cyclical events, although Lin et al. (54) an can be seen in isolated SR or in skinned cells is evidence<br>that sarcolemmal current is not required to trigger the<br>cyclical events, although Lin et al.  $(54)$  and Boyette et<br>al.  $(5)$  have reported a complex relationship

## Current V. The Charge-carrying Mechanism for  $i_{TI}$ ,<br>Membrane Channel versus Exchange Pump<br>Current<br>The cellular basis for  $i_{TI}$  has remained controversial<br>d two different charge-carrying mechanisms for  $i_{TI}$  and

**and two different charge-carrying mechanism for**  $1_{TI}$  (see<br>and two different charge-carrying mechanisms for  $1_{TI}$  are<br>presently hypothesized. One hypothesis (41-43) favors a<br>nonselective cation membrane channel with i **EXECUTE CONSERVABLE CONTINUIST THE CONSERVANCE CONTINUIST AND ABOVE THE PRESENT PRESENTLY INTEREST AND APPRESENT CONSERVATOR CONSERVATOR CONSERVATOR CONSERVATOR CONSERVATOR AND ANCE PER UNIT CAPT.** Under conduction and a The cellular basis for  $i_{TI}$  has remained controversial,<br>and two different charge-carrying mechanisms for  $i_{TI}$  are<br>presently hypothesized. One hypothesis (41–43) favors a<br>anonselective cation membrane channel with its and two different charge-carrying mechanisms for  $i_{TI}$  are<br>presently hypothesized. One hypothesis (41–43) favors a<br>nonselective cation membrane channel with its conduct-<br>ance regulated by intracellular  $Ca^{2+}$ . Under con presently hypothesized. One hypothesis  $(41-43)$  favors a<br>nonselective cation membrane channel with its conduct-<br>ance regulated by intracellular  $Ca^{2+}$ . Under conditions of<br> $Ca^{2+}$  overload, there could occur a cyclical nonselective cation membrane channel with its conduct-<br>ance regulated by intracellular  $Ca^{2+}$ . Under conditions of<br> $Ca^{2+}$  overload, there could occur a cyclical release of  $Ca^{2+}$ <br>from the SR (synchronized by the action  $Ca^{2+}$  overload, there could occur a cyclical release of  $Ca^{2+}$  from the SR (synchronized by the action potential or its repolarization), and this results in a transient increase in the nonselective cation-permeable cha from the SR (synchronized by the action potential or its Ca overload, there collu occur a cyclical release of Ca<br>
from the SR (synchronized by the action potential or its<br>
repolarization), and this results in a transient increase<br>
in the nonselective cation-permeable channel co repolarization), and this results in a transient increase<br>in the nonselective cation-permeable channel conduct-<br>ance, in parallel with activation of the aftercontraction.<br>In voltage-clamped cardiac Purkinje fibers, Tsien in the nonselective cation-permeable channel conduct-<br>ance, in parallel with activation of the aftercontraction.<br>In voltage-clamped cardiac Purkinje fibers, Tsien and<br>his colleagues (43) found the reversal potential for ance, in parallel with activation of the aftercontraction.<br>In voltage-clamped cardiac Purkinje fibers, Tsien and<br>his colleagues (43) found the reversal potential for  $i_{T1}$  to<br>be approximately  $-5$  mV in normal Tyrode's In voltage-clamped cardiac Purkinje fibers, Tsien and<br>his colleagues (43) found the reversal potential for  $i_{TI}$  to<br>be approximately  $-5$  mV in normal Tyrode's solution.<br>In those experiments, the identification of  $i_{TI}$ his colleagues (43) found the reversal potential for  $i_{TI}$  to<br>be approximately  $-5$  mV in normal Tyrode's solution.<br>In those experiments, the identification of  $i_{TI}$  as a  $Ca^{2+}$ -<br>activated current was supported by the In those experiments, the identification of  $i_{TI}$  as a Ca<sup>2+</sup>-<br>activated current was supported by the simultaneous<br>recording of aftercontractions. Evidence that the current<br>resulted from the Ca<sup>2+</sup> release, rather than v In those experiments, the identification of  $i_{TI}$  as a Ca<sup>2+</sup>-<br>activated current was supported by the simultaneous<br>recording of aftercontractions. Evidence that the current<br>resulted from the Ca<sup>2+</sup> release, rather than v activated current was supported by the simultaneo<br>recording of aftercontractions. Evidence that the curre<br>resulted from the  $Ca^{2+}$  release, rather than vice vers<br>included the presence of aftercontractions near the r<br>vers recording of aftercontractions. Evidence that the current<br>resulted from the  $Ca^{2+}$  release, rather than vice versa,<br>included the presence of aftercontractions near the re-<br>versal potential of  $i_{\text{TI}}$ . The reversal pote resulted from the Ca<sup>2+</sup> release, rather than vice versa<br>included the presence of aftercontractions near the re<br>versal potential of  $i_{TI}$ . The reversal potential was sensitive to withdrawal of Na<sup>+</sup> from the bath (becomi included the presence of aftercontractions near the reversal potential of  $i_{\text{TI}}$ . The reversal potential was sensitive to withdrawal of Na<sup>+</sup> from the bath (becoming about  $-35$  mV), but it was insensitive to replaceme versal potential of  $i_{TI}$ . The reversal potential was set<br>ive to withdrawal of Na<sup>+</sup> from the bath (becoming ab<br>-35 mV), but it was insensitive to replacement of cl<br>ride by an impermeant anion. Although changes in<br>revers tive to withdrawal of Na<sup>+</sup> from the bath (becoming ab  $-35$  mV), but it was insensitive to replacement of ch<br>ride by an impermeant anion. Although changes in<br>reversal potential with small manipulations of extrac<br>lular K<sup></sup> -35 mV), but it was insensitive to replacement of chlo-<br>ride by an impermeant anion. Although changes in the<br>reversal potential with small manipulations of extracel-<br>lular K<sup>+</sup> (1 to 8 mM) could not be shown, a K<sup>+</sup> perme ride by an impermeant anion. Although changes in the versal potential with small manipulations of extracel-<br>lular  $K^+$  (1 to 8 mM) could not be shown, a  $K^+$  permeation bility (approximately equal to that of Na<sup>+</sup>) was reversal potential with small manipulations of extracel-<br>lular  $K^+$  (1 to 8 mM) could not be shown, a  $K^+$  permea-<br>bility (approximately equal to that of  $Na^+$ ) was required<br>to account for the value of the reversal pote lular K<sup>+</sup> (1 to 8 mM) could not be shown, a K<sup>+</sup> permeability (approximately equal to that of Na<sup>+</sup>) was required account for the value of the reversal potential in 69).<br>normal Tyrode's solution (assuming that the only c bility (approximately equal to that of Na<sup>+</sup>) was required<br>to account for the value of the reversal potential in<br>normal Tyrode's solution (assuming that the only cur-<br>rent flow was through the  $i_{TI}$  channel). Permeabilit to account for the value of the reversal potential in 69). The initiating sequence for the delayed afterdepo-<br>normal Tyrode's solution (assuming that the only cur-<br>rent flow was through the  $i_{TI}$  channel). Permeability t normal Tyrode's solution (assuming that the only<br>rent flow was through the  $i_{TI}$  channel). Permeabili<br>Ca<sup>2+</sup> also was suggested because the reversal pote<br>remained well positive to the K<sup>+</sup> reversal potential is<br>absence o rent flow was through the i<sub>TI</sub> channel). Permeability to  $Ca^{2+}$  also was suggested because the reversal potential remained well positive to the K<sup>+</sup> reversal potential in the absence of Na<sup>+</sup> (see also ref. 10). The sim  $Ca^{2+}$  also was suggested because the reversal potential remained well positive to the K<sup>+</sup> reversal potential in the absence of Na<sup>+</sup> (see also ref. 10). The simplest explanation for these data, based primarily on the i remained well positive to the  $K^+$  reversal potential in<br>absence of  $Na^+$  (see also ref. 10). The simplest expli<br>tion for these data, based primarily on the identifica<br>of a reversal potential for  $i_{TI}$ , was to postulate absence of Na<sup>+</sup> (see also ref. 10). The simplest<br>tion for these data, based primarily on the ider<br>of a reversal potential for  $i_{TI}$ , was to postulat<br>activated membrane channel with significant p<br>ities to sodium, potassi on for these data, based primarily on the identification fail reversal potential for  $i_{TI}$ , was to postulate a Ca<sup>2+</sup>-<br>tivated membrane channel with significant permeabil-<br>es to sodium, potassium, and calcium ions. With of a reversal potential for  $i_{TI}$ , was to postulate a C-<br>activated membrane channel with significant permea<br>ities to sodium, potassium, and calcium ions.<br>With the development of single channel record<br>techniques (31), rec

activated membrane channel with significant permeabil-<br>ities to sodium, potassium, and calcium ions. In<br>With the development of single channel recording (3<br>techniques (31), recordings in cardiac cells of a nonselec-<br>dive ities to sodium, potassium, and calcium ions.<br>With the development of single channel recording<br>techniques (31), recordings in cardiac cells of a nonselec-<br>tive cation channel activated by intracellular  $Ca^{2+}$  have<br>been o With the development of single channel recording (itechniques (31), recordings in cardiac cells of a nonselec-<br>tive cation channel activated by intracellular  $Ca^{2+}$  have the<br>been obtained by Colquhoun et al. (15) in cult techniques (31), recordings in cardiac cells of a nonsel<br>tive cation channel activated by intracellular  $Ca^{2+}$  h<br>been obtained by Colquhoun et al. (15) in cultured<br>neonatal myocytes and Ehara et al. (21) in adult guin<br>pi

DELAYED AFTERDEPOLARIZATIONS IN HEART MUSCLE<br>Dreakdown" of the membrane, backward transport ity among monovalent cations, but are highly selective<sup>\*</sup> through the Ca<sup>2+</sup> pump, or opening of the SR Ca<sup>2+</sup> against anions, and their gating shows little dependence<br>channels. The most likely mechanism would seem to be on membrane voltage. The unit conductance of the chan-<br>ope ity among monovalent cations, but are highly selective TIONS IN HEART MUSCLE<br>ity among monovalent cations, but are highly selective<br>against anions, and their gating shows little dependence<br>on membrane voltage. The unit conductance of the chan-TIONS IN HEART MUSCLE<br>ity among monovalent cations, but are highly selective<br>against anions, and their gating shows little dependen<br>on membrane voltage. The unit conductance of the chan-<br>nels studied by Colquhoun et al. (1 ity among monovalent cations, but are highly selective<br>against anions, and their gating shows little dependence<br>on membrane voltage. The unit conductance of the chan-<br>nels studied by Colquhoun et al. (15) was 30 to 40 pS<br>( ity among monovalent cations, but are highly selective<br>against anions, and their gating shows little dependence<br>on membrane voltage. The unit conductance of the chan-<br>nels studied by Colquhoun et al. (15) was 30 to 40 pS<br> against anions, and their gating shows little dependence<br>on membrane voltage. The unit conductance of the chan-<br>nels studied by Colquhoun et al. (15) was 30 to 40 pS<br> $(25-27^{\circ}\text{C})$ , and these channels could be activated on membrane voltage. The unit conductance of the channels studied by Colquhoun et al. (15) was 30 to 40 pS (25-27°C), and these channels could be activated by inside Ca<sup>2+</sup> concentrations of  $1 \mu$ M. The channels studied b nels studied by Colquhoun et al. (15) was 30 to 40 pS (25-27°C), and these channels could be activated by inside Ca<sup>2+</sup> concentrations of  $1 \mu$ M. The channels studied by Ehara et al. (21) had a lower unit conductance of a (25-27°C), and these channels could be activated<br>inside Ca<sup>2+</sup> concentrations of 1  $\mu$ M. The channels stud<br>by Ehara et al. (21) had a lower unit conductance<br>about 15 pS (20-25°C). The Ca<sup>2+</sup> concentration thresh<br>for chan inside Ca<sup>2+</sup> concentrations of 1  $\mu$ M. The channels studied<br>by Ehara et al. (21) had a lower unit conductance of<br>about 15 pS (20-25°C). The Ca<sup>2+</sup> concentration threshold<br>for channel activation was 0.3  $\mu$ M, and the op by Ehara et al. (21) had a lower unit conductance<br>about 15 pS (20-25°C). The Ca<sup>2+</sup> concentration thresh<br>for channel activation was 0.3  $\mu$ M, and the open prol<br>bility was half-maximal at a Ca<sup>2+</sup> concentration of<br> $\mu$ M. about 15 pS (20-25°C). The Ca<sup>2+</sup> concentration threshold<br>for channel activation was 0.3  $\mu$ M, and the open proba-<br>bility was half-maximal at a Ca<sup>2+</sup> concentration of 1.2<br> $\mu$ M. Several additional reports of Ca<sup>2+</sup>-acti bility was half-maximal at a  $Ca^{2+}$  concentration of 1.2  $\mu$ M. Several additional reports of  $Ca^{2+}$ -activated nonselective cation channels have appeared for noncardiac tissue beginning with Yellen (88) in neuroblastoma  $\mu$ M. Several additional reports of Ca<sup>2+</sup>-activated nonselective cation channels have appeared for noncardiac tissue beginning with Yellen (88) in neuroblastoma cells (see ref. 21 for references). Hill et al. (34) have  $\mu$ M. Several additional reports of Ca<sup>2+</sup>-activated nonselective cation channels have appeared for noncardiac tissue beginning with Yellen (88) in neuroblastoma cells (see ref. 21 for references). Hill et al. (34) have lective cation channels have appeared for noncardiac<br>tissue beginning with Yellen (88) in neuroblastoma cells<br>(see ref. 21 for references). Hill et al. (34) have reported<br>the occasional incorporation into membrane bilayers tissue beginning with Yellen (88) in neuroblastoma cells<br>(see ref. 21 for references). Hill et al. (34) have reported<br>the occasional incorporation into membrane bilayers of<br>a nonselective cation channel from sarcolemmal v (see ref. 21 for references). Hill et al.  $(34)$  have reporte<br>the occasional incorporation into membrane bilayers a<br>a nonselective cation channel from sarcolemmal vesicle<br>prepared from adult canine ventricular muscle. Th<br> the occasional incorporation into membrane bilayers of a nonselective cation channel from sarcolemmal vesicles prepared from adult canine ventricular muscle. This channel responded to increased  $Ca^{2+}$  by increased probab a nonselective cation channel from sarcolemmal vesicles<br>prepared from adult canine ventricular muscle. This<br>channel responded to increased  $Ca^{2+}$  by increased prob-<br>ability of being open. The single channel conductance<br>w prepared from adult canine ventricular muscle. This<br>channel responded to increased  $Ca^{2+}$  by increased prob-<br>ability of being open. The single channel conductance<br>was 120 pS, and the channel opening was markedly<br>voltage channel responded to increased  $Ca^{2+}$  by increased probability of being open. The single channel conductance was 120 pS, and the channel opening was markedly voltage dependent. While it is interesting to speculate that t ability of being open. The single channel conductance<br>was 120 pS, and the channel opening was markedly<br>voltage dependent. While it is interesting to speculate<br>that this incorporated channel is related to the channels<br>seen was 120 pS, and the channel opening was markedly<br>voltage dependent. While it is interesting to speculate<br>that this incorporated channel is related to the channels<br>seen by Colquhoun et al. (15), Ehara et al. (21), Yellen<br>(8 voltage dependent. While it is interesting to speculate<br>that this incorporated channel is related to the channels<br>seen by Colquhoun et al. (15), Ehara et al. (21), Yellen<br>(88), and others in intact cells, it must be noted that this incorporated channel is related to the channels<br>seen by Colquhoun et al. (15), Ehara et al. (21), Yellen<br>(88), and others in intact cells, it must be noted that the<br>properties of the channel found by Hill et al. seen by Colquhoun et al. (15), Ehara et al. (21), Yellen (88), and others in intact cells, it must be noted that the properties of the channel found by Hill et al. (34) differ in several important ways. In summary, a nons (88), and others in intact cells, it must be noted that the properties of the channel found by Hill et al. (34) differ in several important ways. In summary, a nonselective cation channel activated by intracellular  $Ca^{2+}$ properties of the channel found by Hill et al.  $(34)$  differ<br>in several important ways. In summary, a nonselective<br>cation channel activated by intracellular  $Ca^{2+}$  would<br>explain the experimental data qualitatively, altho in several important ways. In summary, a nonselective cation channel activated by intracellular  $Ca^{2+}$  would explain the experimental data qualitatively, although discrepancies remain in the measured reversal potentials cation channel activated by intracellular  $Ca^{2+}$  would<br>explain the experimental data qualitatively, although<br>discrepancies remain in the measured reversal potentials<br>under different ionic conditions. Membrane channels<br>wi explain the experimental data qualitatively, altho<br>discrepancies remain in the measured reversal potent<br>under different ionic conditions. Membrane change<br>with similar properties have been recorded by pa<br>clamp of heart cell discrepancies remain in the mead<br>under different ionic condition<br>with similar properties have<br>clamp of heart cells and by the is<br>mal vesicles into lipid bilayers.<br>The second mechanism sugge nder different ionic conditions. Membrane chann<br>th similar properties have been recorded by pa<br>amp of heart cells and by the incorporation of sarcole<br>al vesicles into lipid bilayers.<br>The second mechanism suggested for i<sub>TI</sub>

with similar properties have been recorded by p<br>clamp of heart cells and by the incorporation of sarco<br>mal vesicles into lipid bilayers.<br>The second mechanism suggested for  $i_{TI}$  is the ele-<br>genic Na-Ca exchange pump driv clamp of heart cells and by the incorporation of sarcolem-<br>mal vesicles into lipid bilayers.<br>The second mechanism suggested for  $i_{TI}$  is the electro-<br>genic Na-Ca exchange pump driven by the transmem-<br>brane electrochemica mal vesicles into lipid bilayers.<br>
The second mechanism suggested for  $i_{TI}$  is the electro-<br>
genic Na-Ca exchange pump driven by the transmem-<br>
brane electrochemical gradients for Na<sup>+</sup> and Ca<sup>2+</sup> ions<br>
(2, 43, 65). In t The second mechanism suggested for  $i_{TI}$  is the electro-<br>genic Na-Ca exchange pump driven by the transmem-<br>brane electrochemical gradients for Na<sup>+</sup> and Ca<sup>2+</sup> ions<br>(2, 43, 65). In the normally polarized cell, Na<sup>+</sup> ente genic Na-Ca exchange pump driven by the transmem-<br>brane electrochemical gradients for Na<sup>+</sup> and Ca<sup>2+</sup> ions<br>(2, 43, 65). In the normally polarized cell, Na<sup>+</sup> entering<br>via the exchanger will be coupled to Ca<sup>2+</sup> extrusion brane electrochemical gradients for  $Na^+$  and  $Ca^{2+}$  ions (2, 43, 65). In the normally polarized cell,  $Na^+$  entering via the exchanger will be coupled to  $Ca^{2+}$  extrusion. The stoichiometry for charge translocation is (2, 43, 65). In the normally polarized cell, Na<sup>+</sup> ente<br>via the exchanger will be coupled to  $Ca^{2+}$  extrusion.<br>stoichiometry for charge translocation is now gener<br>accepted to be 3:2 (i.e., 3 Na<sup>+</sup> to 1 Ca<sup>2+</sup>; see refs. via the exchanger will be coupled to  $Ca^{2+}$  extrusion. The stoichiometry for charge translocation is now generally accepted to be 3:2 (i.e., 3 Na<sup>+</sup> to 1 Ca<sup>2+</sup>; see refs. 46 and 69). The initiating sequence for the dela stoichiometry for charge translocation is now generally accepted to be 3:2 (i.e., 3 Na<sup>+</sup> to 1 Ca<sup>2+</sup>; see refs. 46 and 69). The initiating sequence for the delayed afterdepolarization, as with the nonselective cation cha accepted to be 3:2 (i.e., 3 Na<sup>+</sup> to 1 Ca<sup>2+</sup>; see refs. 46 and 69). The initiating sequence for the delayed afterdepolarization, as with the nonselective cation channel hypothesis, is Ca<sup>2+</sup> overload, producing cyclical 69). The initiating sequence for the delayed afterdepo-<br>larization, as with the nonselective cation channel hy-<br>pothesis, is  $Ca^{2+}$  overload, producing cyclical release of<br> $Ca^{2+}$  from the SR and giving rise to an oscill larization, as with the nonselective cation channel hypothesis, is  $Ca^{2+}$  overload, producing cyclical release of  $Ca^{2+}$  from the SR and giving rise to an oscillation in myoplasmic  $Ca^{2+}$  and the aftercontraction. An o  $Ca^{2+}$  from the SR and giving rise to an oscillation in<br>myoplasmic  $Ca^{2+}$  and the aftercontraction. An oscillatory<br>reduction in the transmembrane  $Ca^{2+}$  gradient would<br>facilitate  $Ca^{2+}$  extrusion and Na<sup>+</sup> entry by th  $Ca^{2+}$  from the SR and giving rise to an oscillation in<br>myoplasmic  $Ca^{2+}$  and the aftercontraction. An oscillatory<br>reduction in the transmembrane  $Ca^{2+}$  gradient would<br>facilitate  $Ca^{2+}$  extrusion and Na<sup>+</sup> entry by th myoplasmic Ca<sup>2+</sup> and the aftercontraction. An oscillatory reduction in the transmembrane Ca<sup>2+</sup> gradient would facilitate Ca<sup>2+</sup> extrusion and Na<sup>+</sup> entry by the exchanger. In turn, because of the electrogenicity of the facilitate  $Ca^{2+}$  extrusion and Na<sup>+</sup> entry by the exchanger.<br>In turn, because of the electrogenicity of the Na-Ca exchange mechanism, this would result in a transient increase of the net inward movement of positive char (3 Na<sup>+</sup> in for 1 Ca<sup>2+</sup> out), thereby producing  $i_{T1}$ , or a delayed afterdepolarization. It is essential to recognize that the Na-Ca exchange mechanism itself must have a exchange mechanism, this would result in a transient<br>increase of the net inward movement of positive charge<br>(3  $\text{Na}^+$  in for 1  $\text{Ca}^{2+}$  out), thereby producing  $i_{\text{TI}}$ , or a<br>delayed afterdepolarization. It is esse increase of the net inward movement of positive charge (3  $Na^+$  in for 1  $Ca^{2+}$  out), thereby producing  $i_{T1}$ , or a delayed afterdepolarization. It is essential to recognize that the Na-Ca exchange mechanism itself mus (3 Na<sup>+</sup> in for 1 Ca<sup>2+</sup> out), thereby producing i<sub>T1</sub>, or a delayed afterdepolarization. It is essential to recognize that the Na-Ca exchange mechanism itself must have a reversal potential at some voltage, and positive delayed afterdepolarization. It is essential to recognize that the Na-Ca exchange mechanism itself must have a reversal potential at some voltage, and positive to this voltage  $Ca^{2+}$  will be transported into the cell and

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<sup>222</sup> JANUARY AND FOZZARD<br>However, at a fixed transmembrane voltage the effect of in the absence of<br>an oscillatory increase in intracellular Ca<sup>2+</sup> will be to observation in 222<br>However, at a fixed transmembrane voltage the effect<br>an oscillatory increase in intracellular  $Ca^{2+}$  will be<br>alter transiently the current in a net inward direction.<br>The argument favoring the electrogenic Na-Ca e The argument favoring increase in intracellular  $Ca^{2+}$  will be to the transiently the current in a net inward direction.<br>The argument favoring the electrogenic Na-Ca exange mechanism has been supported by several reports

However, at a fixed transmembrane voltage the effect of<br>an oscillatory increase in intracellular  $Ca^{2+}$  will be to<br>alter transiently the current in a net inward direction.<br>The argument favoring the electrogenic Na-Ca exan oscillatory increase in intracellular  $Ca^{2+}$  will be to<br>alter transiently the current in a net inward direction.<br>The argument favoring the electrogenic Na-Ca ex-<br>change mechanism has been supported by several reports<br> alter transiently the current in a net inward direction<br>The argument favoring the electrogenic Na-Ca<br>change mechanism has been supported by several repo<br>of the absence of an experimentally detectable rever<br>potential for  $i$ change mechanism has been supported by several reports rapid replacement of Na<sup>+</sup> with Li<sup>+</sup>, which resulted in the<br>of the absence of an experimentally detectable reversal disappearance of delayed afterdepolarizations. Li of the absence of an experimentally detectable reversal<br>potential for  $i_{TI}$ . Arlock and Katzung (2) studied ouabain-<br>intoxicated papillary muscles using a sucrose gap voltage<br>clamp technique and found that the amplitude intoxicated papillary muscles using a sucrose gap voltage single channel recordings of  $Ca^{2+}$ -activated nonselective<br>clamp technique and found that the amplitude of  $i_{TI}$  cation channels (21, 81). Tseng and Wit (78) arg clamp technique and found that the amplitude of  $i_{TI}$ <br>became progressively smaller at less negative voltages,<br>but it did not reverse its polarity at voltages up to +30<br>mV. One possibility they suggested for the apparent<br> clamp technique and found that the amplitude of  $i_{TI}$  compressively smaller at less negative voltages, that it did not reverse its polarity at voltages up to +30 mV. One possibility they suggested for the apparent crever but it did not reverse its polarity at voltages up to  $+5$ <br>mV. One possibility they suggested for the appare-<br>reversal potential found previously by other investigato<br>was that it could arise from  $Ca^{2+}$ -dependent activat mV. One possibility they suggested for the apparent<br>reversal potential found previously by other investigators<br>was that it could arise from  $Ca^{2+}$ -dependent activation<br>of  $i_{TI}$  channels to carry outward current. Another reversal potential found previously by other investigators<br>was that it could arise from  $Ca^{2+}$ -dependent activation<br>of  $i_{TI}$  channels to carry outward current. Another possi-<br>bility is suggested by the recent finding of was that it could arise from  $Ca^{2+}$ -dependent activation anisof  $i_{TI}$  channels to carry outward current. Another possi-<br>bility is suggested by the recent finding of  $Ca^{2+}$ -activated pote<br>outward  $K^+$  channels in Purki bility is suggested by the recent finding of Ca<sup>2+</sup>-activated potentials has produced conflicting results. In part, this outward K<sup>+</sup> channels in Purkinje cells (9). In sinoatrial could arise from other coexisting membran bility is suggested by the recent finding of  $Ca^{2+}$ -activated pote<br>outward  $K^+$  channels in Purkinje cells (9). In sinoatrial could<br>node tissue, a current resembling  $i_{TI}$  can be induced by from<br>exposure to low  $[K]_0$  outward K<sup>+</sup> channels in Purkinje cells (9). In sinoatriande tissue, a current resembling  $i_{TI}$  can be induced bexposure to low  $[K]_0$  solutions (7). Near voltages where a nonselective cation membrane channel mechanism m node tissue, a current resembling  $i_{TI}$  can be induced by exposure to low  $[K]_0$  solutions (7). Near voltages where a nonselective cation membrane channel mechanism might reverse its polarity, low amplitude current oscil a nonselective cation membrane channel mechanism<br>might reverse its polarity, low amplitude current oscillations<br>lations persisted. The timing of the current oscillation<br>was voltage dependent, which complicated the differen might reverse its polarity, low amplitude current oscil-<br>lations persisted. The timing of the current oscillations shows<br>was voltage dependent, which complicated the differen-<br>tiation of inward from outward transient comp lations persisted. The timing of the current oscillatio was voltage dependent, which complicated the differe tiation of inward from outward transient componen Vassalle and coworkers  $(54)$  studied Purkinje fibers a also r was voltage dependent, which complicated the differen-<br>tiation of inward from outward transient components. ch<br>Vassalle and coworkers (54) studied Purkinje fibers and<br>also reported failure of  $i_{TI}$  to reverse its polarit tiation of inward from outward transient component<br>Vassalle and coworkers (54) studied Purkinje fibers at<br>also reported failure of  $i_{TI}$  to reverse its polarity. Unfor<br>tunately, the range of voltages in their study was l Vassalle and coworkers  $(54)$  studied Purkinje fibers and also reported failure of  $i_{TI}$  to reverse its polarity. Unfortunately, the range of voltages in their study was limited to negative potentials. In embryonic heart also reported failure of  $i_{TI}$  to reverse its polarity. Unfor-<br>tunately, the range of voltages in their study was limited<br>to negative potentials. In embryonic heart cell aggre-<br>gates, a transient inward current resemblin tunately, the range of voltages in their study was limited<br>to negative potentials. In embryonic heart cell aggre-<br>gates, a transient inward current resembling  $i_{TI}$  is in-<br>duced with abrupt exposure to caffeine (13). At to negative potentials. In embryonic heart cell aggre-seen dugates, a transient inward current resembling  $i_{TI}$  is in-<br>duced with abrupt exposure to caffeine (13). At less ouabain<br>megative potentials, its amplitude was d gates, a transient inward current resembling  $i_{T1}$  is in-<br>duced with abrupt exposure to caffeine (13). At less of<br>negative potentials, its amplitude was decreased, but it<br>failed to reverse polarity at potentials up to duced with abrupt exposure to caffeine (13). At less<br>negative potentials, its amplitude was decreased, but it<br>failed to reverse polarity at potentials up to +60 mV. A<br>possible limitation in the interpretation of data obta negative potentials, its amplitude was decreased, but it failed to reverse polarity at potentials up to  $+60$  mV. A possible limitation in the interpretation of data obtained in the studies just cited is that in none of t failed to reverse polarity at potentials up to  $+60$  mV. A possible limitation in the interpretation of data obtained in the studies just cited is that in none of these reports was the presence of an oscillation in intrac possible limitation in the interpretation of data obtained<br>in the studies just cited is that in none of these reports d<br>was the presence of an oscillation in intracellular  $Ca^{2+}$ <br>shown (imaged directly or inferred by rec was the presence of an oscillation in intracellular  $Ca^{2+}$ <br>shown (imaged directly or inferred by recording tension).<br>Arlock and Katzung (2), Noble (65), and Brown et al. (7)<br>were able to fit experimental data to mathemat was the presence of an oscillation in intracellular  $Ca^{2+}$  wishown (imaged directly or inferred by recording tension). getails and Katzung (2), Noble (65), and Brown et al. (7) prevers able to fit experimental data to ma shown (imaged directly or inferred by recording tension).<br>Arlock and Katzung (2), Noble (65), and Brown et al. (7)<br>were able to fit experimental data to mathematical<br>models containing electrogenic Na-Ca exchange, which<br>su Arlock and Katzung (2), Noble (65), and Brown et al. (7) pre<br>were able to fit experimental data to mathematical of<br>models containing electrogenic Na-Ca exchange, which ma<br>supported their conclusions that the Na-Ca exchang were able to fit experimental data to mathematical of models containing electrogenic Na-Ca exchange, which m<br>supported their conclusions that the Na-Ca exchange pip<br>mechanism was the dominant charge carrier for  $i_{T1}$ . L models containing electrogenic Na-Ca exchange, which mapported their conclusions that the Na-Ca exchange pig mechanism was the dominant charge carrier for  $i_{T1}$ . Lipp de and Pott (55) recorded a spontaneous transient in mechanism was the dominant charge carrier for  $i_{T1}$ . Lipp de<br>and Pott (55) recorded a spontaneous transient inward de<br>current in single dialyzed cultured guinea pig ventricular br<br>myocytes. This current was accompanied and Pott (55) recorded a spontaneous transient inward department in single dialyzed cultured guinea pig ventricular bramyocytes. This current was accompanied by a strong for contraction, and it shared many properties with current in single dialyzed cultured guinea pig ventricular bra<br>myocytes. This current was accompanied by a strong for<br>contraction, and it shared many properties with  $i_{T1}$ . The cha<br>current remained inward with voltage s myocytes. This current was accompanied by a strong for contraction, and it shared many properties with  $i_{TI}$ . The current remained inward with voltage steps up to  $+75$  in mV, and its characteristics were most compatible contraction, and it shared many properties with  $i_{TI}$ . The characteristic inward with voltage steps up to +75 incm V, and its characteristics were most compatible with a ANa-Ca exchanger transporting  $3 \text{ Na}^+$  to  $1 \text{ Ca$ current remained inward with voltage steps up to  $+75$  mV, and its characteristics were most compatible with a Na-Ca exchanger transporting 3 Na<sup>+</sup> to 1 Ca<sup>2+</sup>. One unusual feature of the current was that its activation d mV, and its characteristics were most compatible with a<br>Na-Ca exchanger transporting  $3 \text{ Na}^+$  to  $1 \text{ Ca}^{2+}$ . One<br>unusual feature of the current was that its activation did<br>not require  $\text{Ca}^{2+}$  overload. Lipp and Po Na-Ca exchanger transporting  $3 \text{ Na}^+$  to  $1 \text{ Ca}^{2+}$ . One was unusual feature of the current was that its activation did nis not require Ca<sup>2+</sup> overload. Lipp and Pott concluded that not electrogenic Na-Ca exchange was unusual feature of the current was that its activation did<br>not require  $Ca^{2+}$  overload. Lipp and Pott concluded that<br>electrogenic Na-Ca exchange was the dominant charge<br>carrier of the spontaneous transient inward current electrogenic Na-Ca exchange was the dominant charge electrogenic Na-Ca exchange was the dominant charge<br>carrier of the spontaneous transient inward current they<br>studied. They also suggested that Na-Ca exchange might<br>werticipate in establishing conditions [i.e., raising int carrier of the spontaneous transient inward current they<br>studied. They also suggested that Na-Ca exchange might<br>participate in establishing conditions [i.e., raising intra-<br>cellular Ca  $(Ca_i)$ ] needed to initiate transient

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However, at a fixed transmembrane voltage the effect of in the absence of massive cellular  $Ca^{2+}$  overload. A recent<br>
an oscillatory increase in intracellular  $Ca^{2+}$  will be to observation in atrial FOZZARD<br>in the absence of massive cellular  $Ca^{2+}$  overload. A recent<br>observation in atrial coronary sinus cells has been used o FOZZARD<br>in the absence of massive cellular Ca<sup>2+</sup> overload. A recent<br>observation in atrial coronary sinus cells has been used<br>to argue further in favor of a Na-Ca exchange mechanism The absence of massive cellular  $Ca^{2+}$  overload. A recent observation in atrial coronary sinus cells has been used to argue further in favor of a Na-Ca exchange mechanism (78; see also ref. 2). A fast-flow chamber permit in the absence of massive cellular  $Ca^{2+}$  overload. A recent observation in atrial coronary sinus cells has been used to argue further in favor of a Na-Ca exchange mechanism (78; see also ref. 2). A fast-flow chamber per in the absence of massive cellular Ca<sup>2+</sup> overload. A recent observation in atrial coronary sinus cells has been used to argue further in favor of a Na-Ca exchange mechanism (78; see also ref. 2). A fast-flow chamber perm observation in atrial coronary sinus cells has been used<br>to argue further in favor of a Na-Ca exchange mechanism<br>(78; see also ref. 2). A fast-flow chamber permitted the<br>rapid replacement of Na<sup>+</sup> with Li<sup>+</sup>, which result to argue further in favor of a Na-Ca exchange mechanism<br>(78; see also ref. 2). A fast-flow chamber permitted the<br>rapid replacement of Na<sup>+</sup> with Li<sup>+</sup>, which resulted in the<br>disappearance of delayed afterdepolarizations. (78; see also ref. 2). A fast-flow chamber permitted the rapid replacement of Na<sup>+</sup> with Li<sup>+</sup>, which resulted in the disappearance of delayed afterdepolarizations. Li<sup>+</sup> has been reported to substitute nearly equally for rapid replacement of Na<sup>+</sup> with Li<sup>+</sup>, which resulted in the disappearance of delayed afterdepolarizations. Li<sup>+</sup> has been reported to substitute nearly equally for Na<sup>+</sup> in single channel recordings of  $Ca^{2+}$ -activated disappearance of delayed afterdepolarizations. Li<sup>+</sup> has<br>been reported to substitute nearly equally for Na<sup>+</sup> in<br>single channels (21, 81). Tseng and Wit (78) argued that<br>the disappearance of delayed afterdepolarizations w cation channels (21, 81). Tseng and Wit (78) argued that<br>the disappearance of delayed afterdepolarizations was<br>not expected for a Li<sup>+</sup>-permeable nonselective cation<br>channel mechanism, and they interpreted their findings<br> the disappearance of delayed afterdepolarizations was to be consistent with a Na-Ca exchange-mediated mech-

The experimental approach of searching for reversal potentials has produced conflicting results. In part, this to be consistent with a Na-Ca exchange-mediated mech-<br>anism in which Li<sup>+</sup> can not substitute for Na<sup>+</sup>.<br>The experimental approach of searching for reversal<br>potentials has produced conflicting results. In part, this<br>could anism in which Li<sup>+</sup> can not substitute for Na<sup>+</sup>.<br>The experimental approach of searching for reversa<br>potentials has produced conflicting results. In part, this<br>could arise from other coexisting membrane currents and<br>from The experimental approach of searching for reversal<br>potentials has produced conflicting results. In part, this<br>could arise from other coexisting membrane currents and<br>from tissue differences. Therefore, other experimental potentials has produced conflicting results. In part, this could arise from other coexisting membrane currents and from tissue differences. Therefore, other experimental approaches to the mechanism for  $i_{Tl}$  must be sou could arise from other coexisting membrane currents and<br>from tissue differences. Therefore, other experimental<br>approaches to the mechanism for  $i_{TI}$  must be sought, and<br>recent experimental observations have provided furt approaches to the mechanism for  $i_{TI}$  must be sought, and<br>recent experimental observations have provided further<br>insights. The opening (or closing) of a membrane channel<br>should be accompanied by a change in membrane conrecent experimental observations have provided further recent experimental observations have provided furt<br>insights. The opening (or closing) of a membrane chan<br>should be accompanied by a change in membrane c<br>ductance, whereas the movement of charge on an<br>change pump should no insights. The opening (or closing) of a membrane channel<br>should be accompanied by a change in membrane con-<br>ductance, whereas the movement of charge on an ex-<br>change pump should not be associated with a conduct-<br>ance chang should be accompanied by a change in membrane con-<br>ductance, whereas the movement of charge on an ex-<br>change pump should not be associated with a conduct-<br>ance change. In embryonic heart cell aggregates exposed<br>to caffein ductance, whereas the movement of charge on an ex-<br>change pump should not be associated with a conduct-<br>ance change. In embryonic heart cell aggregates exposed<br>to caffeine (13), which induces a transient inward current<br>res change pump should not be associated with a conduct-<br>ance change. In embryonic heart cell aggregates exposed<br>to caffeine (13), which induces a transient inward current<br>resembling  $i_{Ti}$ , no membrane conductance changes wer ance change. In embryonic heart cell aggregates exposed<br>to caffeine (13), which induces a transient inward current<br>resembling  $i_{TI}$ , no membrane conductance changes were<br>seen during the inward current. A similar brief re to caffeine (13), which induces a transient inward current<br>resembling  $i_{TI}$ , no membrane conductance changes were<br>seen during the inward current. A similar brief report<br>has appeared for neonatal rat cardiac cells exposed resembling i<sub>T1</sub>, no membrane conductance changes were<br>seen during the inward current. A similar brief report<br>has appeared for neonatal rat cardiac cells exposed to<br>ouabain  $(1 \times 10^{-4} \text{ M})$  or K<sup>+</sup>-free medium (80). The<br> seen during the inward current. A similar brief report<br>has appeared for neonatal rat cardiac cells exposed to<br>ouabain  $(1 \times 10^{-4} \text{ M})$  or K<sup>+</sup>-free medium (80). The<br>interpretation of these results requires some caution,<br> ouabain  $(1 \times 10^{-4}$  M) or K<sup>+</sup>-free medium (80). The<br>interpretation of these results requires some caution,<br>however, since small conductance changes may not be<br>readily apparent. A decrease in membrane conductance<br>during interpretation of these results requires some caution,<br>however, since small conductance changes may not be<br>readily apparent. A decrease in membrane conductance<br>during  $i_{TI}$  was reported in Purkinje fibers made toxic<br>with however, since small conductance changes may not be readily apparent. A decrease in membrane conductance during  $i_{TI}$  was reported in Purkinje fibers made toxic with strophanthidin (54). The experimental records suggest readily apparent. A decrease in membrane conductance<br>during  $i_{TI}$  was reported in Purkinje fibers made toxic<br>with strophanthidin (54). The experimental records sug-<br>gest that a decrease in the conductance was already<br>pre during  $i_{TI}$  was reported in Purkinje fibers made to<br>with strophanthidin (54). The experimental records su<br>gest that a decrease in the conductance was alrea<br>present at the onset of  $i_{TI}$ , possibly reflecting activation<br> with strophanthidin (54). The experimental records suggest that a decrease in the conductance was already present at the onset of  $i_{TI}$ , possibly reflecting activation of an additional membrane current. Recently, Mechmann gest that a decrease in the conductance was already<br>present at the onset of  $i_{TI}$ , possibly reflecting activation<br>of an additional membrane current. Recently, Mech-<br>mann and Pott (61) observed  $i_{TI}$  in single cultured g present at the onset of  $i_{TI}$ , possibly reflecting activation<br>of an additional membrane current. Recently, Mech-<br>mann and Pott (61) observed  $i_{TI}$  in single cultured guinea<br>pig atrial myocytes. Its induction was associa of an additional membrane current. Recently, M<br>mann and Pott (61) observed  $i_{TI}$  in single cultured gu<br>pig atrial myocytes. Its induction was associated depolarization or with exposure to caffeine. The cur<br>depended on me mann and Pott (61) observed  $i_{TI}$  in single cultured guinea<br>pig atrial myocytes. Its induction was associated with<br>depolarization or with exposure to caffeine. The current<br>depended on membrane potential and on the transm pig atrial myocytes. Its induction was associated with<br>depolarization or with exposure to caffeine. The current<br>depended on membrane potential and on the transmem-<br>brane gradients for Na<sup>+</sup> and Ca<sup>2+</sup> in a manner expected depolarization or with exposure to caffeine. The current<br>depended on membrane potential and on the transmem-<br>brane gradients for  $Na<sup>+</sup>$  and  $Ca<sup>2+</sup>$  in a manner expected<br>for electrogenic  $Na<sup>-</sup>Ca$  exchange. They als depended on membrane potential and on the transmem-<br>brane gradients for Na<sup>+</sup> and Ca<sup>2+</sup> in a manner expected<br>for electrogenic Na-Ca exchange. They also saw single<br>channel currents that were associated with presumptive<br>in ane gradients for Na<sup>+</sup> and Ca<sup>2+</sup> in a manner expected<br>r electrogenic Na-Ca exchange. They also saw single<br>annel currents that were associated with presumptive<br>crease in intracellular Ca<sup>2+</sup> (see also refs. 45 and 55).<br>A for electrogenic Na-Ca exchange. They also saw sin<br>channel currents that were associated with presumpt<br>increase in intracellular  $Ca^{2+}$  (see also refs. 45 and 55<br>Another approach taken by Cannell and Lederer (<br>was to att

channel currents that were associated with presumptive<br>increase in intracellular  $Ca^{2+}$  (see also refs. 45 and 55).<br>Another approach taken by Cannell and Lederer (10)<br>was to attempt to disable the Na-Ca exchange mecha-<br>n increase in intracellular Ca<sup>2+</sup> (see also refs. 45 and 55).<br>Another approach taken by Cannell and Lederer (10)<br>was to attempt to disable the Na-Ca exchange mecha-<br>nism by removal of Na<sup>+</sup>, while leaving the Ca<sup>2+</sup>-activa Another approach taken by Cannell and Lederer (10) was to attempt to disable the Na-Ca exchange mechanism by removal of Na<sup>+</sup>, while leaving the Ca<sup>2+</sup>-activated nonselective cation channel mechanism intact. They reasoned was to attempt to disable the Na-Ca exchange mechanism by removal of  $Na^+$ , while leaving the  $Ca^{2+}$ -activated nonselective cation channel mechanism intact. They reasoned that, if  $i_{TI}$  were the result of the Na-Ca exch nonselective cation channel mechanism intact. They reasoned that, if  $i_{TI}$  were the result of the Na-Ca exchange mechanism, then it should be unavailable, whereas if  $i_{TI}$  were the result of a nonselective cation channe Tyrode's solution to inhibit Na-Ca exchange, and with should be detected. They used  $Na<sup>+</sup>$ -free isotonic  $Ca<sup>2+</sup>$ 

PHARMACOLOGICAL REVIEWS

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**DELAYED AFTERDEPOLARIZA**<br>tions and an oscillatory current resembling  $i_{TI}$  with a<br>reversal potential near  $-40$  mV. Power spectral analysis<br>of the current and tension records showed similar fre-DELAYED AFTERDEPOLARIS<br>tions and an oscillatory current resembling  $i_{TI}$  with a<br>reversal potential near -40 mV. Power spectral analysis<br>of the current and tension records showed similar fre-<br>quency contents, and a depende tions and an oscillatory current resembling  $i_{TI}$  with a reversal potential near  $-40$  mV. Power spectral analysis of the current and tension records showed similar frequency contents, and a dependence of current amplitu tions and an oscillatory current resembling  $i_{TI}$  with a reversal potential near  $-40$  mV. Power spectral analysis of the current and tension records showed similar frequency contents, and a dependence of current amplitu reversal potential near  $-40$  mV. Power spectral analysis the<br>of the current and tension records showed similar fre-<br>quency contents, and a dependence of current amplitude<br>on the tension amplitude was shown. Because their of the current and tension records showed similar fre-<br>quency contents, and a dependence of current amplitude<br>on the tension amplitude was shown. Because their find-<br>ings were obtained in a Na<sup>+</sup>-free environment, they<br>co quency contents, and a dependence of current amplitude<br>on the tension amplitude was shown. Because their find-<br>ings were obtained in a  $Na<sup>+</sup>$ -free environment, they<br>concluded that inward  $Na<sup>-</sup>Ca$  exchange current cou on the tension amplitude was shown. Because their findings were obtained in a Na<sup>+</sup>-free environment, they concluded that inward Na-Ca exchange current could not be present. Rather, the persistence of the transient inward ings were obtained in a Na<sup>+</sup>-free environment, they<br>concluded that inward Na-Ca exchange current could<br>not be present. Rather, the persistence of the transient<br>inward current constituted a powerful argument in favor<br>of a concluded that inward Na-Ca exchange current could<br>not be present. Rather, the persistence of the transient<br>inward current constituted a powerful argument in favor<br>of a Ca<sup>2+</sup>-activated membrane channel mechanism for<br>i<sub>TI</sub> not be present. Rather, the persistence of the transient<br>inward current constituted a powerful argument in favor<br>of a  $Ca^{2+}$ -activated membrane channel mechanism for<br> $i_{TI}$ , with  $Ca^{2+}$  carrying the depolarizing current inward current constituted a powerful argument in favor of a  $Ca^{2+}$ -activated membrane channel mechanism for  $i_{TI}$ , with  $Ca^{2+}$  carrying the depolarizing current under these conditions. These data seem to provide the m these conditions. These data seem to provide the most<br>direct test of the mechanisms proposed for  $i_{TI}$ . An unre-<br>solved question is why attempts to inhibit the Na-Ca<br>exchange mechanism with sodium substitutes other than<br> direct test of the mechanisms proposed for  $i_{T1}$ . An unre-<br>solved question is why attempts to inhibit the Na-Ca<br>exchange mechanism with sodium substitutes other than<br>Ca<sup>2+</sup> (Li<sup>+</sup>, TRIS, choline, sucrose, and TMA) (see solved question is why attempts to inhibit the Na-Ca<br>exchange mechanism with sodium substitutes other than<br>Ca<sup>2+</sup> (Li<sup>+</sup>, TRIS, choline, sucrose, and TMA) (see refs.<br>10, 36, and 40) produce  $i_{TI}$  only transiently, before exchange mechanism with sodium substitutes other than  $Ca^{2+}$  ( $Li^+$ , TRIS, choline, sucrose, and TMA) (see refs.<br>10, 36, and 40) produce  $i_{T1}$  only transiently, before it then disappears under steady-state conditions.  $Ca^{2+}$  (Li<sup>+</sup>, TRIS, choline, sucrose, and TMA) (see refs.<br>
10, 36, and 40) produce  $i_{T1}$  only transiently, before it then<br>
disappears under steady-state conditions. One possibility<br>
is that the  $Ca^{2+}$  overload adequa 10, 36, and 40) produce  $i_{TI}$  only transiently, before it then<br>disappears under steady-state conditions. One possibility<br>is that the Ca<sup>2+</sup> overload adequate to sustain  $i_{TI}$  cannot<br>be maintained unless the external Ca<sup></sup> disappears under steady-state conditions. One possibility<br>is that the Ca<sup>2+</sup> overload adequate to sustain  $i_{TI}$  cannot<br>be maintained unless the external Ca<sup>2+</sup> concentration is<br>very high. Cannell and Lederer (10) pointed is that the Ca<sup>2+</sup> overload adequate to sustain  $i_{TI}$  cannot<br>be maintained unless the external Ca<sup>2+</sup> concentration is<br>very high. Cannell and Lederer (10) pointed out that,<br>while their data support a Ca<sup>2+</sup>-activated non be maintained unless the external  $Ca^{2+}$  concentration very high. Cannell and Lederer (10) pointed out t while their data support a  $Ca^{2+}$ -activated nonselection channel as the major mechanism for  $i_{TI}$ , the results di very high. Cannell and Lederer (10) pointed out that,<br>while their data support a  $Ca^{2+}$ -activated nonselective<br>cation channel as the major mechanism for  $i_{TI}$ , their<br>mesults did not exclude Na-Ca exchange from contribut while their data support a  $Ca^{2+}$ -activated nonselective<br>cation channel as the major mechanism for  $i_{TI}$ , the<br>results did not exclude Na-Ca exchange from contribu<br>ing to delayed afterdepolarizations. They also suggest<br>t cation channel as the major mechanism for  $i_{TI}$ , their<br>results did not exclude Na-Ca exchange from contribut-<br>ing to delayed afterdepolarizations. They also suggested<br>that  $i_{TI}$  might be activated by the transient rise results did not exclude Na-Ca exchange from contribut-<br>ing to delayed afterdepolarizations. They also suggested<br>that  $i_{TI}$  might be activated by the transient rise in intra-<br>cellular Ca<sup>2+</sup> that occurs during normal acti ing to delayed afterdepolarizations. They also suggested<br>that  $i_{TI}$  might be activated by the transient rise in intra-<br>cellular  $Ca^{2+}$  that occurs during normal action potentials<br>and, if so, it would contribute to the p that  $i_{TI}$  might be activated by the transient rise in intracellular  $Ca^{2+}$  that occurs during normal action potentials and, if so, it would contribute to the plateau phase of the cardiac action potential. Recently, Kim cellular Ca<sup>2+</sup> that occurs during normal action potentials<br>and, if so, it would contribute to the plateau phase of the<br>cardiac action potential. Recently, Kimura (45) has re-<br>ported the presence of an i<sub>T1</sub>-like current and, if so, it would contribute to the plateau phase of the cardiac action potential. Recently, Kimura (45) has reported the presence of an i<sub>T1</sub>-like current in Ca<sup>2+</sup>-loaded isolated guinea pig ventricular cells. The cu cardiac action potential. Recently, Kimura (45) has reported the presence of an  $i_{TT}$ -like current in Ca<sup>2+</sup>-loaded Easiolated guinea pig ventricular cells. The current was inward at both negative and positive voltages. ported the presence of an i<sub>T1</sub>-like current in Ca<sup>2+</sup>-loaded<br>isolated guinea pig ventricular cells. The current was<br>inward at both negative and positive voltages. Block of<br>the Na-Ca exchanger by the replacement of Na<sup>+</sup> isolated guinea pig ventricular cells. The current was<br>inward at both negative and positive voltages. Block of<br>the Na-Ca exchanger by the replacement of Na<sup>+</sup> with<br>Li<sup>+</sup> reduced the current amplitude (but failed to abolish inward at both negative and positive voltages. Block of<br>the Na-Ca exchanger by the replacement of Na<sup>+</sup> with<br>Li<sup>+</sup> reduced the current amplitude (but failed to abolish<br>ti), and it reversed polarity near 0 mV. These prelim the Na-Ca exchanger by the replacement of Na<sup>+</sup> w<br>Li<sup>+</sup> reduced the current amplitude (but failed to abol<br>it), and it reversed polarity near 0 mV. These preliminings were interpreted to suggest the presence of b<br>Na-Ca exc Li<sup>+</sup> reduced the current amp<br>it), and it reversed polarity no<br>findings were interpreted to :<br>Na-Ca exchange current an<br>cific cation channel current.<br>In summary, there are two , and it reversed polarity near 0 mV. These preliminary<br>Idings were interpreted to suggest the presence of both<br>a-Ca exchange current and a  $Ca^{2+}$ -activated nonspe-<br>ic cation channel current.<br>In summary, there are two hy findings were interpreted to suggest the presence of both<br>Na-Ca exchange current and a  $Ca^{2+}$ -activated nonspe-<br>cific cation channel current.<br>In summary, there are two hypotheses to explain de-<br>layed afterdepolarizations

Na-Ca exchange current and a Ca<sup>2+</sup>-activated nonspecific cation channel current.<br>In summary, there are two hypotheses to explain de-<br>layed afterdepolarizations or  $i_{TI}$ , both dependent on a<br>process sensitive to intracel cific cation channel current.<br>
In summary, there are two hypotheses to explain de-<br>
layed afterdepolarizations or  $i_{TI}$ , both dependent on a<br>
process sensitive to intracellular  $Ca^{2+}$ . A nonselective<br>
sarcolemmal cation In summary, there are two hypotheses to explain de-<br>layed afterdepolarizations or  $i_{TI}$ , both dependent on a diprocess sensitive to intracellular  $Ca^{2+}$ . A nonselective<br>sarcolemmal cation channel that is activated by  $Ca$ layed afterdepolarizations or  $i_{TI}$ , both dependent on<br>process sensitive to intracellular  $Ca^{2+}$ . A nonselective<br>sarcolemmal cation channel that is activated by  $Ca^{2+}$  hi<br>been identified, and it would be sufficient to process sensitive to intracellular Ca<sup>-1</sup>. A nonselective<br>sarcolemmal cation channel that is activated by  $Ca^{2+}$  has<br>been identified, and it would be sufficient to explain the<br>membrane phenomena. Alternatively, increased sarcolemmal cation channel that is activated by  $Ca^{2+}$  has<br>been identified, and it would be sufficient to explain the<br>membrane phenomena. Alternatively, increased intra-<br>cellular  $Ca^{2+}$  will activate Na-Ca exchange to i been identified, and it would be sufficient to explain the<br>membrane phenomena. Alternatively, increased intra-<br>cellular Ca<sup>2+</sup> will activate Na-Ca exchange to increase<br>Ca<sup>2+</sup> efflux and Na<sup>+</sup> influx; and this results in an cellular Ca<sup>2+</sup> will activate Na-Ca exchange to increase  $\frac{1}{111}$  and its aftercontraction can be induced separately in Ca<sup>2+</sup> efflux and Na<sup>+</sup> influx; and this results in an inward, tissue already having early afterde depolarizing exchange current. Persuasive evidence ex-<br>ists for both mechanisms, and it seems increasingly likely<br>ists for both could be involved. The sensitivity for each bility of L-type  $Ca^{2+}$  current (36). One mechan with small rises in  $Ca^{2+}$  activating only Na-Ca exchange, depolarizing exchange current. Persuasive evidence exists for both mechanisms, and it seems increasingly likely that both could be involved. The sensitivity for each mechanism to a rise in  $Ca^{2+}$ , however, may be differe ists for both mechanisms, and it seems increasingly likely<br>that both could be involved. The sensitivity for each<br>mechanism to a rise in  $Ca^{2+}$ , however, may be different<br>with small rises in  $Ca^{2+}$  activating only Na-Ca that both could be involved. The sensitivity for each mechanism to a rise in  $Ca^{2+}$ , however, may be different with small rises in  $Ca^{2+}$  activating only Na-Ca exchange whereas with larger rises in  $Ca^{2+}$ , both the Namechanism to a rise in  $Ca^{2+}$ , however, may be different tult with small rises in  $Ca^{2+}$  activating only Na-Ca exchange, in whereas with larger rises in  $Ca^{2+}$ , both the Na-Ca exchange and the  $Ca^{2+}$ -activated nonsele with small rises in  $Ca^{2+}$  activating only Na-Ca exchange,<br>whereas with larger rises in  $Ca^{2+}$ , both the Na-Ca ex-<br>change and the  $Ca^{2+}$ -activated nonselective cation chan-<br>nel mechanisms may operate. Determination of change and the  $Ca^{2+}$ -activated nonselective cation channel mechanisms may operate. Determination of the quantitative contribution of each mechanism in the various experimental models used will require development

tions and an oscillatory current resembling  $i_{TI}$  with a of specific blockers of the nonspecific cation channel and<br>reversal potential near  $-40$  mV. Power spectral analysis the Na-Ca exchange system and further study of TIONS IN HEART MUSCLE<br>of specific blockers of the nonspecific cation channel and<br>the Na-Ca exchange system and further study of their TIONS IN HEART MUSCLE 223<br>of specific blockers of the nonspecific cation channel and<br>the Na-Ca exchange system and further study of their<br>separate dependencies on  $Ca^{2+}$ . separate dependencies on  $Ca^{2+}$ .<br>VI. Early Afterdepolarizations—Is the Exercific blockers of the nonspecific cation channel an a-Ca exchange system and further study of the the dependencies on  $Ca^{2+}$ .<br>VI. Early Afterdepolarizations—Is the Mechanism the Same? ers of the honspectric cation<br>hange system and further st<br>lencies on Ca<sup>2+</sup>.<br>Mechanism the Same?<br>polarizations are secondary

of a  $Ca^{2+}$ -activated membrane channel mechanism for arrhythmogenic mechanism. The basis for early after-<br>  $i_{TI}$ , with  $Ca^{2+}$  carrying the depolarizing current under<br>
these conditions. These data seem to provide the mo solved question is why attempts to inhibit the Na-Ca<br>exchange mechanism with sodium substitutes other than<br> $Ca^{2+}$  (Li<sup>+</sup>, TRIS, choline, sucrose, and TMA) (see refs.<br> $Ca^{2+}$  (Li<sup>+</sup>, TRIS, choline, sucrose, and TMA) (see parate dependencies on  $Ca^{2+}$ .<br>
VI. Early Afterdepolarizations --- Is the<br>
Mechanism the Same?<br>
Early afterdepolarizations are secondary depolarization<br>
ons that occur before complete repolarization of VI. Early Afterdepolarizations --- Is the<br>Mechanism the Same?<br>Early afterdepolarizations are secondary depolariza-<br>tions that occur before complete repolarization of the<br>cardiac action potential. They are another potential v1. Early Alterdepolarizations—is the<br>Mechanism the Same?<br>Early afterdepolarizations are secondary depolariza-<br>tions that occur before complete repolarization of the<br>cardiac action potential. They are another potentially<br>a mechanism the same?<br>Early afterdepolarizations are secondary depolarizations that occur before complete repolarization of the cardiac action potential. They are another potentially<br>arrhythmogenic mechanism. The basis for e Early afterdepolarizations are secondary depolariza-<br>tions that occur before complete repolarization of the<br>cardiac action potential. They are another potentially<br>arrhythmogenic mechanism. The basis for early after-<br>depola tions that occur before complete repolarization of the cardiac action potential. They are another potentially arrhythmogenic mechanism. The basis for early after-<br>depolarizations is poorly understood, and several cellular<br> cardiac action potential. They are another potentially<br>arrhythmogenic mechanism. The basis for early after-<br>depolarizations is poorly understood, and several cellular<br>processes have been implicated in their generation (for arrhythmogenic mechanism. The basis for early after-<br>depolarizations is poorly understood, and several cellular<br>processes have been implicated in their generation (for<br>reviews, see refs. 37 and 86). It also has been shown<br> depolarizations is poorly understood, and several cellular<br>processes have been implicated in their generation (for<br>reviews, see refs. 37 and 86). It also has been shown<br>recently that early afterdepolarizations may be initi processes have been implicated in their generation (freviews, see refs. 37 and 86). It also has been show<br>recently that early afterdepolarizations may be initiat<br>from more than one range of voltages (17) which m<br>suggest mo anism is that both early and delayed afterdepolarizations recently that early afterdepolarizations may be initiat<br>from more than one range of voltages  $(17)$  which m<br>suggest more than one mechanism. One postulated mec<br>anism is that both early and delayed afterdepolarizatio<br>may h from more than one range of voltages  $(17)$  which may suggest more than one mechanism. One postulated mechanism is that both early and delayed afterdepolarizations may have a common basis in intracellular  $Ca^{2+}$  oscillat suggest more than one mechanism. One postulated mechanism is that both early and delayed afterdepolarizations may have a common basis in intracellular  $Ca^{2+}$  oscillations resulting from  $Ca^{2+}$  overload of the SR (11). P anism is that both early and delayed afterdepolarize<br>may have a common basis in intracellular Ca<sup>2+</sup> oscillations resulting from Ca<sup>2+</sup> overload of the SR (11).<br>haps the strongest evidence supporting a common<br>for intracel may have a common basis in intracellular  $Ca^{2+}$  oscillations resulting from  $Ca^{2+}$  overload of the SR (11). Perhaps the strongest evidence supporting a common role for intracellular  $Ca^{2+}$  oscillations is that "afterco tions resulting from  $Ca^{2+}$  overload of the SR (11). Perhaps the strongest evidence supporting a common role for intracellular  $Ca^{2+}$  oscillations is that "aftercontractions" can be recorded with early as well as delaye for intracellular  $Ca^{2+}$  oscillations is that "aftercontractions" can be recorded with early as well as delayed after<br>depolarizations (37). Furthermore, both early and delayed after<br>depolarizations are forms of triggered tions" can be recorded with early as well as delayed<br>afterdepolarizations (37). Furthermore, both early and<br>delayed afterdepolarizations are forms of triggered activ-<br>ity and require an initiating event, such as one or mor afterdepolarizations (37). Furthermore, both early and afterdepolarizations (37). Furthermore, both early a delayed afterdepolarizations are forms of triggered act<br>ity and require an initiating event, such as one or mo<br>action potentials. Both early and delayed afterdepola<br>zati delayed afterdepolarizations are forms of triggered activity and require an initiating event, such as one or more action potentials. Both early and delayed afterdepolarizations can be suppressed by a number of drugs, inclu ity and require an initiating event, such as one or<br>action potentials. Both early and delayed afterdepo<br>zations can be suppressed by a number of drugs, in<br>ing Ca<sup>2+</sup> channel-blocking drugs. However, several<br>of evidence sug action potentials. Both early and delayed afterdepolarizations can be suppressed by a number of drugs, including  $Ca^{2+}$  channel-blocking drugs. However, several lines of evidence suggest that early and delayed afterdepol zations can be suppressed by a number of drugs, in<br>ing Ca<sup>2+</sup> channel-blocking drugs. However, several<br>of evidence suggest that early and delayed afterdep<br>izations may not share the same cellular mechanism<br>Early afterdepol ing  $Ca^{2+}$  channel-blocking drugs. However, several lines<br>of evidence suggest that early and delayed afterdepolar-<br>izations may not share the same cellular mechanism.  $(a)$ <br>Early afterdepolarizations, unlike delayed after of evidence suggest that early and delayed afterdepolizations may not share the same cellular mechanism.<br>Early afterdepolarizations, unlike delayed afterdepolarizations, are increasingly likely to occur at low stimulatifre izations may not share the same cellular mechanism.  $(a)$ <br>Early afterdepolarizations, unlike delayed afterdepolarizations, are increasingly likely to occur at low stimulation<br>frequencies and commonly are associated with pr Early afterdepolarizations, unlike delayed afterdepolarizations, are increasingly likely to occur at low stimulation<br>frequencies and commonly are associated with prolongation of the cardiac action potential. (b) When cons zations, are increasingly likely to occur at low stimulation<br>frequencies and commonly are associated with prolon-<br>gation of the cardiac action potential.  $(b)$  When constant<br>current pulses are used to polarize the cell mem frequencies and commonly are associated with prolongation of the cardiac action potential.  $(b)$  When constant current pulses are used to polarize the cell membrane to different initiating voltages, the resulting early or gation of the cardiac action potential. (b) When constant current pulses are used to polarize the cell membrane to different initiating voltages, the resulting early or delayed afterdepolarizations reach different peak vo current pulses are used to polarize the cell membran<br>different initiating voltages, the resulting early or<br>layed afterdepolarizations reach different peak volta<br>For early afterdepolarizations, this relationship ha<br>steep in different initiating voltages, the resulting early or de-<br>layed afterdepolarizations reach different peak voltages.<br>For early afterdepolarizations, this relationship has a<br>steep inverse slope (37), whereas for delayed afte layed afterdepolarizations reach different peak volta<br>For early afterdepolarizations, this relationship has<br>teep inverse slope (37), whereas for delayed afterdencianarizations, the slope of the relationship is in the oppo<br> For early afterdepolarizations, this relationship has a steep inverse slope (37), whereas for delayed afterdepolarizations, the slope of the relationship is in the opposite direction (82). (c) The peak voltage of early af steep inverse slope (37), whereas for delayed afterdepo-<br>larizations, the slope of the relationship is in the opposite<br>direction (82). (c) The peak voltage of early afterdepo-<br>larizations in Purkinje fibers may exceed the larizations, the slope of the relationship is in the opposite<br>direction (82). (c) The peak voltage of early afterdepo-<br>larizations in Purkinje fibers may exceed the reversal<br>potential reported for  $i_{\text{TI}}$  (37). (d) Inte direction (82). *(c)* The peak voltage of early afterdepolarizations in Purkinje fibers may exceed the reversal potential reported for  $i_{TI}$  (37). *(d)* Interventions that modify intracellular  $Ca^{2+}$  (e.g., BAPTA, ryano larizations in Purkinje fibers may exceed the reversal<br>potential reported for  $i_{\text{TI}}$  (37). (d) Interventions that<br>modify intracellular Ca<sup>2+</sup> (e.g., BAPTA, ryanodine) sup-<br>press delayed but not early afterdepolarizatio potential reported for  $i_{\text{TI}}$  (37). (*d*) Interventions that<br>modify intracellular Ca<sup>2+</sup> (e.g., BAPTA, ryanodine) sup-<br>press delayed but not early afterdepolarizations (59). (*e*)<br> $i_{\text{TI}}$  and its aftercontraction can modify intracellular Ca<sup>2+</sup> (e.g., BAPTA, ryanodine) suppress delayed but not early afterdepolarizations (59). (*e*)  $i_{\text{TI}}$  and its aftercontraction can be induced separately in tissue already having early afterdepolar press delayed but not early afterdepolarizations  $(59)$ .  $(e)$  $i_{\text{TI}}$  and its aftercontraction can be induced separately in tissue already having early afterdepolarizations (36). ( $f$ )<br>Early afterdepolarizations arising at action potential pla-<br>teau voltages have been shown to depend on the availa-<br>bility of L-type Ca<sup>2+</sup> current (36). One mec Early afterdepolarizations arising at action potential plateau voltages have been shown to depend on the availability of L-type  $Ca^{2+}$  current (36). One mechanism postulated to explain early afterdepolarizations is that teau voltages have been shown to depend on the availability of L-type Ca<sup>2+</sup> current (36). One mechanism potulated to explain early afterdepolarizations is that the induction requires lengthening of the action potential p bility of L-type Ca<sup>2+</sup> current (36). One mechanism postulated to explain early afterdepolarizations is that their induction requires lengthening of the action potential plateau within a voltage range where L-type Ca<sup>2+</sup> tulated to explain early afterdepolarizations is that their induction requires lengthening of the action potential plateau within a voltage range where L-type Ca<sup>2+</sup> channels can recover from inactivated to closed states, induction requires lengthening of the action potential<br>plateau within a voltage range where L-type  $Ca^{2+}$  chan-<br>nels can recover from inactivated to closed states, and<br>then reopen. Thus with repolarization, recovery of d plateau within a voltage range where L-type Ca<sup>2+</sup> chanels can recover from inactivated to closed states, an then reopen. Thus with repolarization, recovery of d polarizing current could occur through the L-type Ca "window

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JANUARY AND FOZZARD<br>(35-37). This mechanism best describes early afterde-<br>polarizations initiated at action potential plateau volt-<br>process the 224 JANUARY<br>
(35–37). This mechanism best describes early after<br>
polarizations initiated at action potential plateau volt-<br>
ages, and it does not require  $Ca^{2+}$  overload of the cardiac 224<br>
a JANUARY AND<br>
(35-37). This mechanism best describes early after<br>
polarizations initiated at action potential plateau volt-<br>
ages, and it does not require Ca<sup>2+</sup> overload of the cardiac<br>
cell. A role may still exist (35–37). This mechanism best describes early afterde-<br>polarizations initiated at action potential plateau volt-<br>ages, and it does not require  $Ca^{2+}$  overload of the cardiac<br>cell. A role may still exist for intracellular (35–37). This mechanism best describes early afterde-<br>polarizations initiated at action potential plateau volt-<br>ages, and it does not require  $Ca^{2+}$  overload of the cardiac<br>cell. A role may still exist for intracellular polarizations initiated at action potential plateau volt-<br>ages, and it does not require  $Ca^{2+}$  overload of the cardiac<br>cell. A role may still exist for intracellular  $Ca^{2+}$ , however,<br>since it modulates the transmembrane cell. A role may still exist for intracellular  $Ca^{2+}$ , however,<br>since it modulates the transmembrane  $Ca^{2+}$  ion gradient,<br>and together with voltage it regulates the inactivation<br>kinetics of  $Ca^{2+}$  channels. and together with voltage it regulates the inactivation

## VII. Relationship of Ca<sup>2+</sup> and Delayed<br>Afterdepolarizations to Clinical Arrhythmias

netics of  $Ca^{2+}$  channels.<br>
VII. Relationship of  $Ca^{2+}$  and Delayed<br>
Afterdepolarizations to Clinical Arrhythmias<br>
It has long been recognized by physicians that toxic<br>
ncentrations of cardiac glycosides cause arrhythmi VII. Relationship of Ca<sup>2+</sup> and Delayed<br>Afterdepolarizations to Clinical Arrhythmias<br>It has long been recognized by physicians that toxic<br>concentrations of cardiac glycosides cause arrhythmias<br>that sometimes can be fatal ( VII. Relationship of Ca<sup>-1</sup> and Delayed<br>Afterdepolarizations to Clinical Arrhythmias<br>It has long been recognized by physicians that toxic<br>concentrations of cardiac glycosides cause arrhythmias<br>that sometimes can be fatal ( Afterdepolarizations to Clinical Arrhythmias<br>It has long been recognized by physicians that toxiconcentrations of cardiac glycosides cause arrhythmia<br>that sometimes can be fatal (for review see ref. 75). Usin<br>extracellular It has long been recognized by physicians that toxic<br>concentrations of cardiac glycosides cause arrhythmias<br>that sometimes can be fatal (for review see ref. 75). Using<br>extracellular recording techniques in isolated tissue concentrations of cardiac glycosides cause arrhythmias<br>that sometimes can be fatal (for review see ref. 75). Using<br>extracellular recording techniques in isolated tissue prep-<br>in<br>arations, early investigators (6) introduce that sometimes can be fatal (for review see ref. 75). Usin<br>extracellular recording techniques in isolated tissue prep<br>arations, early investigators (6) introduced the idea tha<br>an oscillatory electrical event was triggered extracellular recording techniques in isolated tissue preparations, early investigators (6) introduced the idea that<br>an oscillatory electrical event was triggered by the action<br>potential and might cause arrhythmias. Subseq arations, early investigators  $(6)$  introduced the idea that<br>an oscillatory electrical event was triggered by the action<br>potential and might cause arrhythmias. Subsequent stud-<br>ies showed that toxic concentrations of card an oscillatory electrical event was triggered by the action<br>potential and might cause arrhythmias. Subsequent stud-<br>ies showed that toxic concentrations of cardiac glycosides<br>led to altered ventricular excitability (for ex potential and might cause arrhythmias. Subsequent studies showed that toxic concentrations of cardiac glycosides<br>led to altered ventricular excitability (for example, see<br>ref. 56) and caused an overdrive-dependent accelera ies showed that toxic concentrations of cardiac glycosides<br>led to altered ventricular excitability (for example, see<br>ref. 56) and caused an overdrive-dependent acceleration<br>in ventricular pacemaker rate (for example, see led to altered ventricular excitability (for example, see<br>ref. 56) and caused an overdrive-dependent acceleration<br>in ventricular pacemaker rate (for example, see ref. 87).<br>This set the stage for the present method of prov ref. 56) and caused an overdrive-dependent acceleration<br>in ventricular pacemaker rate (for example, see ref. 87).<br>This set the stage for the present method of provoking<br>delayed afterdepolarizations in isolated tissue by u in ventricular pacemaker rate (for example, see ref. 87).<br>This set the stage for the present method of provoking<br>delayed afterdepolarizations in isolated tissue by using<br>rapid pacing combined with exposure of the tissue t This set the stage for the present method of provoking<br>delayed afterdepolarizations in isolated tissue by using<br>rapid pacing combined with exposure of the tissue to<br>high levels of cardiotonic steroids, catecholamines, or<br> delayed afterdepolarizations in isolated tissue by using<br>rapid pacing combined with exposure of the tissue to<br>high levels of cardiotonic steroids, catecholamines, or<br>other interventions that promote  $Ca^{2+}$  overload. The<br> rapid pacing combined with exposure of the tissue to<br>high levels of cardiotonic steroids, catecholamines, or<br>other interventions that promote  $Ca^{2+}$  overload. The<br>ability to generate delayed afterdepolarizations under<br>la high levels of cardiotonic steroids, catecholamines, or<br>other interventions that promote  $Ca^{2+}$  overload. The<br>ability to generate delayed afterdepolarizations under<br>laboratory conditions that resembled clinical states su other interventions that promote  $Ca^{2+}$  overload. The ability to generate delayed afterdepolarizations under laboratory conditions that resembled clinical states supported the idea that delayed afterdepolarizations could arrhythmias.

laboratory conditions that resembled clinical states supported the idea that delayed afterdepolarizations could<br>be an important mechanism underlying some cardiac<br>arrhythmias.<br>Evidence supporting a role for delayed afterdep arrhythmias.<br>Evidence supporting a role for delayed afterdepolarizations in myocardial ischemia can be found. Triggered<br>rhythms have been reported in association with delayed<br>afterdepolarizations in canine endocardial tiss Evidence supporting a role for delayed afterdepolarizations in myocardial ischemia can be found. Triggered rhythms have been reported in association with delayed afterdepolarizations in canine endocardial tissue obtained f zations in myocardial ischemia can be found. Triggered<br>
rhythms have been reported in association with delayed<br>
afterdepolarizations in canine endocardial tissue oblights of vent<br>
tained from 1-day-old myocardial infarcti rhythms have been reported in association with delayed<br>afterdepolarizations in canine endocardial tissue ob-<br>tained from 1-day-old myocardial infarctions (24). En-<br>hancement of the delayed afterdepolarizations with low<br>co afterdepolarizations in canine endocardial tissue obtained from 1-day-old myocardial infarctions (24). Enhancement of the delayed afterdepolarizations with low econcentrations of cardiac glycosides has been suggested as a tained from 1-day-old myocardial infarctions  $(24)$ . Enhancement of the delayed afterdepolarizations with low<br>concentrations of cardiac glycosides has been suggested with<br>as a basis for the potentially deleterious effects hancement of the delayed afterdepolarizations with<br>concentrations of cardiac glycosides has been sugges<br>as a basis for the potentially deleterious effects of card<br>glycosides in acute myocardial infarction (32). Studie<br>chro concentrations of cardiac glycosides has been suggested<br>as a basis for the potentially deleterious effects of cardiac<br>glycosides in acute myocardial infarction (32). Studies in<br>chronically and recently infarcted tissue usi as a basis for the potentially deleterious effects of cardiac glycosides in acute myocardial infarction (32). Studies in chronically and recently infarcted tissue using ion-selective microelectrodes (20, 47) have shown de glycosides in acute myocardial infarction (32). Studies in<br>chronically and recently infarcted tissue using ion-selec-<br>tive microelectrodes (20, 47) have shown depolarization arrh<br>of the cell membrane and elevation of intr chronically and recently infarcted tissue using ion-selec-<br>tive microelectrodes (20, 47) have shown depolarization<br>of the cell membrane and elevation of intracellular Na<sup>+</sup>,<br>both of which could promote  $Ca^{2+}$  loading of tive microelectrodes  $(20, 47)$  have shown depolarization of the cell membrane and elevation of intracellular Ne both of which could promote  $Ca^{2+}$  loading of the cells. isolated tissues, both induction and suppression o of the cell membrane and elevation of intracellular Na<sup>+</sup>, from<br>both of which could promote  $Ca^{2+}$  loading of the cells. In<br>isolated tissues, both induction and suppression of de-<br>flayed afterdepolarizations have been ob both of which could promote  $Ca^{2+}$  loading of the cells.<br>isolated tissues, both induction and suppression of c<br>layed afterdepolarizations have been observed in experimental ischemia-reperfusion models (14, 29, 33, 57), a isolated tissues, both induction and suppression of delayed afterdepolarizations have been observed in exper-<br>imental ischemia-reperfusion models  $(14, 29, 33, 57)$ , and zavidence exists supporting  $Ca^{2+}$  overload as the layed afterdepolarizations have been observed in e<br>imental ischemia-reperfusion models  $(14, 29, 33, 57)$ <br>evidence exists supporting  $Ca^{2+}$  overload as the u<br>lying mechanism. Finally, electrophysiologically a<br>toxic ische imental ischemia-reperfusion models  $(14, 29, 33, 57)$ , arevidence exists supporting  $Ca^{2+}$  overload as the undelying mechanism. Finally, electrophysiologically activations it toxic ischemic metabolites (i.e., lysophosph evidence exists supporting  $Ca^{2+}$  overload as the under-<br>lying mechanism. Finally, electrophysiologically active<br>toxic ischemic metabolites (i.e., lysophosphatidylcholine,<br>etc.) have been reported to provoke afterdepolar ing mechanism. Finally, electrophysiologically active after the since it are in the case of the case of the calculation is calculated the capacity in isolated cardiac tissue  $(3, 68)$ . In the for Ca<sup>2+</sup> overload and Ca<sup>2+</sup>

toxic ischemic metabolites (i.e., lysophosphatidylcholine,<br>etc.) have been reported to provoke afterdepolarizations<br>and triggered activity in isolated cardiac tissue (3, 68).<br>A role for Ca<sup>2+</sup> overload and Ca<sup>2+</sup>-dependent etc.) have been reported to provoke afterdepolarizations car<br>and triggered activity in isolated cardiac tissue  $(3, 68)$ . pro<br>A role for  $Ca^{2+}$  overload and  $Ca^{2+}$ -dependent ionic rap<br>currents in both the *initiation* a and triggered activity in isolated cardiac tissue  $(3, 68)$ .<br>A role for  $Ca^{2+}$  overload and  $Ca^{2+}$ -dependent ionicurrents in both the *initiation* and *maintenance* of ventricular fibrillation has been proposed by Clusi

o FOZZARD<br>that its maintenance was mediated by the same cellular<br>process that gave rise to the initiation of afterdepolariprocess that gave rise to the initiation of afterdepolential system in the initiation of afterdepolarions and abnormal automaticity. This hypothesis POZZARD<br>
that its maintenance was mediated by the same cellular<br>
process that gave rise to the initiation of afterdepolari-<br>
zations and abnormal automaticity. This hypothesis pro-<br>
vided a mechanism for the reported benef that its maintenance was mediated by the same cellular<br>process that gave rise to the initiation of afterdepolari-<br>zations and abnormal automaticity. This hypothesis pro-<br>vided a mechanism for the reported beneficial effect that its maintenance was mediated by the same cellula<br>process that gave rise to the initiation of afterdepolar<br>zations and abnormal automaticity. This hypothesis pre<br>vided a mechanism for the reported beneficial effects process that gave rise to the initiation of afterdepolarizations and abnormal automaticity. This hypothesis provided a mechanism for the reported beneficial effects of  $Ca^{2+}$  channel blockers in experimental ventricular zations and abnormal automaticity. This hypothesis provided a mechanism for the reported beneficial effects of  $Ca^{2+}$  channel blockers in experimental ventricular fibrillation as well as for deleterious effects of  $\beta$ -a vided a mechanism for the reported beneficial effects of  $Ca^{2+}$  channel blockers in experimental ventricular fibrillation as well as for deleterious effects of  $\beta$ -adrenergic receptor agonists. Findings supportive of th Ca<sup>2+</sup> channel blockers in experimental ventricular fibrillation as well as for deleterious effects of  $\beta$ -adrenergic receptor agonists. Findings supportive of this hypothesis were reported recently by Merillat et al. (6 lation as well as for deleterious effects of  $\beta$ -adrenergic<br>receptor agonists. Findings supportive of this hypothesis<br>were reported recently by Merillat et al. (63). They<br>provoked ventricular fibrillation in rabbit heart receptor agonists. Findings supportive of this hypothesis<br>were reported recently by Merillat et al. (63). They<br>provoked ventricular fibrillation in rabbit hearts loaded<br>with  $Ca^{2+}$  by removal of  $[K]_0$  or exposure to oua were reported recently by Merillat et al. (63). They<br>provoked ventricular fibrillation in rabbit hearts loaded<br>with Ca<sup>2+</sup> by removal of  $[K]_0$  or exposure to ouabain.<br>Subsequent lowering of extracellular Ca<sup>2+</sup> to 80  $\mu$ provoked ventricular fibrillation in rabbit hearts loaded<br>with  $Ca^{2+}$  by removal of  $[K]_0$  or exposure to ouabain.<br>Subsequent lowering of extracellular  $Ca^{2+}$  to 80  $\mu$ M was<br>shown to abolish the ventricular fibrillatio with Ca<sup>2+</sup> by removal of  $[K]_0$  or exposure to ouabain.<br>Subsequent lowering of extracellular Ca<sup>2+</sup> to 80  $\mu$ M was<br>shown to abolish the ventricular fibrillation. They con-<br>cluded that Ca<sup>2+</sup> overload caused ventricular Subsequent lowering of extracellular Ca<sup>2+</sup> to 80  $\mu$ M was shown to abolish the ventricular fibrillation. They concluded that Ca<sup>2+</sup> overload caused ventricular fibrillation in their model, which ceased when Ca<sup>2+</sup> overl cluded that Ca<sup>2+</sup> overload caused ventricular fibrillati<br>in their model, which ceased when Ca<sup>2+</sup> overload w<br>reversed. Kusuoka et al. (48) studied perfused fer-<br>hearts loaded with Ca<sup>2+</sup> by exposure to strophanthic<br>and a in their model, which ceased when  $Ca^{2+}$  overload was<br>reversed. Kusuoka et al. (48) studied perfused ferret<br>hearts loaded with  $Ca^{2+}$  by exposure to strophanthid<br>and also showed the development of ventricular fibrilla-<br> reversed. Kusuoka et al.  $(48)$  studied perfused ferret hearts loaded with  $Ca^{2+}$  by exposure to strophanthidin and also showed the development of ventricular fibrillation and an associated pressure oscillation thought t hearts loaded with  $Ca^{2+}$  by exposure to strophanthic and also showed the development of ventricular fibril<br>tion and an associated pressure oscillation thought<br>reflect contractile asynchrony. The addition of ryanodi<br>to t and also showed the development of ventricular fibrillation and an associated pressure oscillation thought to reflect contractile asynchrony. The addition of ryanodine to the perfusate rapidly eliminated the pressure oscil tion and an associated pressure oscillation thought to<br>reflect contractile asynchrony. The addition of ryanodine<br>to the perfusate rapidly eliminated the pressure oscilla-<br>tions, but failed to stop the ventricular fibrillat reflect contractile asynchrony. The addition of ryanod<br>to the perfusate rapidly eliminated the pressure osci<br>tions, but failed to stop the ventricular fibrillation. T<br>concluded that the ventricular fibrillation they stud<br> to the perfusate rapidly eliminated the pressure oscillations, but failed to stop the ventricular fibrillation. They concluded that the ventricular fibrillation they studied was not maintained by a primary oscillation of concluded that the ventricular fibrillation they studied<br>was not maintained by a primary oscillation of intracelconcluded that the ventricular fibrillation they studied<br>was not maintained by a primary oscillation of intracel-<br>lular Ca<sup>2+</sup>, and they suggested that other arrhythmogenic<br>mechanisms, such as reentry or abnormal automati was not maintained by a primary oscillation of intracel-<br>lular Ca<sup>2+</sup>, and they suggested that other arrhythmogenic<br>mechanisms, such as reentry or abnormal automaticity,<br>might sustain the arrhythmia. These results, howeve mechanisms, such as reentry or abnormal automaticity,<br>might sustain the arrhythmia. These results, however,<br>did not exclude a role for mechanisms dependent on Ca<sup>2+</sup><br>overload in the initiation of ventricular fibrillation. might sustain the arrhythmia. These results, however,<br>did not exclude a role for mechanisms dependent on  $Ca^{2+}$ <br>overload in the initiation of ventricular fibrillation. Com-<br>parison of these recent reports is difficult, i might sustain the arrhythmia. These results, however<br>did not exclude a role for mechanisms dependent on  $Ca^2$ <br>overload in the initiation of ventricular fibrillation. Com<br>parison of these recent reports is difficult, in pa did not exclude a role for mechanisms dependent on  $Ca^{2+}$ <br>overload in the initiation of ventricular fibrillation. Com-<br>parison of these recent reports is difficult, in part because<br>of differences between the experimental overload in the initiation of ventricular fibrillation. Comparison of these recent reports is difficult, in part because of differences between the experimental models and techniques. Further experimental insight is neede parison of these recent reports is difficult,<br>of differences between the experimental m<br>niques. Further experimental insight is nee<br>role of  $Ca^{2+}$  overload in the initiation and<br>of ventricular fibrillation can be defined differences between the experimental models and<br>ques. Further experimental insight is needed befole of Ca<sup>2+</sup> overload in the initiation and mainte<br>ventricular fibrillation can be defined.<br>It has yet to be proved that dela

A role for Ca<sup>2+</sup> overload and Ca<sup>2+</sup>-dependent ionic rapid pacing, the relationship of the escape interval to currents in both the *initiation* and *maintenance* of ven-<br>tricular fibrillation has been proposed by Clusin miques. Further experimental insight is needed before the role of  $Ca^{2+}$  overload in the initiation and maintenance of ventricular fibrillation can be defined.<br>It has yet to be proved that delayed afterdepolarizations ca role of  $Ca^{2+}$  overload in the initiation and maintenance<br>of ventricular fibrillation can be defined.<br>It has yet to be proved that delayed afterdepolariza-<br>tions cause clinical arrhythmias. The majority of clinical<br>evide of ventricular fibrillation can be defined.<br>It has yet to be proved that delayed afterdepolariza-<br>tions cause clinical arrhythmias. The majority of clinical<br>evidence derives from the extrapolation of data obtained<br>with exp It has yet to be proved that delayed afterdepolariza-<br>tions cause clinical arrhythmias. The majority of clinical<br>evidence derives from the extrapolation of data obtained<br>with experimental pacing protocols used to produce d tions cause clinical arrhythmias. The majority of clinical<br>evidence derives from the extrapolation of data obtained<br>with experimental pacing protocols used to produce de-<br>layed afterdepolarizations and initiate spontaneous evidence derives from the extrapolation of data obtained<br>with experimental pacing protocols used to produce de-<br>layed afterdepolarizations and initiate spontaneous<br>rhythms in isolated tissue. Certain clinical criteria have with experimental pacing protocols used to produce d<br>layed afterdepolarizations and initiate spontaneor<br>rhythms in isolated tissue. Certain clinical criteria have<br>been developed that may be useful in differentiatio<br>arrhyth layed afterdepolarizations and initiate spontaned<br>rhythms in isolated tissue. Certain clinical criteria habeen developed that may be useful in differentiation<br>arrhythmias initiated by delayed afterdepolarization<br>from those rhythms in isolated tissue. Certain clinical criteria have<br>been developed that may be useful in differentiating<br>arrhythmias initiated by delayed afterdepolarizations<br>from those initiated by other arrhythmogenic mecha-<br>nis been developed that may be useful in differentiating<br>arrhythmias initiated by delayed afterdepolarizations<br>from those initiated by other arrhythmogenic mecha-<br>nisms (58, 70, 86). The major differentiation is from<br>reentry, from those initiated by other arrhythmogenic mechanisms (58, 70, 86). The major differentiation is from reentry, since abnormal automaticity is generally not included as a triggered rhythm, and early afterdepolarinisms (58, 70, 86). The major differentiation is from nisms (58, 70, 86). The major differentiation is from<br>reentry, since abnormal automaticity is generally not<br>included as a triggered rhythm, and early afterdepolari-<br>zations are bradycardia dependent. The clinical criteria<br> reentry, since abnormal automaticity is generally not<br>included as a triggered rhythm, and early afterdepolari-<br>zations are bradycardia dependent. The clinical criteria<br>suggested that cardiac arrhythmias induced by delayed<br> included as a triggered rhythm, and early afterdepolarizations are bradycardia dependent. The clinical criteria<br>suggested that cardiac arrhythmias induced by delayed<br>afterdepolarizations should include the characteristics<br> suggested that cardiac arrhythmias induced by delayed<br>afterdepolarizations should include the characteristics<br>that the rhythm is triggered and how this occurs (i.e.,<br>cardiac glycoside toxicity, catecholamines, etc.), its r suggested that cardiac arrhythmias induced by delayed<br>afterdepolarizations should include the characteristics<br>that the rhythm is triggered and how this occurs (i.e.,<br>cardiac glycoside toxicity, catecholamines, etc.), its r afterdepolarizations should include the characteristics<br>that the rhythm is triggered and how this occurs (i.e.,<br>cardiac glycoside toxicity, catecholamines, etc.), its re-<br>producibility and probability of enhancement with p that the rhythm is triggered and how this occurs (i.e., cardiac glycoside toxicity, catecholamines, etc.), its reproducibility and probability of enhancement with prior rapid pacing, the relationship of the escape interval cardiac glycoside toxicity, catecholamines, etc.), its reproducibility and probability of enhancement with prior<br>rapid pacing, the relationship of the escape interval to<br>the preceding dominant cycle length or pacing freque producibility and probability of enhancement with prior<br>rapid pacing, the relationship of the escape interval to<br>the preceding dominant cycle length or pacing frequency,<br>and the characteristics and reproducibility of arrhy rapid pacing, the relationship of the escape interval to<br>the preceding dominant cycle length or pacing frequency,<br>and the characteristics and reproducibility of arrhythmia<br>termination by single impulses and overdrive pacin

**REVIEW** 

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DELAYED AFTERDEPOLARIZ<br>ful criteria for defining underlying cellular mechanisms<br>(58), the unequivocal separation of arrhythmogenic DELAYED AFTERDEPOLARI<br>
ful criteria for defining underlying cellular mechanisms<br>
(58), the unequivocal separation of arrhythmogenic<br>
mechanisms by these clinical criteria frequently is not DELAYED AFTERDEPOLARIZA<br>ful criteria for defining underlying cellular mechanisms<br>(58), the unequivocal separation of arrhythmogenic<br>mechanisms by these clinical criteria frequently is not<br>possible, and recent studies (38) ful criteria for defining underlying cellular mechanism (58), the unequivocal separation of arrhythmogeni<br>mechanisms by these clinical criteria frequently is no<br>possible, and recent studies (38) showing that the char<br>acter ful criteria for defining underlying cellular mechanisms lular mechanisms at the clinical level is complex, and it (58), the unequivocal separation of arrhythmogenic is likely to require new drugs that are highly selective mechanisms by these clinical criteria frequently is not mechanisms by these clinical criteria frequently is no possible, and recent studies (38) showing that the chand<br>acteristics of delayed afterdepolarizations are not the same in different parts of the heart may further confu possible, and recent studies (38) showing that the chacteristics of delayed afterdepolarizations are not same in different parts of the heart may further conf the interpretation of clinical criteria. At this point, st ies same in different parts of the heart may further confuse<br>the interpretation of clinical criteria. At this point, stud-<br>ies utilizing surface and invasive electrophysiological<br>techniques indicate that the strongest evidenc same in different parts of the heart may further confus<br>the interpretation of clinical criteria. At this point, stud<br>ies utilizing surface and invasive electrophysiologics<br>techniques indicate that the strongest evidence fo the interpretation of clinical criteria. At this point, studies utilizing surface and invasive electrophysiological 2. A techniques indicate that the strongest evidence for a role of delayed afterdepolarizations is in acce tional rhythms in digitalis toxicity (71), and possibly in some forms of ventricula tachycardia (see refs. 8, 58, and 86). delayed afterdepolarizations is in accelerated junc-<br>
onal rhythms in digitalis toxicity (71), and possibly in<br>
me forms of ventricula tachycardia (see refs. 8, 58, and<br>
).<br>
Direct recordings from the endocardial or epicar

tional rhythms in digitalis toxicity (71), and possibly<br>some forms of ventricula tachycardia (see refs. 8, 58, a<br>86).<br>Direct recordings from the endocardial or epicard<br>surfaces of the heart permit the recording of the mon<br> some forms of ventricula tachycardia (see refs. 8, 58, and<br>86).<br>Direct recordings from the endocardial or epicardial<br>surfaces of the heart permit the recording of the mono-<br>phasic action potential and are an additional app 86). Direct recordings from the endocardial or epicardia<br>surfaces of the heart permit the recording of the mono<br>phasic action potential and are an additional approact<br>to studying the role of delayed afterdepolarizations. A Direct recordings from the endocardial or epicardial<br>surfaces of the heart permit the recording of the mono-<br>phasic action potential and are an additional approach<br>to studying the role of delayed afterdepolarizations. Al-<br> phasic action potential and are an additional approach<br>to studying the role of delayed afterdepolarizations. Al-<br>though the theoretical basis for these contact recordings<br>is incompletely explained, experimental validation phasic action potential and are an additional approach  $\frac{6.1}{7.1}$  though the theoretical basis for these contact recordings is incompletely explained, experimental validation suggests that the scaled monophasic action to studying the role of delayed afterdepolarizations. A<br>though the theoretical basis for these contact recordin<br>is incompletely explained, experimental validation su<br>gests that the scaled monophasic action potential is<br>rea though the theoretical basis for these contact recordings<br>is incompletely explained, experimental validation suggests that the scaled monophasic action potential is a<br>reasonable approximation of the directly recorded trans is incompletely explained, experimental validation<br>gests that the scaled monophasic action potential<br>reasonable approximation of the directly recorded to<br>membrane action potential (30, 53). Furthermore,<br>technique may permi gests that the scaled monophasic action potential is<br>reasonable approximation of the directly recorded tran<br>membrane action potential (30, 53). Furthermore, the<br>dechnique may permit the identification of afterdepolar<br>izati reasonable approximation of the directly recorded tran<br>membrane action potential (30, 53). Furthermore, the<br>technique may permit the identification of afterdepola<br>izations in vivo (see ref. 53), and the approach of recor<br>i membrane action potential (30, 53). Furthermore, this<br>technique may permit the identification of afterdepolar-<br>izations in vivo (see ref. 53), and the approach of record-<br>ing the monophasic action potential seems to be a p technique may permit the identification of afterdepolarizations in vivo (see ref. 53), and the approach of recording the monophasic action potential seems to be a promising new methodology. While valuable, these types of izations in vivo (see ref. 53), and the approach of recording the monophasic action potential seems to be a promising new methodology. While valuable, these types of recordings potentially are limited by their focal natur ing the monophasic action potential seems to be a promising new methodology. While valuable, these types of recordings potentially are limited by their focal nature and by complexities arising from the "field of view" of ising new methodology. While valuable, these types<br>recordings potentially are limited by their focal natural<br>and by complexities arising from the "field of view"<br>the contact electrode (see ref. 52). Another approach<br>the id recordings potentially are limited by their focal nature<br>and by complexities arising from the "field of view" of<br>the contact electrode (see ref. 52). Another approach to<br>the identification of underlying arrhythmogenic mec and by complexities arising from the "field of view"<br>the contact electrode (see ref. 52). Another approach<br>the identification of underlying arrhythmogenic mech<br>nisms in the pattern of excitability as defined by the<br>strengt the contact electrode (see ref. 52). Another approache identification of underlying arrhythmogenic me<br>nisms in the pattern of excitability as defined by<br>strength-interval relationship. Intracellular and ex-<br>cellular stimul the identification of underlying arrhythmogenic mechanisms in the pattern of excitability as defined by the strength-interval relationship. Intracellular and extracellular stimulation techniques have shown characteristic b nisms in the pattern of excitability as defined by the strength-interval relationship. Intracellular and extracellular stimulation techniques have shown characteristic biphasic changes in excitability in association with d strength-interval relationship. Intracellular and extra-<br>cellular stimulation techniques have shown characteris-<br>tic biphasic changes in excitability in association with<br>delayed afterdepolarizations, and they may be a mar cellular stimulation techniques have shown characteristic biphasic changes in excitability in association with delayed afterdepolarizations, and they may be a marker for their presence (73, 77). Finally, the direct imagin tic biphasic changes<br>delayed afterdepolar<br>for their presence  $(75)$ <br>intracellular  $Ca^{2+}$  is<br>powerful new tool.<br>In addition to t layed afterdepolarizations, and they may be a marker<br>r their presence  $(73, 77)$ . Finally, the direct imaging of<br>tracellular  $Ca^{2+}$  in the intact heart may provide a<br>werful new tool.<br>In addition to the direct initiation

for their presence (73, 77). Finally, the direct imaging of<br>intracellular  $Ca^{2+}$  in the intact heart may provide a<br>powerful new tool.<br>In addition to the direct initiation of abnormal<br>rhythms by the delayed afterdepolariz intracellular  $Ca^{2+}$  in the intact heart may provide a 18 powerful new tool.<br>In addition to the direct initiation of abnormal 18 rhythms by the delayed afterdepolarization reaching threshold voltage, other possible arrhy powerful new tool.<br>
In addition to the direct initiation of abnormal 19. In<br>
rhythms by the delayed afterdepolarization reaching<br>
threshold voltage, other possible arrhythmogenic roles 20. In<br>
exist for them. Delayed after In addition to the direct initiation of abnormal 19.<br>
rhythms by the delayed afterdepolarization reaching<br>
threshold voltage, other possible arrhythmogenic roles 20.<br>
exist for them. Delayed afterdepolarizations failing t rhythms by the delayed afterdepolarization reaching<br>threshold voltage, other possible arrhythmogenic roles  $20.1$ <br>exist for them. Delayed afterdepolarizations failing to<br>reach threshold voltage themselves are associated w threshold voltage, other possible arrhythmogenic roles  $20.1$ <br>exist for them. Delayed afterdepolarizations failing to<br>reach threshold voltage themselves are associated with<br>substantial changes in current threshold (77). I exist for them. Delayed afterdepolarizations failing to reach threshold voltage themselves are associated with substantial changes in current threshold (77). It has also long been known that delayed afterdepolarizations ca reach threshold voltage themselves are associated with<br>substantial changes in current threshold (77). It has also  $^{21.}$  E<br>long been known that delayed afterdepolarizations can<br>alter conduction velocity and may produce c substantial changes in current threshold (77). It has also<br>long been known that delayed afterdepolarizations can<br>alter conduction velocity and may produce conduction<br>block (67, 73), presumably as a result of a change in<br>ex long been known that delayed afterdepolarizations can<br>alter conduction velocity and may produce conduction<br>block (67, 73), presumably as a result of a change in<br>excitability (19). These changes could provide the con-<br>ditio alter conduction velocity and may produce conduction  $22$ .<br>block (67, 73), presumably as a result of a change in  $23$ .<br>excitability (19). These changes could provide the con-<br>ditions necessary to establish conduction bloc block (67, 73), presumably as a result of a change<br>excitability (19). These changes could provide the c<br>ditions necessary to establish conduction block such t<br>reentrant rhythms could be initiated. In this way<br>afterdepolari excitability (19). These changes could provide the conditions necessary to establish conduction block such the reentrant rhythms could be initiated. In this way the afterdepolarization would serve to initiate the tachya rh ditions necessary to establish conduction block such that<br>reentrant rhythms could be initiated. In this way the<br>afterdepolarization would serve to initiate the tachyar-<br>rhythmia, but would not be required for its maintenan reentrant rhythms could be initiated. In this way the afterdepolarization would serve to initiate the tachyar-<br>rhythmia, but would not be required for its maintenance.<br>Another possible role for delayed afterdepolarization afterdepolarization would serve to initiate the tachyar-<br>rhythmia, but would not be required for its maintenance.<br>Another possible role for delayed afterdepolarizations is<br>that the associated time-dependent changes in dias rhythmia, but would not be required for its maintenance.<br>Another possible role for delayed afterdepolarizations is<br>that the associated time-dependent changes in diastolic<br>excitability also could contribute to rate-dependen

TIONS IN HEART MUSCLE<br>lular mechanisms at the clinical level is complex, and it<br>is likely to require new drugs that are highly selective for TIONS IN HEART MUSCLE 225<br>
lular mechanisms at the clinical level is complex, and it<br>
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