# **Experimental Therapeutics**<br>
The Pharmacology of Mechanogated Membrane Ion<br>
The Pharmacology of Mechanogated Membrane Ion **Channels**

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I. Introduction a<br>More than 30 years ago, A.S. Paintal (1964) reviewed this Journal the pharmacology of vertebrate mech-I. Introduction<br>More than 30 years ago, A.S. Paintal (1964) review<br>in this Journal the pharmacology of vertebrate mech-<br>anoreceptors. His review summarized drug effects on **a** m<br>**Alternal School Controls 20 years ago, A.S. Paintal (1964) reviewed<br>in this Journal the pharmacology of vertebrate mech-<br>anoreceptors. His review summarized drug effects on a<br>variety of specialized mechanosensory re** I. HITOGLICION<br>in this Journal the pharmacology of vertebrate mechanoseceptors. His review summarized drug effects or<br>variety of specialized mechanosensory receptors, inclu<br>ing cutaneous, muscle and visceral receptors. His More than 30 years ago, A.S. Paintal  $(1964)$  reviewed<br>in this Journal the pharmacology of vertebrate mech-<br>anoreceptors. His review summarized drug effects on a<br>variety of specialized mechanosensory receptors, includ-<br>in in this Journal the pharmacology of vertebrate mech-<br>anoreceptors. His review summarized drug effects on a<br>variety of specialized mechanosensory receptors, includ-<br>ing cutaneous, muscle and visceral receptors. His main<br>co anoreceptors. His review summarized drug effects of variety of specialized mechanosensory receptors, incling cutaneous, muscle and visceral receptors. His monclusion was that the drugs then known to inhibit stimulate mecha variety of specialized mechanosensory receptors, including cutaneous, muscle and visceral receptors. His main conclusion was that the drugs then known to inhibit or stimulate mechanosensation did not act on mechano-transdu ing cutaneous, muscle and visceral receptors. His main conclusion was that the drugs then known to inhibit or<br>stimulate mechanosensation did not act on mechano-<br>transduction itself but rather on ancillary processes<br>such as conclusion was that the drugs then known to inhibit or<br>stimulate mechanosensation did not act on mechano-<br>transduction itself but rather on ancillary processes<br>such as the action potential or muscular/vascular tone.<br>He fur stimulate mechanosensation did not act on mechan<br>transduction itself but rather on ancillary process<br>such as the action potential or muscular/vascular to<br>He further concluded that mechanotransduction usua<br>has a low suscept transduction itself but rather on ancillary processes<br>such as the action potential or muscular/vascular tone.<br>He further concluded that mechanotransduction usually<br>has a low susceptibility to chemical influence. In subse-<br> such as the action potential or muscular/vascular tone.<br>He further concluded that mechanotransduction usually<br>has a low susceptibility to chemical influence. In subse-<br>quent years, voltage clamp studies confirmed that spe-He further concluded that mechanotransduction usually<br>has a low susceptibility to chemical influence. In subse-<br>quent years, voltage clamp studies confirmed that spe-<br>cific drugs reviewed by Paintal such as local anesthet has a low susceptibility to chemical influence. In subsequent years, voltage clamp studies confirmed that specific drugs reviewed by Paintal such as local anesthetic and veratrum alkaloids were indeed potent blockers an a quent years, voltage clamp studies confirmed that specific drugs reviewed by Paintal such as local anesthetics<br>and veratrum alkaloids were indeed potent blockers and<br>activators, respectively, of the voltage-gated Na<sup>+</sup> cha cific drugs reviewed by Paintal such as local anesthetics<br>and veratrum alkaloids were indeed potent blockers and<br>activators, respectively, of the voltage-gated Na<sup>+</sup> chan-<br>nel (Hille, 1992). Since Paintal's review, a vast and veratrum alkaloids were indeed potent blockers an activators, respectively, of the voltage-gated Na<sup>+</sup> chan-<br>nel (Hille, 1992). Since Paintal's review, a vast numbor new drugs and toxins have been discovered that sele activators, respectively, of the voltage-gated Na<sup>+</sup> channel (Hille, 1992). Since Paintal's review, a vast number hof new drugs and toxins have been discovered that sequelectively act on various voltage- and ligand-gated

a means of classifying, purifying and studying the func-<br>ion of many of these channels. Unfortunately, the large the means of classifying, purifying and studying the function of many of these channels. Unfortunately, the large majority of these drugs has not been systematically a means of classifying, purifying and studying the function of many of these channels. Unfortunately, the large majority of these drugs has not been systematically studied for possible effects on mechanotransduction. a means of classifying, purifying and studying the<br>tion of many of these channels. Unfortunately, the<br>majority of these drugs has not been systemat<br>studied for possible effects on mechanotransdu<br>This may be partially becau a means of classifying, purifying and studying the function of many of these channels. Unfortunately, the large majority of these drugs has not been systematically studied for possible effects on mechanotransduction.<br>This tion of many of these channels. Unfortunately, the<br>majority of these drugs has not been systemated<br>studied for possible effects on mechanotransdu<br>This may be partially because of the practical prob<br>direct recording from sp majority of these drugs has not been systematically<br>studied for possible effects on mechanotransduction.<br>This may be partially because of the practical problem of<br>direct recording from specialized sensory mechanotrans-<br>duc drugs that act on mechanosensors, such as those medi-<br>direct recording from specialized sensory mechanotrans-<br>ducers. However, it is also clear that the discovery of<br>drugs that act on mechanosensors, such as those medi-<br>at ducers. However, it is also clear that the discovery of drugs that act on mechanosensors, such as those mediating various cardiovascular reflexes or specific forms of visceral pain, would have profound clinical significanc cers. However, it is also clear that the discovery of<br>ugs that act on mechanosensors, such as those medi-<br>ing various cardiovascular reflexes or specific forms of<br>sceral pain, would have profound clinical significance.<br>Ove

lectively act on various voltage- and ligand-gated chan-<br>nels (Hille, 1992). This wealth of new drugs has provided<br>nels (Hille, 1992). This wealth of new drugs has provided<br>stimulation can also modulate voltage- and ligand drugs that act on mechanosensors, such as those medi-<br>ating various cardiovascular reflexes or specific forms of<br>visceral pain, would have profound clinical significance.<br>Over the last 10 years, there has been a resurgence ating various cardiovascular reflexes or specific forms of visceral pain, would have profound clinical significance.<br>Over the last 10 years, there has been a resurgence of interest in mechanotransduction because of a numbe visceral pain, would have profound clinical significal<br>Over the last 10 years, there has been a resurgence<br>interest in mechanotransduction because of a numbe<br>technical and conceptual advances. In particular, pa<br>clamp recor Over the last 10 years, there has been a resurgence of interest in mechanotransduction because of a number of technical and conceptual advances. In particular, patch clamp recording, with its inherent ability to mechanical interest in mechanotransduction because of a number of technical and conceptual advances. In particular, patch<br>clamp recording, with its inherent ability to mechanically stimulate a membrane patch while simultaneously<br>meas technical and conceptual advances. In particular, patch<br>clamp recording, with its inherent ability to mechani-<br>cally stimulate a membrane patch while simultaneously<br>measuring the current response (Hamill et al., 1981),<br>has clamp recording, with its inherent ability to mechanically stimulate a membrane patch while simultaneously measuring the current response (Hamill et al., 1981), has revealed the existence of a class of mechanogated (MG) me cally stimulate a membrane patch while simultaneously<br>measuring the current response (Hamill et al., 1981),<br>has revealed the existence of a class of mechanogated<br>(MG) membrane ion channels. This class appears dis-<br>tinct fr measuring the current response (Hamill et al., 1981),<br>has revealed the existence of a class of mechanogated<br>(MG) membrane ion channels. This class appears dis-<br>tinct from voltage- and ligand-gated channels (Sachs<br>1988), al has revealed the existence of a class of mechanogated (MG) membrane ion channels. This class appears distinct from voltage- and ligand-gated channels (Sachs, 1988), although recent studies indicate that mechanical stimulat (MG) membrane ion channels. This class appears dis-<br>tinct from voltage- and ligand-gated channels (Sachs,<br>1988), although recent studies indicate that mechanical<br>stimulation can also modulate voltage- and ligand-gated<br>chan tinct from voltage- and ligand-gated channels (Sachs,<br>1988), although recent studies indicate that mechanical<br>stimulation can also modulate voltage- and ligand-gated<br>channels (see Section II, B). For practical reasons re-<br> 1988), although recent studies indicate that mechanical<br>stimulation can also modulate voltage- and ligand-gated<br>channels (see Section II, B). For practical reasons re-<br>lated to the inaccessibility of tissue embedded or fin

neis (Time, 1992). This weath of hew urugs has provided<br>Address for correspondence: Dr. Owen P. Hamill, Department of<br>Physiology/Biophysics, The University of Texas, Medical Branch<br>Galveston, TX 77555-0641. Address for correspon<br>Physiology/Biophysics, T<br>Galveston, TX 77555-064

PHARM<br>REV

PHARMACOLOGICAL REVIEWS

232<br>MG channels have been studied mainly in nonsensory et al., 1992;<br>cell types and have been shown to be expressed in cell differences i Example and the studied mainly in nonsensory<br>Cell types and have been studied mainly in nonsensory<br>cell types representative of all five living kingdoms (Marti-HAMILL<br>MG channels have been studied mainly in nonsense<br>cell types and have been shown to be expressed in c<br>types representative of all five living kingdoms (Mar<br>nac, 1992). MG channels form a complex class, displa MG channels have been studied mainly in nonsens<br>cell types and have been shown to be expressed in types representative of all five living kingdoms (Manac, 1992). MG channels form a complex class, displ<br>ing different mechan MG channels have been studied mainly in nonsensory et and the expressed in cell different mechanosensitivities, gating dynamics and it is modalities, and open channel properties (Howard et al., promodalities, and open cha cell types and have been shown to be expressed in cell<br>types representative of all five living kingdoms (Marti-<br>nac, 1992). MG channels form a complex class, display-<br>ing different mechanosensitivities, gating dynamics and types representative of all five living kingdoms (Marti-binac, 1992). MG channels form a complex class, display-<br>ing different mechanosensitivities, gating dynamics and<br>it modalities, and open channel properties (Howard et nac, 1992). MG channels form a complex class, display-<br>ing different mechanosensitivities, gating dynamics and<br>it is modalities, and open channel properties (Howard et al., pro<br>1988; Sachs, 1988; Morris, 1990; French, 1992 ing different mechanosensitivities, gating dynamics and<br>modalities, and open channel properties (Howard et al.,<br>1988; Sachs, 1988; Morris, 1990; French, 1992; Petrov<br>and Usherwood, 1994; Sackin, 1995; Hamill and<br>McBride, 1 modalities, and open channel properties (Howard et al., pr<br>1988; Sachs, 1988; Morris, 1990; French, 1992; Petrov ceg<br>and Usherwood, 1994; Sackin, 1995; Hamill and sa<br>McBride, 1995a). Presumably, the different properties<br>re 1966, Sachs, 1966, Morris, 1990, French, 1992, Fetrov cep<br>and Usherwood, 1994; Sackin, 1995; Hamill and san<br>McBride, 1995a). Presumably, the different properties<br>reflect different roles played by MG channels in the<br>various and Usherwood, 1994, Sackin, 1999, Hamin and sa<br>McBride, 1995a). Presumably, the different properties<br>reflect different roles played by MG channels in the<br>various cell types. Although the role of MG channels in<br>mechanosens reflect different roles played by MG channels in the various cell types. Although the role of MG channels in mechanosensory cells is obvious, they have also been implicated in such basic functions as cell volume regulation mechanosensory cells is obvious, they have also been<br>implicated in such basic functions as cell volume regu-<br>lation (Hamill, 1983a; Christensen, 1987; Sackin, 1989)<br>and development (Medina and Bregestovski, 1988; how-<br>ever implicated in such basic functions as cell volume regu-<br>lation (Hamill, 1983a; Christensen, 1987; Sackin, 1989) v<br>and development (Medina and Bregestovski, 1988; how-<br>ever, see Wilkinson et al., 1996a, b). Nevertheless, th lation (Hamill, 1983a; Christensen, 1987; Sackin, 198<br>and development (Medina and Bregestovski, 1988; ho<br>ever, see Wilkinson et al., 1996a, b). Nevertheless, the<br>exact role(s) in many nonsensory cells remains unknoo<br>(Morri and development (Medina and Bregestovski, 1988; how-<br>ever, see Wilkinson et al., 1996a, b). Nevertheless, their<br>exact role(s) in many nonsensory cells remains unknown<br>(Morris, 1992). For this reason, high specificity inhib ever, see Wilkinson et al., 1996a, b). Nevertheless, their exact role(s) in many nonsensory cells remains unknown<br>(Morris, 1992). For this reason, high specificity inhibitors or stimulators of MG channels would be extremel exact role(s) in many nonsensory cells remains unknown<br>(Morris, 1992). For this reason, high specificity inhibi-<br>tors or stimulators of MG channels would be extremely<br>useful for implicating them in specific cellular proces (Morris, 1992). For this reason, high specificity inhibitors or stimulators of MG channels would be extremely chase the useful for implicating them in specific cellular processes. spectral facilitate protein could label sp tors or stimulators of MG channels would be extremely<br>useful for implicating them in specific cellular processes.<br>Furthermore, the existence of high affinity ligands that<br>could label specific MG channels would facilitate p useful for implicating them in specific cellular processes. sponse<br>Furthermore, the existence of high affinity ligands that vate)<br>could label specific MG channels would facilitate protein channe<br>purification procedures (Su r in the finder hote, the existence of ingit antihity inguities that<br>could label specific MG channels would facilitate protein cl<br>purification procedures (Sukharev et al., 1993). Al-<br>though no "ideal" high specificity/affi could label specific MG channels would facilitate protein channel<br>purification procedures (Sukharev et al., 1993). Al- to non<br>though no "ideal" high specificity/affinity drug for MG record<br>channels has yet been found, rece purification procedures (Sukharev et al., 1993). Although no "ideal" high specificity/affinity drug for MG channels has yet been found, recent studies have begun to reveal a number of agents that do affect different MG cha though no "ideal" high specificit<br>channels has yet been found, recto<br>reveal a number of agents tha<br>channel activities. The purpose<br>cuss this emerging pharmacolog<br>IL Cleasifications of 1 II. Classifications of MG Channels<br>II. Classifications of MG Channels<br> **II. Classifications of MG Channels**<br> **II. Classifications of MG Channels** 

annel activities. The purpose of this review is to dis-<br>ss this emerging pharmacology.<br>II. Classifications of MG Channels<br>To better appreciate the possible mechanisms and cha<br>es of drug action on MG channels, the various c cuss this emerging pharmacology.<br>
II. Classifications of MG Channels<br>
To better appreciate the possible mechanisms and<br>
sites of drug action on MG channels, the various class<br>
fications and mechanisms of MG channel activat II. Classifications of MG Channels<br>To better appreciate the possible mechanisms and<br>sites of drug action on MG channels, the various classi-<br>fications and mechanisms of MG channel activation will<br>be summarized. In general, II. CLASSIFICATIONS OF MG CHANNERS<br>To better appreciate the possible mechanisms and<br>sites of drug action on MG channels, the various classi-<br>fications and mechanisms of MG channel activation will<br>be summarized. In general, To better appreciate the possible mechanisms and<br>sites of drug action on MG channels, the various classi-<br>fications and mechanisms of MG channel activation will<br>be summarized. In general, membrane ion channels<br>tend to be c fications and mechanisms of MG channel activation will cell type or a general property of the so-called SI channel<br>be summarized. In general, membrane ion channels remains to be determined.<br>tend to be classified in terms o fications and mechanisms of MG channel activation will consider summarized. In general, membrane ion channels retend to be classified in terms of either their open channel properties and/or their gating properties. These be summarized. In general, membrane ion channe<br>tend to be classified in terms of either their open chann<br>properties and/or their gating properties. These tw<br>properties can be considered independent in the sent<br>that knowled **Properties and/or their gatify properties can be considered that knowledge of one does no<br>A. Open Channel Properties<br>MG channels. like voltage** 

operties can be considered independent in the sense<br>at knowledge of one does not determine the other.<br>Open Channel Properties<br>MG channels, like voltage-gated and ligand-gated<br>annels, display a variety of open channel prope channels, display a variety of open channels, display a variety of open channel properties<br>with different ion selectivities (e.g., cation, anion, K<sup>+</sup> A. Open Channel Properties<br>MG channels, like voltage-gated and ligand-gated<br>channels, display a variety of open channel properties<br>with different ion selectivities (e.g., cation, anion, K<sup>+</sup><br>and nonselective) and single c A. Open Channel Properties<br>
MG channels, like voltage-gated and ligand-gated<br>
channels, display a variety of open channel properties<br>
site with different ion selectivities (e.g., cation, anion,  $K^+$  br<br>
and nonselective) MG channels, like voltage-gated and ligand-gated 197 channels, display a variety of open channel properties siti with different ion selectivities (e.g., cation, anion, K<sup>+</sup> bra and nonselective) and single channel conduct channels, display a variety of open channel prope<br>with different ion selectivities (e.g., cation, anion<br>and nonselective) and single channel conductances<br>to 2000 pS). However, in general, the ion selectivity<br>conductance of with different ion selectivities (e.g., cation, anion,  $K^+$  br and nonselective) and single channel conductances ( $\sim$ 20 rito 2000 pS). However, in general, the ion selectivity and chanductance of biological channels are and nonselective) and single channel conductances  $(\sim 20$  ris<br>to 2000 pS). However, in general, the ion selectivity and chand<br>conductance of biological channels are not mechanosen-<br>sitive (but see Opsahl and Webb, 1994). to 2000 pS). However, in general, the ion selectivity and chanductance of biological channels are not mechanosensitive (but see Opsahl and Webb, 1994). Although some the cells express only one type of MG channel, there are sitive (but see Opsahl and Webb, 1994). Although some<br>cells express only one type of MG channel, there are also<br>cells that express as many as five types, which can be<br>distinguished by their open channel properties (Berrier

MCBRIDE<br>et al., 1992; Ruknudin et al., 1993). Presumably, such<br>differences reflect variations in the pore structure (i.e., MCBRIDE<br>et al., 1992; Ruknudin et al., 1993). Presumably, such<br>differences reflect variations in the pore structure (i.e.,<br>binding sites and geometry) of the channels. In terms of MCBRIDE<br>et al., 1992; Ruknudin et al., 1993). Presumably, such<br>differences reflect variations in the pore structure (i.e.,<br>binding sites and geometry) of the channels. In terms of<br>drugs that act by binding to specific pore et al., 1992; Ruknudin et al., 1993). Presumably, such<br>differences reflect variations in the pore structure (i.e.,<br>binding sites and geometry) of the channels. In terms of<br>drugs that act by binding to specific pore lining et al., 1992; Ruknudin et al., 1993). Presumably, such<br>differences reflect variations in the pore structure (i.e.,<br>binding sites and geometry) of the channels. In terms of<br>drugs that act by binding to specific pore lining differences reflect variations in the pore structure (i.e., binding sites and geometry) of the channels. In terms of drugs that act by binding to specific pore lining residues, it is conceivable that channels that share o binding sites and geometry) of the channels. In terms of drugs that act by binding to specific pore lining residues, it is conceivable that channels that share open channel properties (e.g.,  $K^+$  or cation selectivity) m drugs that act by binding to spit is conceivable that channel<br>properties (e.g., K<sup>+</sup> or cation<br>ceptible to pore occlusion or exame drug or class of drugs.

# **B.** *Gating Properties*

implicated in such basic functions as cell volume regu-<br>lation (Hamill, 1983a; Christensen, 1987; Sackin, 1989) whether they are opened or closed by mechanical stim-<br>and development (Medina and Bregestovski, 1988; how-<br>lat In terms of gating, MG channels have tended to be same drug or class of drugs.<br>
B. Gating Properties<br>
In terms of gating, MG channels have tended to be<br>
divided into two broad groups, namely stretch-activated<br>
(SA) and stretch-inactivated (SI), depending upon B. Gating Properties<br>
In terms of gating, MG channels have tended to be<br>
divided into two broad groups, namely stretch-activated<br>
(SA) and stretch-inactivated (SI), depending upon<br>
whether they are opened or closed by mech Example Truperties<br>In terms of gating, MG channels have tended to b<br>divided into two broad groups, namely stretch-activate<br>(SA) and stretch-inactivated (SI), depending upor<br>whether they are opened or closed by mechanical s In terms of gating, MG channels have tended to be<br>divided into two broad groups, namely stretch-activated<br>(SA) and stretch-inactivated (SI), depending upon<br>whether they are opened or closed by mechanical stim-<br>ulation, res divided into two broad groups, namely stretch-activated<br>(SA) and stretch-inactivated (SI), depending upon<br>whether they are opened or closed by mechanical stim-<br>ulation, respectively (Guharay and Sachs, 1984; Morris<br>and Sig (SA) and stretch-inactivated (SI), depending upon<br>whether they are opened or closed by mechanical stim-<br>ulation, respectively (Guharay and Sachs, 1984; Morris<br>and Sigurdson, 1989). However, this basic distinction<br>may be co whether they are opened or closed by mechanical stimulation, respectively (Guharay and Sachs, 1984; Morris and Sigurdson, 1989). However, this basic distinction may be complicated by dynamic or nonstationary kinetic prope ulation, respectively (Guharay and Sachs, 1984; Morris and Sigurdson, 1989). However, this basic distinction may be complicated by dynamic or nonstationary kinetic properties of the SA channel. For example, certain SA chan and Sigurason, 1989). However, this basic distinction<br>may be complicated by dynamic or nonstationary kinetic<br>properties of the SA channel. For example, certain SA<br>channels show rapid and complete adaptation in re-<br>sponse t properties of the SA channel. For example, certain SA<br>channels show rapid and complete adaptation in re-<br>sponse to sustained stimulation (i.e., appear to inacti-<br>vate) (Hamill and McBride, 1992). Furthermore, SA<br>channel ac channels show rapid and complete adaptation in response to sustained stimulation (i.e., appear to inactivate) (Hamill and McBride, 1992). Furthermore, SA channel activity can shift irreversibly from an adapting to nonadapt vate) (Hamill and McBride, 1992). Furthermore, SA<br>channel activity can shift irreversibly from an adapting<br>to nonadapting mode during the course of patch clamp<br>recording (Hamill and McBride, 1992). Another possible<br>complic ulation, respectively (Guharay and Sachs, 1984; Morris<br>and Sigurdson, 1989). However, this basic distinction<br>may be complicated by dynamic or nonstationary kinetic<br>properties of the SA channel. For example, certain SA<br>chan to nonadapting mode during the course of patch clamp to nonadapting mode during the course of patch clament recording (Hamill and McBride, 1992). Another possib complication concerns the SI channel terminology an relates to a recent demonstration that specific MG channels ca recording (Hamill and McBride, 1992). Another possible complication concerns the SI channel terminology an relates to a recent demonstration that specific MG channels can respond differentally, depending on the direction o complication concerns the SI channel terminology and<br>relates to a recent demonstration that specific MG chan-<br>nels can respond differentally, depending on the direc-<br>tion of patch curvature. For example, in rat aortic endo relates to a recent demonstration that specific MG channels can respond differentally, depending on the direction of patch curvature. For example, in rat aortic endothelial cells, suction applied to the patch decreases cha nels can respond differentally, depending on the direction of patch curvature. For example, in rat aortic endo-<br>thelial cells, suction applied to the patch decreases<br>channel activity, whereas applied pressure increases<br>cha tion of patch curvature. For example, in rat aortic endo-<br>thelial cells, suction applied to the patch decreases<br>channel activity, whereas applied pressure increases<br>channel activity (Marchenko and Sage, 1996). Whether<br>this thelial cells, suction applied to the patch decreases<br>channel activity, whereas applied pressure increases<br>channel activity (Marchenko and Sage, 1996). Whether<br>this phenomenon is specific to the MG channel of this<br>cell typ channel activity, wherea<br>channel activity (Marche<br>this phenomenon is speci<br>cell type or a general prop<br>remains to be determined<br>Another aspect of MG o annel activity (Marchenko and Sage, 1996). Whether<br>is phenomenon is specific to the MG channel of this<br>ll type or a general property of the so-called SI channel<br>mains to be determined.<br>Another aspect of MG channel gating r

this phenomenon is specific to the MG channel of this<br>cell type or a general property of the so-called SI channel<br>remains to be determined.<br>Another aspect of MG channel gating relates to their<br>sensitivity to the magnitude cell type or a general property of the so-called SI channel<br>remains to be determined.<br>Another aspect of MG channel gating relates to their<br>sensitivity to the magnitude of mechanical stimulation<br>(see Hamill and McBride, 199 remains to be determined.<br>
Another aspect of MG channel gating relates to their<br>
sensitivity to the magnitude of mechanical stimulation<br>
(see Hamill and McBride, 1994a). Some MG channels<br>
are so sensitive that they can be Another aspect of MG channel gating relates to their<br>sensitivity to the magnitude of mechanical stimulation<br>(see Hamill and McBride, 1994a). Some MG channels<br>are so sensitive that they can be gated by random fluc-<br>tuations sensitivity to the magnitude of mechanical stimulation<br>(see Hamill and McBride, 1994a). Some MG channels<br>are so sensitive that they can be gated by random fluc-<br>tuations in thermal noise (Denk and Webb, 1989) or<br>sub-Angstr (see Hamill and McBride, 1994a). Some MG channe<br>are so sensitive that they can be gated by random flu<br>tuations in thermal noise (Denk and Webb, 1989)<br>sub-Angstrom displacements (Brownell and Farle<br>1979), whereas other MG c are so sensitive that they can be gated by random flu<br>tuations in thermal noise (Denk and Webb, 1989) esub-Angstrom displacements (Brownell and Farle<br>1979), whereas other MG channels are relatively inser<br>sitive and require tuations in thermal noise (Denk and Webb, 1989) or<br>sub-Angstrom displacements (Brownell and Farley,<br>1979), whereas other MG channels are relatively insen-<br>sitive and require stimulation that often causes mem-<br>brane patch ( sub-Angstrom displacements (Brownell and Farley,  $\frac{a}{20}$ , 1979), whereas other MG channels are relatively insensitive and require stimulation that often causes membrane patch (Vandorpe et al., 1994) or cell rupture (Mo 1979), whereas other MG channels are relatively insensitive and require stimulation that often causes membrane patch (Vandorpe et al., 1994) or cell rupture (Morris and Horn, 1991). However, the large majority of MG chann sitive and require stimulation that often causes mem-<br>brane patch (Vandorpe et al., 1994) or cell rupture (Mor-<br>ris and Horn, 1991). However, the large majority of MG<br>channels appear to be activated by modest stimuli,<br>abov brane patch (Vandorpe et al., 1994) or cell rupture (Morris and Horn, 1991). However, the large majority of MG<br>channels appear to be activated by modest stimuli,<br>above the thermal noise level yet well below the level<br>that ris and Horn, 1991). However, the large majority of MG<br>channels appear to be activated by modest stimuli,<br>above the thermal noise level yet well below the level<br>that causes membrane damage (Hamill and McBride,<br>1994a). Apar above the thermal noise level yet well below the level<br>that causes membrane damage (Hamill and McBride,<br>1994a). Apart from the magnitude or quantitative as-<br>pects of the mechanical stimulus, there are also quali-<br>tative as above the thermal noise level yet well below the level<br>that causes membrane damage (Hamill and McBride,<br>1994a). Apart from the magnitude or quantitative as-<br>pects of the mechanical stimulus, there are also quali-<br>tative as that causes membrane damage (Hamill and McBride, 1994a). Apart from the magnitude or quantitative aspects of the mechanical stimulus, there are also qualitative aspects concerning its form. For example, cell stretch and co 1994a). Apart from the magnitude or quantitative aspects of the mechanical stimulus, there are also qualitative aspects concerning its form. For example, cell stretch and compression, osmotic swelling, fluid shear stress, pects of the mechanical stimulus, there are also quali-<br>tative aspects concerning its form. For example, cell<br>stretch and compression, osmotic swelling, fluid shear<br>stress, and suction or pressure applied to the membrane<br>p tative aspects concerning its form. For example, cell<br>stretch and compression, osmotic swelling, fluid shear<br>stress, and suction or pressure applied to the membrane<br>patch are all forms of mechanical stimulation, yet each<br>m stretch and compression, osmotic swelling, fluid sheaftness, and suction or pressure applied to the membrane patch are all forms of mechanical stimulation, yet each may be expected to perturb, at the molecular level, the m stress, and suction or pressure applied to the membrane<br>patch are all forms of mechanical stimulation, yet each<br>may be expected to perturb, at the molecular level, the<br>membrane in different manners. Indeed, specific mem-<br>b patch are all forms of mechanical stimulation, yet each may be expected to perturb, at the molecular level, the membrane in different manners. Indeed, specific membrane channels have been found that selectively respond to

distinguished by their open channel properties (Berrier<br>Abbreviations: MG, mechanogated; SA, stretch-activated; SI,<br>stretch-inactivated; MS, mechanosensitive; IP<sub>3</sub>, inositol trisphosdistinguished by their open channel properties (Bern<br>Abbreviations: MG, mechanogated; SA, stretch-activated;<br>stretch-inactivated; MS, mechanosensitive; IP<sub>3</sub>, inositol trisp<br>phate; IC<sub>50</sub>, concentration that inhibits 50%; Abbreviations: MG, mechanogated; SA, stretch-activated; SI, stretch-inactivated; MS, mechanosensitive; IP<sub>3</sub>, inositol trisphos-<br>phate; IC<sub>50</sub>, concentration that inhibits 50%; *E. coli, Escherichia coli*;<br>TTX, tetrodotoxi Abbreviations: MG, mechanogated; SA, stretch-activated; SI<br>stretch-inactivated; MS, mechanosensitive; IP<sub>3</sub>, inositol trisphos<br>phate;  $IC_{so}$ , concentration that inhibits 50%; *E. coli, Escherichia coli*<br>TTX, tetrodotoxin; stantines. They, incenting accurations, They, incontractivated, Theoreth-inactivated, MS, mechanosensitive; IP<sub>3</sub>, inositiol trisphos-<br>phate; IC<sub>50</sub>, concentration that inhibits 50%; E. coli, Escherichia coli;<br>TTX, tetrodo spatulation contration that inhibits 50%; E. coli, Escherichia coli;<br>phate; IC<sub>80</sub>, concentration that inhibits 50%; E. coli, Escherichia coli;<br>TTX, tetrodotoxin; TEA, tetraethylammonium; K<sub>d</sub>, dissociation con-<br>stant; TC, **methoxy-5-nitrobenzamil.**

PHARMACOLOGY OF MECHANOGATED MEMBRANE ION CHANNELS 233

PHARMACOLOGY OF MECHANOGATI<br>(Olesen et al., 1988; Burton and Hutter, 1990; Sasaki et<br>al., 1992). On the other hand, there are channels that PHARMACOLOGY OF MECHANOGA<sup>.</sup><br>(Olesen et al., 1988; Burton and Hutter, 1990; Sasaki et al., 1992). On the other hand, there are channels that respond to multiple forms of mechanical stimulation PHARMACOLOGY OF MECHANOGAT<br>(Olesen et al., 1988; Burton and Hutter, 1990; Sasaki et<br>al., 1992). On the other hand, there are channels that<br>respond to multiple forms of mechanical stimulation<br>(Christensen, 1987; Ubl et al., (Olesen et al., 1988; Burton and Hutter, 1990; Sasaki et al., 1992). On the other hand, there are channels that respond to multiple forms of mechanical stimulation (Christensen, 1987; Ubl et al., 1988; Sackin, 1989; Oliet al., 1992). On the other hand, there are channels that<br>respond to multiple forms of mechanical stimulation<br>(Christensen, 1987; Ubl et al., 1988; Sackin, 1989; Oliet<br>and Bourque, 1993). In this review, attention is focused<br> respond to multiple forms of mechanical stimulation<br>(Christensen, 1987; Ubl et al., 1988; Sackin, 1989; Oliet<br>and Bourque, 1993). In this review, attention is focused<br>almost exclusively on MG channels gated by suction/<br>pre (Christensen, 1987; Ubl et al., 1988; Sackin, 1989; Oliet and Bourque, 1993). In this review, attention is focused<br>almost exclusively on MG channels gated by suction/<br>pressure applied to the membrane patch. In most cases, and Bourque, 1993). In this review, attention is focused in almost exclusively on MG channels gated by suction  $\ell$  pressure applied to the membrane patch. In most cases, cressure and suction are equally effective in activ almost exclusively on MG channels gated by suction/<br>pressure applied to the membrane patch. In most cases,<br>pressure and suction are equally effective in activating<br>the MG channel (Sachs, 1988; Morris, 1990; McBride<br>and Ham pressure applied to the membrane patth. In most cases, cent<br>pressure and suction are equally effective in activating if<br>the MG channel (Sachs, 1988; Morris, 1990; McBride nat<br>and Hamill, 1992), which is consistent with the the MG channel (Sachs, 1988; Morris, 1990; McBride<br>and Hamill, 1992), which is consistent with the channel<br>responding to membrane tension rather than pressure<br>itself. However, as stated above, some MG channels may<br>be sensi and Hamill, 1992), which is consistent with the chanies<br>responding to membrane tension rather than pressitiself. However, as stated above, some MG channels m<br>be sensitive to the direction of membrane curvatt<br>(Bowman et al. itself. However, as stated above, some MG channels may made.<br>
be sensitive to the direction of membrane curvature Both direct and indirect mechanisms may be subdi-<br>
(Bowman et al., 1992; Bowman and Lohr, 1996; March-vided itself. However, as stated above, some MG channels m<br>be sensitive to the direction of membrane curvatu<br>(Bowman et al., 1992; Bowman and Lohr, 1996; Marc<br>enko and Sage, 1996). Presumably, these different M<br>channel gating se cellular/membrane/cytoskeleton interactions. owman et al., 1992; Bowman and Lohr, 1996; Marchelend Rond Sage, 1996). Presumably, these different Mannel gating sensitivities depend upon specific extrement and parameter than being exclu-<br>Finally, some MG channels, rath

enko and Sage, 1996). Presumably, these different MG bila<br>channel gating sensitivities depend upon specific extra-<br>cellular/membrane/cytoskeleton interactions. This<br>is Finally, some MG channels, rather than being exclu-<br>ac channel gating sensitivities depend upon specific extra-<br>cellular/membrane/cytoskeleton interactions.<br>Finally, some MG channels, rather than being exclu-<br>sively gated by membrane stretch, are also gated by<br>nonmechanical st cellular/membrane/cytoskeleton interactions.<br>
Finally, some MG channels, rather than being exclusively gated by membrane stretch, are also gated by<br>
nonmechanical stimulation such as ligands (Kirber et al.,<br>
1992; Vandorpe Finally, some MG channels, rather than being exclusively gated by membrane stretch, are also gated by nonmechanical stimulation such as ligands (Kirber et al., 1992; Vandorpe and Morris, 1992; Van Wagoner, 1993; Paoletti a sively gated by membrane stretch, are also gated by<br>nonmechanical stimulation such as ligands (Kirber et al.,<br>1992; Vandorpe and Morris, 1992; Van Wagoner, 1993;<br>Paoletti and Ascher, 1994; Vandorpe et al., 1994) and/or<br>mem nonmechanical stimulation such as ligands (Kirber et al., 1992; Vandorpe and Morris, 1992; Van Wagoner, 1993;<br>Paoletti and Ascher, 1994; Vandorpe et al., 1994) and/or<br>membrane voltage (Hisada et al., 1991; Kirber et al., 1 1992; Vandorpe and Morris, 1992; Van Wagoner, 1993; invo<br>Paoletti and Ascher, 1994; Vandorpe et al., 1994) and/or or r<br>membrane voltage (Hisada et al., 1991; Kirber et al., 1992; 199<br>Chang and Loretz, 1992; Davidson, 1993; Paoletti and Ascher, 1994; Vandorpe et al., 1994) and/or<br>membrane voltage (Hisada et al., 1991; Kirber et al., 1992;<br>Chang and Loretz, 1992; Davidson, 1993; Langton, 1993;<br>Ben-Tabou et al., 1994; Hamill and McBride, 1996a) membrane voltage (Hisada et al., 1991; Kirber et al., 1992;<br>Chang and Loretz, 1992; Davidson, 1993; Langton, 1993;<br>Ben-Tabou et al., 1994; Hamill and McBride, 1996a). In<br>specific cases, membrane stretch may only modulate a Chang and Loretz, 1992; Davidson, 1993; Langton, 199<br>Ben-Tabou et al., 1994; Hamill and McBride, 1996a).<br>specific cases, membrane stretch may only modulate activa-<br>rativar rather than directly gate the channel (Kirber et a Ben-Tabou et al., 1994; Hamill and McBride, 1996a). In specific cases, membrane stretch may only modulate activity rather than directly gate the channel (Kirber et al., 1992; Paoletti and Ascher, 1994). Such polymodal acti specific cases, membrane stretch may only modulate activity rather than directly gate the channel (Kirber et al., 1992; Paoletti and Ascher, 1994). Such polymodal activation of a membrane ion channel complicates, from a bi 1992; Paoletti and Ascher, 1994). Such polymodal active tion of a membrane ion channel complicates, from a biphysical viewpoint, the characterization and classification of the channel but nevertheless may be critical in it tion of a membrane ion channel complicates, from a bio-<br>physical viewpoint, the characterization and classification lu<br>of the channel but nevertheless may be critical in its role(s)<br>it<br>under different physiological and/or physical viewpoint, the characterization and classification luls<br>of the channel but nevertheless may be critical in its role(s) its<br>under different physiological and/or pathological condi-<br>factions. Clearly, recognition of of the channel but nevert<br>
under different physiol<br>
tions. Clearly, recognitio<br>
a channel is essential<br>
effects on that channel.<br>
C. Melevilar Mechanic *Clearly, recognition* of<br>*a* channel is essential for<br>effects on that channel.<br>*C. Molecular Mechanisms*<br>Mechanisms of mechano

effects on that channel.<br>
C. Molecular Mechanisms<br>
Mechanisms of mechanosensitivity can be classified<br>
into either direct or indirect, according to the way me-<br>
chanical energy is coupled to the gating mechanism of chanisms is<br>
chanisms of mechanosensitivity can be classified<br>
cinto either direct or indirect, according to the way me-<br>
chanical energy is coupled to the gating mechanism of ch<br>
the channel. In the direct mechanism, mech C. *Motecutar mechanosensitivity* can be classified<br>into either direct or indirect, according to the way me-<br>chanical energy is coupled to the gating mechanism of<br>the channel. In the direct mechanism, mechanical en-<br>ergy i Mechanisms of mechanosensitivity can be classifie<br>into either direct or indirect, according to the way me<br>chanical energy is coupled to the gating mechanism of<br>the channel. In the direct mechanism, mechanical energy is dir into either direct or indirect, according to the way me-<br>chanical energy is coupled to the gating mechanism of<br>the channel. In the direct mechanism, mechanical en-<br>ergy is directly coupled to the MG channel protein with-<br>o chanical energy is coupled to the gating mechanism of<br>the channel. In the direct mechanism, mechanical energy is directly coupled to the MG channel protein with<br>out the intervention of biochemical reactions, although<br>energ the channel. In the direct mechanism, mechanical ergy is directly coupled to the MG channel protein wisout the intervention of biochemical reactions, althous energy may be focused onto the channel via cytoskele and/or extr ergy is directly coupled to the MG channel protein with-<br>out the intervention of biochemical reactions, although in<br>energy may be focused onto the channel via cytoskeletal<br>and/or extracellular elements. In the indirect mec out the intervention of biochemical reactions, although in<br>energy may be focused onto the channel via cytoskeletal<br>and/or extracellular elements. In the indirect mecha-<br>nism, there are intervening biochemical steps between energy may be focused onto the channel via cytoskeletal<br>and/or extracellular elements. In the indirect mecha-<br>nism, there are intervening biochemical steps between<br>the initial mechanical event and channel gating such as<br>a and/or extracellular elements. In the indirect mechanism, there are intervening biochemical steps betwee<br>the initial mechanical event and channel gating such  $\varepsilon$ <br>a membrane bound mechanosensitive (MS) enzyme<br>which regul mism, there are intervening biochemical steps between The initial mechanical event and channel gating such as con<br>a membrane bound mechanosensitive (MS) enzyme, channel mechanosensitive (MS) enzyme, channels a second-messe the initial mechanosche and channel gating such as considered under two general categories involving either<br>a membrane bound mechanosensitive (MS) enzyme, channel block or channel activation. Within these two<br>which regula a membrane bound mechanosensitive (MS) enzyme,<br>which regulates a second-messenger and, in turn, influ-<br>ences sensitive channels. For instance, activation of a<br>mechanosensitive phospholipase C (Brophy et al., 1993)<br>would e which regulates a second-messenger and, in turn, influ-<br>ences sensitive channels. For instance, activation of a<br>mechanosensitive phospholipase C (Brophy et al., 1993)<br>would elevate inositol trisphosphate (IP<sub>3</sub>), in turn ences sensitive channels. For instance, activation of a mechanosensitive phospholipase C (Brophy et al., 1993) would elevate inositol trisphosphate (IP<sub>3</sub>), in turn releasing  $Ca^{2+}$  from IP<sub>3</sub>-sensitive internal  $Ca^{2+}$  mechanosensitive phosphonpase C (Brophy et al., 1993)<br>would elevate inositol trisphosphate  $(\text{IP}_3)$ , in turn re-<br>leasing  $\text{Ca}^{2+}$  from  $\text{IP}_3$ -sensitive internal  $\text{Ca}^{2+}$  stores<br>(Boitano et al., 1994) and, in this (Boitano et al., 1994) and, in this way, stimulating  $Ca^{2+}$ . A. Blockers<br>sensitive channels in the plasma and possibly organelle of the various chemicals and drugs that block MG<br>membranes. In this example, both  $Ca^{2+}$ -r

al., 1992). On the other hand, there are channels that distinguishing between direct and indirect mechanisms<br>respond to multiple forms of mechanical stimulation involves measuring the latency of channel turn-on after<br>(Chri ED MEMBRANE ION CHANNELS<br>without themselves being directly MS. One criterion for<br>distinguishing between direct and indirect mechanisms ED MEMBRANE ION CHANNELS<br>without themselves being directly MS. One criterion for<br>distinguishing between direct and indirect mechanisms<br>involves measuring the latency of channel turn-on after ED MEMBRANE ION CHANNELS 233<br>without themselves being directly MS. One criterion for<br>distinguishing between direct and indirect mechanisms<br>involves measuring the latency of channel turn-on after<br>a step change in stimulatio without themselves being directly MS. One criterion for distinguishing between direct and indirect mechanisms<br>involves measuring the latency of channel turn-on after<br>a step change in stimulation (Corey and Hudspeth<br>1979; O without themselves being directly MS. One criterion for<br>distinguishing between direct and indirect mechanisms<br>involves measuring the latency of channel turn-on after<br>a step change in stimulation (Corey and Hudspeth,<br>1979; distinguishing between direct and indirect mechanisms<br>involves measuring the latency of channel turn-on after<br>a step change in stimulation (Corey and Hudspeth,<br>1979; Ordway et al., 1991; McBride and Hamill, 1993).<br>Another involves measuring the latency of channel turn-on after<br>a step change in stimulation (Corey and Hudspeth,<br>1979; Ordway et al., 1991; McBride and Hamill, 1993).<br>Another criterion is to compare mechanosensitivities in<br>cell-a a step change in stimulation (Corey and Hudsper 1979; Ordway et al., 1991; McBride and Hamill, 199<br>Another criterion is to compare mechanosensitivities<br>cell-attached and cell-free patches to determine the r<br>if any, of cyto 1979; Ordway et al., 1991; McBride and Hamill, 1<br>Another criterion is to compare mechanosensitivit<br>cell-attached and cell-free patches to determine the<br>if any, of cytoplasmic second-messengers. Un<br>nately, for many channels cell-attached and cell-free patches to determine the role,<br>if any, of cytoplasmic second-messengers. Unfortu-<br>nately, for many channels that display mechanosensiif any, of cytoplasmic second-messengers. Unfortumade. tivity, this most basic distinction between direct and

1992; Paoletti and Ascher, 1994). Such polymodal activa-<br>tion of a membrane ion channel complicates, from a bio-<br>physical viewpoint, the characterization and classification<br>of the channel but nevertheless may be critical indirect mechanisms of activation has not always been<br>mode.<br>Both direct and indirect mechanisms may be subdi-<br>vided into intrinsic or extrinsic mechanisms according to<br>bilayer versus cytoskeletal (or extracellular) involv indirect mechanisms of activation has not always be<br>made.<br>Both direct and indirect mechanisms may be sub<br>vided into intrinsic or extrinsic mechanisms according<br>bilayer versus cytoskeletal (or extracellular) invol<br>ment in t made.<br>Both direct and indirect mechanisms may be sub<br>vided into intrinsic or extrinsic mechanisms according<br>bilayer versus cytoskeletal (or extracellular) invol-<br>ment in the gating mechanism. In the intrinsic mech<br>nism, me Both direct and indirect mechanisms may be subd<br>vided into intrinsic or extrinsic mechanisms according<br>bilayer versus cytoskeletal (or extracellular) involve<br>ment in the gating mechanism. In the intrinsic mechanism, mechan vided into intrinsic or extrinsic mechanisms according to<br>bilayer versus cytoskeletal (or extracellular) involve-<br>ment in the gating mechanism. In the intrinsic mecha-<br>nism, mechanosensitivity is dependent upon inter-<br>acti bilayer versus cytoskeletal (or extracellular) involvement in the gating mechanism. In the intrinsic mechanism, mechanosensitivity is dependent upon interactions exclusively within the membrane bilayer (Martinac et al., 19 ment in the gating mechanism. In the intrinsic mechanism, mechanosensitivity is dependent upon inter-<br>actions exclusively within the membrane bilayer<br>(Martinac et al., 1990; Sukharev et al., 1993; Opsahl and<br>Webb, 1994). F actions exclusively within the membrane bilayer<br>(Martinac et al., 1990; Sukharev et al., 1993; Opsahl and<br>Webb, 1994). For example, intrinsic mechanisms may actions exclusively within the membrane bilayer (Martinac et al., 1990; Sukharev et al., 1993; Opsahl and Webb, 1994). For example, intrinsic mechanisms may involve tension-dependent protein subunit recruitment or realignm (Martinac et al., 1990; Sukharev et al., 1993; Opsahl and<br>Webb, 1994). For example, intrinsic mechanisms may<br>involve tension-dependent protein subunit recruitment<br>or realignment within the bilayer (Opsahl and Webb,<br>1994; H Webb, 1994). For example, intrinsic mechanisms may<br>involve tension-dependent protein subunit recruitment<br>or realignment within the bilayer (Opsahl and Webb,<br>1994; Hamill and McBride, 1994a). In the extrinsic<br>mechanism, mec or realignment within the bilayer (Opsahl and Webb, 1994; Hamill and McBride, 1994a). In the extrinsic mechanism, mechanical stimulation is applied to the 1994; Hamill and McBride, 1994a). In the extrinsic 1994; Hamill and McBride, 1994a). In the extrin mechanism, mechanical stimulation is applied to the channel or membrane enzyme via cytoskeletal or ext cellular elements (Guharay and Sachs, 1984; Howard al., 1988; Hamill an mechanism, mechanical stimulation is applied to the<br>channel or membrane enzyme via cytoskeletal or extra-<br>cellular elements (Guharay and Sachs, 1984; Howard et<br>al., 1988; Hamill and McBride, 1992). In this mechanica<br>mism, cellular elements (Guharay and Sachs, 1984; Howard et al., 1988; Hamill and McBride, 1992). In this mechaal., 1986, Hamill and McBride, 1992). In this mechanical<br>mism, mechanosensitivity might be lost if mechanical<br>coupling between the channel and cytoskeletal/extracel-<br>lular elements is disrupted without rupturing the patch<br> coupling between the channel and cytoskeletal/extracel-<br>
lular elements is disrupted without rupturing the patch<br>
itself (Assad et al., 1991; Hamill and McBride, 1992). In<br>
fact, such disruption can arise during the cours lular elements is disrupted without rupturing the<br>itself (Assad et al., 1991; Hamill and McBride, 199<br>fact, such disruption can arise during the course  $\alpha$ <br>tine patch recordings and can result in modifie<br>channel propertie relf (Assad et al., 1991; Hamill and McBride, 1992). In tt, such disruption can arise during the course of rou-<br>ne patch recordings and can result in modified MG<br>annel properties (Hamill and McBride, 1992).<br>In considering

a channel is essential for proper interpretation of drug channel properties (Hamill and McBride, 1992).<br>
In considering the site of action of a drug, the type of<br>
mechanism underlying mechanosensitivity may be crit-<br>
C. Mo fact, such disruption can arise during the course of routine patch recordings and can result in modified MG channel properties (Hamill and McBride, 1992).<br>In considering the site of action of a drug, the type of mechanism tine patch recordings and can result in modified MG<br>channel properties (Hamill and McBride, 1992).<br>In considering the site of action of a drug, the type of<br>mechanism underlying mechanosensitivity may be crit-<br>ical. For exa channel properties (Hamill and McBride, 1992).<br>In considering the site of action of a drug, the type of<br>mechanism underlying mechanosensitivity may be crit-<br>ical. For example, in the indirect mechanism, a drug<br>could block In considering the site of action of a drug, the type of<br>mechanism underlying mechanosensitivity may be crit-<br>ical. For example, in the indirect mechanism, a drug<br>could block mechanosensitivity by acting along the bio-<br>che mechanism underlying mechanosensitivity may be crit-<br>ical. For example, in the indirect mechanism, a drug<br>could block mechanosensitivity by acting along the bio-<br>chemical pathway with or without a direct action on the<br>chan ical. For example, in the indirect mechanism, a drug<br>could block mechanosensitivity by acting along the bio-<br>chemical pathway with or without a direct action on the<br>channel or MS enzyme. Similarly, with the extrinsic<br>mecha could block mechanosensitivity by acting along the bio-<br>chemical pathway with or without a direct action on the<br>channel or MS enzyme. Similarly, with the extrinsion<br>mechanism, a drug could be active because of its action<br>o chemical pathway with or without a direct a<br>channel or MS enzyme. Similarly, with t<br>mechanism, a drug could be active because<br>on the cytoskeleton or extracellular matrix<br>ing any direct effect on the channel itself. **III. MG Channel Drugs**<br> **III. MG Channel Drugs**<br>
hat affect MG channel actions<br>
hat affect MG channel actions ing any direct effect on the channel itself.<br>III. MG Channel Drugs<br>The drugs that affect MG channel activity will be

ing any direct effect on the channel itself.<br>
III. MG Channel Drugs<br>
The drugs that affect MG channel activity will be<br>
considered under two general categories involving either<br>
channel block or channel activation. Within III. MG Channel Drugs<br>The drugs that affect MG channel activity will be<br>considered under two general categories involving either<br>channel block or channel activation. Within these two<br>classes, further distinctions may be ma **CHE THE SET OF STATE IS THE SET OF STATE IS THE SET OF STATE IS CONSIDERED SET OF STATE CONSIDERATION**<br>considered under two general categories involving either<br>channel block or channel activation. Within these two<br>classes The drugs that affect MG channel activity will be considered under two general categories involving either channel block or channel activation. Within these two classes, further distinctions may be made depending upon, for considered under two general categories involving either<br>channel block or channel activation. Within these two<br>classes, further distinctions may be made depending<br>upon, for example, the drug's exact mechanism of action<br>(e. channel block or channel activation. Within<br>classes, further distinctions may be made (<br>upon, for example, the drug's exact mechanism<br>(e.g., open versus closed channel block) or its<br>of action (e.g., protein, bilayer or cyt of action (e.g., protein, bilayer or cytoskeleton).

g., open versus closed channel block) or its likely site<br>action (e.g., protein, bilayer or cytoskeleton).<br>Blockers<br>Of the various chemicals and drugs that block MG<br>annels, three groups have received the most attention. of action (e.g., protein, bilayer or cytoskeleton).<br>A. Blockers<br>Channels, three groups have received the most attention.<br>These include amiloride and its analogs, aminoglycosid A. Blockers<br>Of the various chemicals and drugs that block MG<br>channels, three groups have received the most attention<br>These include amiloride and its analogs, aminoglycoside

antibiotics and the lanthanides, in particular, gado-HAMILL AND<br>antibiotics and the lanthanides, in particular, gado-<br>linium. In addition to these three groups, other less well<br>characterized blocking agents will also be considered. HAMILI<br>antibiotics and the lanthanides, in particular, gad<br>inium. In addition to these three groups, other less we<br>characterized blocking agents will also be considered<br>1. Amiloride and analogs. Amiloride is discussed fit 1. **1.1. The United States and the lanthanides**, in particular, gado-<br>
1. Amiloride and analogs. Amiloride is discussed first<br>
1. Amiloride and analogs. Amiloride is discussed first<br>
cause it has been the most rigorously s

antibiotics and the lanthanides, in particular, gado-<br>cellinium. In addition to these three groups, other less well<br>most rigorously studied and<br>*1. Amiloride and analogs*. Amiloride is discussed first can<br>because it has be linium. In addition to these three groups, other less well methanized blocking agents will also be considered. as  $1$ . Amiloride and analogs. Amiloride is discussed first capped also because it has been the most rigorousl characterized blocking agents will also be considered.<br>
1. Amiloride and analogs. Amiloride is discussed first<br>
because it has been the most rigorously studied and<br>
is the only drug that has been quantitatively modeled<br>
in 1. Amiloride and analogs. Amiloride is discussed first calculated and the consequent is the only drug that has been quantitatively modeled S.<br>in terms of its blocking mechanism (Lane et al., 1991; no Ruesch et al., 1994). because it has been the most rigorously studied and (L<br>is the only drug that has been quantitatively modeled SA<br>in terms of its blocking mechanism (Lane et al., 1991; ne<br>Ruesch et al., 1994). Amiloride is a member of a gro in terms of its blocking mechanism (Lane et al., 1991; Ruesch et al., 1994). Amiloride is a member of a group of over 1000 structurally related compounds known as pyrazinecarboxyamides (Kleyman and Cragoe, 1988, 1990). Ami over 1000 structurally related compounds known as Ruesch et al., 1994). Amiloride is a member of a grous<br>over 1000 structurally related compounds known<br>pyrazinecarboxyamides (Kleyman and Cragoe, 19<br>1990). Amiloride and many of its analogs are pot<br>diuretics that act by blo over 1000 structurally related compounds known as<br>pyrazinecarboxyamides (Kleyman and Cragoe, 1988,<br>1990). Amiloride and many of its analogs are potent<br>diuretics that act by blocking, in nanomolar to micromo-<br>lar concentrat pyrazinecarboxyamides (Kleyman and Cragoe, 1988, glass). Amiloride and many of its analogs are potent altiture<br>tics that act by blocking, in nanomolar to micromo-<br>lar concentrations, the epithelial Na<sup>+</sup> channel (Benos, b 1990). Amiloride and many of its analogs are pot<br>diuretics that act by blocking, in nanomolar to micron<br>lar concentrations, the epithelial Na<sup>+</sup> channel (Ber<br>1982). Although the native epithelial Na<sup>+</sup> channel<br>not been di diuretics that act by blocking, in nanomolar to micromo-<br>lar concentrations, the epithelial Na<sup>+</sup> channel (Benos,<br>1982). Although the native epithelial Na<sup>+</sup> channel has<br>not been directly demonstrated to be mechanosensiti lar concentrations, the epithelial Na<sup>+</sup> channel (Benos, both the hair cell and oocyte MG channels. In both cases, 1982). Although the native epithelial Na<sup>+</sup> channel has inward current recorded at negative potential is r recent cloning studies of the rat epithelial Na<sup>+</sup> channel not been directly demonstrated to be mechanosensitive, duce<br>recent cloning studies of the rat epithelial Na<sup>+</sup> channel tial<br>indicate that the three subunits  $(\alpha\beta\gamma)$  that compose it<br>show strong sequence homology to *Caen* recent cloning studies of the rat epithelial Na<sup>+</sup> channel<br>indicate that the three subunits  $(\alpha\beta\gamma)$  that compose it<br>show strong sequence homology to *Caenorhabditis el-<br>egans* genes, cloned from touch-insensitive mutant indicate that the three subunits  $(\alpha\beta\gamma)$  that compose it Lashow strong sequence homology to *Caenorhabditis elgans* genes, cloned from touch-insensitive mutants and nel believed to encode MG channel proteins (Canessa et show strong sequence homology to *Caenorhabditis elegans* genes, cloned from touch-insensitive mutants and nel<br>believed to encode MG channel proteins (Canessa et al., the<br>1993, 1994; Driscoll and Chalfie, 1991; Huang and egans genes, cloned from touch-insensitive mutants and nelieved to encode MG channel proteins (Canessa et al., the 1993, 1994; Driscoll and Chalfie, 1991; Huang and we Chalfie, 1994; Hong and Driscoll, 1994). Furthermore, believed to encode MG channel proteins (Canessa 1993, 1994; Driscoll and Chalfie, 1991; Huang Chalfie, 1994; Hong and Driscoll, 1994). Furtherm recent report indicates that the  $\alpha$ -subunit of the b renal epithelial Na<sup>+</sup> 1993, 1994; Driscoll and Chalfie, 1991; Huang and with Chalfie, 1994; Hong and Driscoll, 1994). Furthermore, a iza recent report indicates that the  $\alpha$ -subunit of the bovine too renal epithelial Na<sup>+</sup> channel may form a Chalfie, 1994; Hong and Driscoll, 1994). Furthermore, a<br>recent report indicates that the  $\alpha$ -subunit of the bovine<br>renal epithelial Na<sup>+</sup> channel may form a stretch-sensi-<br>tive Na<sup>+</sup> channel when reconstituted into paint recent report indicates that the  $\alpha$ -subunit of the bovine<br>renal epithelial Na<sup>+</sup> channel may form a stretch-sensi-<br>tive Na<sup>+</sup> channel when reconstituted into painted lipid<br>soc<br>bilayers in which tension was altered hydro renal epithelial Na<sup>+</sup> channel may form a stretch-sens<br>tive Na<sup>+</sup> channel when reconstituted into painted lipid<br>bilayers in which tension was altered hydrostatical<br>(Awayada et al., 1995). However, this result must l<br>consi tive Na<sup>+</sup> channel when reconstituted into painted lipid so<br>bilayers in which tension was altered hydrostatically ag<br>(Awayada et al., 1995). However, this result must be op<br>considered tentative, because with painted lipid bilayers in which tension was altered hydrostatically (Awayada et al., 1995). However, this result must be considered tentative, because with painted lipid bilayers, the membrane tension is not simply a function of the hyd (Awayada et al., 1995). However, this result must be considered tentative, because with painted lipid bilaters, the membrane tension is not simply a function of the hydrostatic pressure gradient (e.g., see Fettiplace et a considered tentative, because with painted lipid bilay- (e.g. ers, the membrane tension is not simply a function of the ride hydrostatic pressure gradient (e.g., see Fettiplace et al., wou 1971; Fettiplace personal communi ers, the membrane tension is not simply a function of the richydrostatic pressure gradient (e.g., see Fettiplace et al., worderly 1971; Fettiplace personal communication). In fact, membrane tension will be determined by th hydrostatic pressure gradient (e.g., see Fettiplace et al., we<br>1971; Fettiplace personal communication). In fact, mem-<br>brane tension will be determined by the equilibrium<br>distribution of lipids between the bilayer itself a 1971; Fettiplace personal communication). In fact, membrane tension will be determined by the equilibrium distribution of lipids between the bilayer itself and the surrounding meniscus. On this basis, the result should be brane tension will be determined by the equilibrium Podiatribution of lipids between the bilayer itself and the the surrounding meniscus. On this basis, the result should fice confirmed under conditions in which membrane t distribution of lipids between the bilayer itself and the<br>surrounding meniscus. On this basis, the result should<br>be confirmed under conditions in which membrane ten-<br>sion can be better controlled (e.g., by using the patch<br> surrounding meniscus. On this basis, the result should fict be confirmed under conditions in which membrane tension can be better controlled (e.g., by using the patch clamp tip-dip method (Opsahl and Webb, 1994)). Perhaps be confirmed under conditions in which membrane tension can be better controlled (e.g., by using the patch clamp tip-dip method (Opsahl and Webb, 1994)). Perhaps it is even more relevant to determine whether the heterolig sion can be better controlled (e.g., by using the patch<br>clamp tip-dip method (Opsahl and Webb, 1994)). Per-<br>haps it is even more relevant to determine whether the<br>heteroligomeric  $(\alpha\beta\gamma)$  or native Na<sup>+</sup> channel displays clamp tip-dip method (Opsahl and Webb, 1994)). Per-<br>haps it is even more relevant to determine whether the<br>heteroligomeric  $(\alpha\beta\gamma)$  or native Na<sup>+</sup> channel displays ce<br>mechanosensitivity. Unfortunately, two recent studie haps it is even more relevant to determine whether the<br>heteroligomeric  $(\alpha\beta\gamma)$  or native  $\text{Na}^+$  channel displays<br>mechanosensitivity. Unfortunately, two recent studies<br>attempting to directly address this important iss heteroligomeric  $(\alpha\beta\gamma)$  or native Na<sup>+</sup> channel displa<br>mechanosensitivity. Unfortunately, two recent studi<br>attempting to directly address this important issue ha<br>not resolved it. In one case, the inability to obtain co<br> mechanosensitivity. Omortunately, two recent studies<br>attempting to directly address this important issue have<br>not resolved it. In one case, the inability to obtain con-<br>sistent results regarding the stretch sensitivity or not resolved it. In one case, the inability to obtain con-<br>second, the concentration dependence of amiloride block<br>sistent results regarding the stretch sensitivity or insen-<br>sitivity of the epithelial Na<sup>+</sup> channel in ce sitivity of the epithelial  $Na<sup>+</sup>$  channel in cells of the rat cortical collecting tubule precluded a resolution (Palmer and Frindt, 1996). In the other case, the lack of controls with regard to both the magnitude and f cortical collecting tubule precluded a resolution (Palmer seems unlikely within a single file permeation pathway.<br>and Frindt, 1996). In the other case, the lack of controls Third, amiloride block does not depend on current cortical collecting tubule precluded a resolution (Palmer see and Frindt, 1996). In the other case, the lack of controls The with regard to both the magnitude and form (i.e., compression versus stretch) of the mechanical and Frindt, 1996). In the other case, the lack of controls<br>with regard to both the magnitude and form (i.e., com-<br>pression versus stretch) of the mechanical stimulation<br>casts doubt on the reported stretch sensitivity of t with regard to both the<br>pression versus stretch<br>casts doubt on the rep<br>Na<sup>+</sup> currents measu<br>(Achard et al., 1996).<br>The original indicat ession versus stretch) of the mechanical stimulation by v<br>sts doubt on the reported stretch sensitivity of the the<br> $a^+$  currents measured in human  $\beta$  lymphocytes In<br>chard et al., 1996). can<br>The original indication that casts doubt on the reported stretch sensitivity of the Na<sup>+</sup> currents measured in human  $\beta$  lymphocytes (Achard et al., 1996).<br>The original indication that amiloride might act on MG channels arose from observations that

 $Na<sup>+</sup>$  currents measured in human  $\beta$  lymphocytes (Achard et al., 1996).<br>
The original indication that amiloride might act on MG channels arose from observations that amiloride blocked mechanosensitivity in both the l (Achard et al., 1996).<br>The original indication that amiloride might act on<br>MG channels arose from observations that amilorid<br>blocked mechanosensitivity in both the lateral line or<br>gan of *Necturus* and the skin of *Xenopus* The original indication that amiloride might act on domestions that amiloride Reflocked mechanosensitivity in both the lateral line orchanosensitivity in both the lateral line orchanosensitivity in both the lateral line or MG channels arose from observations that amiloride left blocked mechanosensitivity in both the lateral line organ of *Necturus* and the skin of *Xenopus* (Jorgensen, 1985). Subsequently, amiloride was shown to directly blo

MCBRIDE<br>cells of the chick (Jorgensen and Ohmori, 1988) and<br>mouse (Ruesch et al., 1994) inner ear. The first study of MCBRIDE<br>cells of the chick (Jorgensen and Ohmori, 1988) and<br>mouse (Ruesch et al., 1994) inner ear. The first study of<br>amiloride block at the single MG channel level was MCBRIDE<br>cells of the chick (Jorgensen and Ohmori, 1988) and<br>mouse (Ruesch et al., 1994) inner ear. The first study of<br>amiloride block at the single MG channel level was<br>carried out on the SA cation channel of *Xenopus* ooc cells of the chick (Jorgensen and Ohmori, 1988) and<br>mouse (Ruesch et al., 1994) inner ear. The first study of<br>amiloride block at the single MG channel level was<br>carried out on the SA cation channel of *Xenopus* oocytes<br>(La cells of the chick (Jorgensen and Ohmori, 1988) and<br>mouse (Ruesch et al., 1994) inner ear. The first study of<br>amiloride block at the single MG channel level was<br>carried out on the SA cation channel of *Xenopus* oocytes<br>(La mouse (Ruesch et al., 1994) inner ear. The first study a<br>amiloride block at the single MG channel level ws<br>carried out on the SA cation channel of *Xenopus* oocyte<br>(Lane et al., 1991, 1992, 1993; Hamill et al., 1992). Th<br>S amiloride block at the single MG channel level was carried out on the SA cation channel of *Xenopus* occytes (Lane et al., 1991, 1992, 1993; Hamill et al., 1992). This SA channel shows basic similarities to the hair cell carried out on the SA cation channel of *Xenopus* oocy<br>(Lane et al., 1991, 1992, 1993; Hamill et al., 1992). T<br>SA channel shows basic similarities to the hair cell channel in terms of its cation selectivity (i.e., conduct (Lane et al., 1991, 1992, 1993; Hamill et al., 1992). This SA channel shows basic similarities to the hair cell channel in terms of its cation selectivity (i.e., conducts Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup>) conductance ( $\sim$ 50 pS) an SA channel shows basic similarities to the hair cell channel in terms of its cation selectivity (i.e., conducts  $Na^+$ ,  $K^+$  and  $Ca^{2+}$ ) conductance ( $\sim 50$  pS) and rapid activation and adaptation kinetics (Howard et al nel in terms of its cation selectivity (i.e., conducts Na<sup>+</sup>,  $K^+$  and  $Ca^{2+}$ ) conductance ( $\sim$ 50 pS) and rapid activation and adaptation kinetics (Howard et al., 1988; Taglietti and Toselli 1988; Yang and Sachs, 1989;  $K^+$  and  $Ca^{2+}$ ) conductance  $(\sim 50 \text{ pS})$  and rapid activation and adaptation kinetics (Howard et al., 1988; Taglietti and Toselli 1988; Yang and Sachs, 1989; Hamill and McBride, 1992, 1994b). Furthermore, external ami tion and adaptation kinetics (Howard et al., 1988; Taglietti and Toselli 1988; Yang and Sachs, 1989; Hamill and McBride, 1992, 1994b). Furthermore, external amiloride causes a similar voltage-dependent block of both the ha glietti and Toselli 1988; Yang and Sachs, 1989; Hamill<br>and McBride, 1992, 1994b). Furthermore, external<br>amiloride causes a similar voltage-dependent block of<br>both the hair cell and oocyte MG channels. In both cases,<br>inward and McBride, 1992, 1994b). Furthermore, extern<br>amiloride causes a similar voltage-dependent block<br>both the hair cell and oocyte MG channels. In both case<br>inward current recorded at negative potential is 1<br>duced, but outwar amiloride causes a similar voltage-dependent block of<br>both the hair cell and oocyte MG channels. In both cases,<br>inward current recorded at negative potential is re-<br>duced, but outward current recorded at positive poten-<br>ti both the hair cell and oocyte MG channels. In both case<br>inward current recorded at negative potential is reduced, but outward current recorded at positive potentials is almost unaffected (Jorgensen and Ohmori, 1988<br>Lane et

duced, but outward current recorded at positive potentials is almost unaffected (Jorgensen and Ohmori, 1988;<br>Lane et al., 1991).<br>a. MECHANISM OF AMILORIDE BLOCK. At the single chan-<br>nel level, amiloride block involves brie tials is almost unaffected (Jorgensen and Ohmori, 1988;<br>Lane et al., 1991).<br>a. MECHANISM OF AMILORIDE BLOCK. At the single chan-<br>nel level, amiloride block involves brief interruptions in<br>the inward current events that inc Lane et al., 1991).<br>
a. MECHANISM OF AMILORIDE BLOCK. At the single ch<br>
nel level, amiloride block involves brief interruptions<br>
the inward current events that increase in frequent<br>
with amiloride concentration but decreas a. MECHANISM OF AMILORIDE BLOCK. At the single channel level, amiloride block involves brief interruptions in the inward current events that increase in frequency with amiloride concentration but decrease with depolarizati nel level, amiloride block involves brief interruptions in<br>the inward current events that increase in frequency<br>with amiloride concentration but decrease with depolar-<br>ization (Lane et al., 1991). Because the interruptions the inward current events that increase in frequency<br>with amiloride concentration but decrease with depolar-<br>ization (Lane et al., 1991). Because the interruptions are<br>too brief to resolve fully, they result in an apparent with amiloride concentration but decrease with depolar<br>ization (Lane et al., 1991). Because the interruptions are<br>too brief to resolve fully, they result in an apparent<br>reduction in single channel current amplitude with as ization (Lane et al., 1991). Because the interruptions are<br>too brief to resolve fully, they result in an apparent<br>reduction in single channel current amplitude with as-<br>sociated increased open channel noise. This type of v too brief to resolve fully, they result in an apparent reduction in single channel current amplitude with associated increased open channel noise. This type of voltage-dependent "flickery" block is often taken to reflect o reduction in single channel current amplitude with a sociated increased open channel noise. This type of vo<br>age-dependent "flickery" block is often taken to refle<br>open channel or pore block with intermediate kineti<br>(e.g., sociated increased open channel noise. This type of voltage-dependent "flickery" block is often taken to reflect<br>open channel or pore block with intermediate kinetics<br>(e.g., see Hamill, 1983b). According to this model, ami age-dependent "flickery" block is often taken to reflect<br>open channel or pore block with intermediate kinetics<br>(e.g., see Hamill, 1983b). According to this model, amilo-<br>ride, which is positively charged at physiological p open channel or pore block with intermediate kinetics (e.g., see Hamill, 1983b). According to this model, amilo-<br>ride, which is positively charged at physiological pH,<br>would be driven by negative potentials into the open<br>c (e.g., see Hamill, 1983b). According to this model, amilo-<br>ride, which is positively charged at physiological pH,<br>would be driven by negative potentials into the open<br>channel, where it would occlude or "plug" the channel. ride, which is positively charged at physiological pl<br>would be driven by negative potentials into the ope<br>channel, where it would occlude or "plug" the channe<br>Positive potentials would reverse this block by drivir<br>the impe would be driven by negative potentials into the open<br>channel, where it would occlude or "plug" the channel.<br>Positive potentials would reverse this block by driving<br>the impermeant blocker back out of the channel. Modi-<br>fica channel, where it would occlude or "plug" the channel Positive potentials would reverse this block by drivitie impermeant blocker back out of the channel. Modelications of the simple plug model include the part and permean Positive potentials would reverse this block by driving<br>the impermeant blocker back out of the channel. Modi-<br>fications of the simple plug model include the partial<br>and permeant block models (see Lane et al., 1991).<br>Althou

fications of the simple plug model include the partial<br>and permeant block models (see Lane et al., 1991).<br>Although the various plug models are intuitively at-<br>tractive, a number of observations argue against their<br>relevanc fications of the simple plug model include the partial<br>and permeant block models (see Lane et al., 1991).<br>Although the various plug models are intuitively at-<br>tractive, a number of observations argue against their<br>relevanc and permeant block models (see Lane et al., 1991).<br>Although the various plug models are intuitively at-<br>tractive, a number of observations argue against their<br>relevance to amiloride block in both the occyte and hair<br>cell ( Although the various plug models are intuitively at-<br>tractive, a number of observations argue against their<br>relevance to amiloride block in both the oocyte and hair<br>cell (Lane et al., 1991; Ruesch et al., 1994). In the fir tractive, a number of observations argue against their relevance to amiloride block in both the oocyte and hair cell (Lane et al., 1991; Ruesch et al., 1994). In the first place, the channel conductance in amiloride reache relevance to amiloride block in both the oocyte and hair<br>cell (Lane et al., 1991; Ruesch et al., 1994). In the first<br>place, the channel conductance in amiloride reaches a<br>voltage-independent value at hyperpolarized potenti cell (Lane et al., 1991; Ruesch et al., 1994). In the find<br>place, the channel conductance in amiloride reaches<br>voltage-independent value at hyperpolarized potentia<br>Second, the concentration dependence of amiloride blo<br>yiel place, the channel conductance in amiloride reaches a<br>voltage-independent value at hyperpolarized potentials.<br>Second, the concentration dependence of amiloride block<br>yields a Hill coefficient of 2, which indicates two amil voltage-independent value at hyperpolarized potentials.<br>Second, the concentration dependence of amiloride block<br>yields a Hill coefficient of 2, which indicates two amilo-<br>ride molecules are required to block the channel; t yields a Hill coefficient of 2, which indicates two amilo-<br>ride molecules are required to block the channel; this<br>seems unlikely within a single file permeation pathway.<br>Third, amiloride block does not depend on current fl seems unlikely within a single file permeation pathway. through the MG channel, thus ruling out a mechanism hird, amiloride block does not depend on current flux<br>rough the MG channel, thus ruling out a mechanism<br>which permeating ions are able to knock amiloride off<br>e channel.<br>In contrast to plug models, a "conformational" model<br>

through the MG channel, thus ruling out a mechanis<br>by which permeating ions are able to knock amiloride<br>the channel.<br>In contrast to plug models, a "conformational" mo<br>can explain both the voltage and concentration depe<br>den by which permeating ions are able to knock amiloride off<br>the channel.<br>In contrast to plug models, a "conformational" model<br>can explain both the voltage and concentration depen-<br>dence of external amiloride block (Lane et al the channel.<br>In contrast to plug models, a "conformational" model<br>can explain both the voltage and concentration depen-<br>dence of external amiloride block (Lane et al., 1991;<br>Ruesch et al., 1994). This model assumes that th In contrast to plug models, a "conformational" r<br>can explain both the voltage and concentration d<br>dence of external amiloride block (Lane et al.,<br>Ruesch et al., 1994). This model assumes that the<br>channel can exist in one o can explain both the voltage and concentration dependence of external amiloride block (Lane et al., 1991; Ruesch et al., 1994). This model assumes that the open channel can exist in one of two different voltage-dependent c dence of external amiloride block (Lane et al., 1999).<br>Ruesch et al., 1994). This model assumes that the ope<br>channel can exist in one of two different voltage-deper<br>dent conformations. The open channel conformation fa<br>vore Ruesch et al., 1994). This model assumes that the open<br>channel can exist in one of two different voltage-depen-<br>dent conformations. The open channel conformation fa-<br>vored at negative potentials reveals two amiloride bind-

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PHARMACOLOGY OF MECHAL<br>positive potentials is such that these sites are inacces-<br>sible to amiloride. Thus, at positive potentials, amilor PHARMACOLOGY OF MECHANOGAT<br>positive potentials is such that these sites are inacces-<br>sible to amiloride. Thus, at positive potentials, amiloride<br>binds to the exposed sites in a cooperative, voltagepositive potentials is such that these sites are inaccesible to amiloride. Thus, at positive potentials, amilor has no effect, whereas at negative potentials, amilor binds to the exposed sites in a cooperative, volta indep positive potentials is such that these sites are inacce<br>sible to amiloride. Thus, at positive potentials, amiloric<br>has no effect, whereas at negative potentials, amiloric<br>binds to the exposed sites in a cooperative, voltag sible to amiloride. Thus, at positive potentials, amiloride has no effect, whereas at negative potentials, amiloride binds to the exposed sites in a cooperative, voltage-independent manner to block the channel. Furthermore has no effect, whereas at negative potentials, amiloride debinds to the exposed sites in a cooperative, voltage-<br>independent manner to block the channel. Furthermore, has at least in the hair cell, relaxation measurements binds to the exposed sites in a cooperative, voltage independent manner to block the channel. Furthermore at least in the hair cell, relaxation measurements denoted rectly demonstrate that amiloride analogs block the open independent manner to block the channel. Furthermore, has<br>at least in the hair cell, relaxation measurements di-<br>rectly demonstrate that amiloride analogs block the  $Ca^2$ <br>open rather than closed channel conformation at ne rectly demonstrate that amiloride analogs block the<br>open rather than closed channel conformation at nega-<br>tive potentials. Although most attention has focused on<br>external block, in the oocyte, internally applied amilo-<br>rid rectly demonstrate that amiloride analogs block the Ca<br>open rather than closed channel conformation at nega-<br>tive potentials. Although most attention has focused on<br>external block, in the oocyte, internally applied amilotive potentials. Although most attention has focused on external block, in the oocyte, internally applied amiloride produces a low potency voltage-independent block that was not observed in the hair cell.<br>b. IONIC EFFECTS b. **IONIC EFFECTS** ON MILORIDE BLOCK. External amide produces a low potency voltage-independent block was not observed in the hair cell.<br>b. IONIC EFFECTS ON AMILORIDE BLOCK. External amide is 10 times less effective in blo

ride produces a low potency voltage-independent block par<br>that was not observed in the hair cell. in the interval and interval in the is 10 times less effective in blocking the occyte fere<br>channel (concentration that inhi that was not observed in the hair cell.<br>b. IONIC EFFECTS ON AMILORIDE BLOCK. External amilo-<br>ride is 10 times less effective in blocking the oocyte<br>channel (concentration that inhibits  $50\%$  (IC<sub>50</sub>) = 500<br> $\mu$ M) compare b. IONIC EFFECTS ON AMILORIDE BLOCK. External amilo-<br>
ride is 10 times less effective in blocking the oocyte fere<br>
channel (concentration that inhibits  $50\%$  (IC<sub>50</sub>) = 500 indi<br>  $\mu$ M) compared with the hair cell channe ride is 10 times less effective in blocking the occyte ferconnel (concentration that inhibits  $50\%$  (IC<sub>50</sub>) = 500 ind  $\mu$ M) compared with the hair cell channel (IC<sub>50</sub> = 50  $\mu$ M). latter This difference in potency was channel (concentration that inhibits  $50\%$  (IC<sub>50</sub>) = 500 in  $\mu$ M) compared with the hair cell channel (IC<sub>50</sub> = 50  $\mu$ M). lat This difference in potency was shown not to be caused by pothe different ionic recording co  $\mu$ M) compared with the hair cell channel (IC<sub>50</sub> = 50  $\mu$ M). late<br>This difference in potency was shown not to be caused by pote<br>the different ionic recording conditions used in the two<br>preparations (Lane et al., 1993). This difference in potency was shown not to be caused by<br>the different ionic recording conditions used in the two<br>preparations (Lane et al., 1993). To be specific, in the<br>original occyte study, amiloride block was measure the different ionic recording conditions used in the two<br>preparations (Lane et al., 1993). To be specific, in the<br>original occyte study, amiloride block was measured in<br>the absence of external  $Ca^{2+}$  as well as other div preparations (Lane et al., 1993). To be specific, in the original oocyte study, amiloride block was measured in the absence of external  $Ca^{2+}$  as well as other divalent cations and in the presence of high (100 mM) extern original oocyte study, amiloride block was measured in<br>the absence of external  $Ca^{2+}$  as well as other divalent<br>cations and in the presence of high (100 mM) external K<sup>+</sup><br>and low (5 mM) external Na<sup>+</sup>. In contrast, hair the absence of external  $Ca^{2+}$  as well as other divalent<br>cations and in the presence of high (100 mM) external  $K^+$ <br>and low (5 mM) external Na<sup>+</sup>. In contrast, hair cell<br>measurements were made in the presence of divalen cations and in the presence of high  $(100 \text{ mM})$  external  $\text{K}^+$ <br>and low  $(5 \text{ mM})$  external  $\text{Na}^+$ . In contrast, hair cell<br>measurements were made in the presence of divalent<br>cations  $(2 \text{ mM})$  with high external  $\text{Na$ and low (5 mM) external Na<sup>+</sup>. In contrast, hair cell fin<br>measurements were made in the presence of divalent for<br>cations (2 mM) with high external Na<sup>+</sup> and low K<sup>+</sup> cat<br>(Jorgensen and Ohmori, 1988; Ruesch et al., 1994). measurements were made in the presence of divalent for<br>cations  $(2 \text{ mM})$  with high external Na<sup>+</sup> and low K<sup>+</sup> cat<br>(Jorgensen and Ohmori, 1988; Ruesch et al., 1994). Fur-<br>nee<br>thermore, it has been suggested that amiloride cations (2 mM) with high external Na<sup>+</sup> and low K<br>(Jorgensen and Ohmori, 1988; Ruesch et al., 1994). Furthermore, it has been suggested that amiloride bloc<br>requires the presence of external Ca<sup>2+</sup> (Cuthbert an<br>Wong, 1972; (Jorgensen and Ohmori, 1988; Ruesch et al., 1994). Fur-<br>thermore, it has been suggested that amiloride block<br>requires the presence of external  $Ca^{2+}$  (Cuthbert and<br>Wong, 1972; but see Desmedt et al., 1991) and is influ-<br> thermore, it has been suggested that amiloride block<br>requires the presence of external  $Ca^{2+}$  (Cuthbert and<br>Wong, 1972; but see Desmedt et al., 1991) and is influ-<br>enced by changes in external Na<sup>+</sup> concentration (Benos, requires the presence of external  $Ca^{2+}$  (Cuthbert and<br>Wong, 1972; but see Desmedt et al., 1991) and is influ-<br>enced by changes in external Na<sup>+</sup> concentration (Benos, hai<br>1982). However, direct experiments with the oocy Wong, 1972; but see Desmedt et al., 1991) and is influ-<br>enced by changes in external Na<sup>+</sup> concentration (Benos, hait<br>1982). However, direct experiments with the oocyte in-<br>dicate that inclusion of 2 mM Ca<sup>2+</sup> in fact red enced by changes in external Na<sup>+</sup> concentration (Benos, 1982). However, direct experiments with the oocyte indicate that inclusion of 2 mM Ca<sup>2+</sup> in fact reduced (by a factor of 2) rather than increased amiloride potency

PHARMACOLOGY OF MECHANOGATED MEMBRANE ION CHANNELS 235<br>positive potentials is such that these sites are inacces- had no effect (Lane et al., 1993). The potency reduction TED MEMBRANE ION CHANNELS<br>had no effect (Lane et al., 1993). The potency reduction<br>by  $Ca^{2+}$  was shown to occur without altering the voltage TED MEMBRANE ION CHANNELS 235<br>had no effect (Lane et al., 1993). The potency reduction<br>by  $Ca^{2+}$  was shown to occur without altering the voltage<br>dependence of block and could be modeled by a screening TED MEMBRANE ION CHANNELS 235<br>had no effect (Lane et al., 1993). The potency reduction<br>by  $Ca^{2+}$  was shown to occur without altering the voltage<br>dependence of block and could be modeled by a screening<br>of surface negative had no effect (Lane et al., 1993). The potency reduction<br>by  $Ca^{2+}$  was shown to occur without altering the voltage<br>dependence of block and could be modeled by a screening<br>of surface negative charges (Lane et al., 1993). had no effect (Lane et al., 1993). The potency reduction<br>by  $Ca^{2+}$  was shown to occur without altering the voltage<br>dependence of block and could be modeled by a screening<br>of surface negative charges (Lane et al., 1993). by  $Ca^{2+}$  was shown to occur without altering the voltage dependence of block and could be modeled by a screening of surface negative charges (Lane et al., 1993). If  $Ca^{2+}$  has a similar effect in the hair cells, then a dependence of block and could be modeled by a screening<br>of surface negative charges (Lane et al., 1993). If  $Ca^{2+}$ <br>has a similar effect in the hair cells, then amiloride may<br>be even more potent in situ (i.e.,  $IC_{50} < 50 \$ of surface negative charges (Lane et al., 1993). If  $Ca^{2+}$ <br>has a similar effect in the hair cells, then amiloride may<br>be even more potent in situ (i.e.,  $IC_{50} < 50 \mu$ M) because<br> $Ca^{2+}$  concentration in the normal endolym

external block, in the oocyte, internally applied amilo-<br>
ride potency for MG channels in hair cells com-<br>
ride produces a low potency voltage-independent block<br>
that was not observed in the hair cell.<br>
b. IONIC EFFECTS O be even more potent in situ (i.e.,  $IC_{50} < 50 \mu$ M) because  $Ca^{2+}$  concentration in the normal endolymph is only  $\sim$ 50  $\mu$ M (Crawford et al., 1991).<br>c. STRUCTURE-ACTIVITY STUDIES. The difference in amiloride potency for Ca<sup>2+</sup> concentration in the normal endolymph is only  $\sim$ 50  $\mu$ M (Crawford et al., 1991).<br>c. STRUCTURE-ACTIVITY STUDIES. The difference in amiloride potency for MG channels in hair cells compared with oocytes presumably  $\sim$ 50  $\mu$ M (Crawford et al., 1991).<br>c. STRUCTURE-ACTIVITY STUDIES. The difference in<br>amiloride potency for MG channels in hair cells com-<br>pared with occytes presumably reflects real differences<br>in the binding affinities c. STRUCTURE-ACTIVITY STUDIES. The difference in amiloride potency for MG channels in hair cells compared with occytes presumably reflects real differences in the binding affinities for sites on the two channels. Although amiloride potency for MG channels in hair cells<br>pared with occytes presumably reflects real diffe<br>in the binding affinities for sites on the two cha<br>Although these difference may indicate structur<br>ferences in the sites, "p pared with oocytes presumably reflects real differences<br>in the binding affinities for sites on the two channels.<br>Although these difference may indicate structural dif-<br>ferences in the sites, "potency-sequence-fingerprintin in the binding affinities for sites on the two channels.<br>Although these difference may indicate structural differences in the sites, "potency-sequence-fingerprinting"<br>indicates that the binding sites may be structurally re Although these difference may indicate structural differences in the sites, "potency-sequence-fingerprinting"<br>indicates that the binding sites may be structurally re-<br>lated. For example, examination of the order of blockin ferences in the sites, "potency-sequence-fingerprinting"<br>indicates that the binding sites may be structurally re-<br>lated. For example, examination of the order of blocking<br>potency of a series of amiloride analogs indicates indicates that the binding sites may be structurally related. For example, examination of the order of blockin<br>potency of a series of amiloride analogs indicates bo<br>channels display identical potency sequences (Lane<br>al., 1 lated. For example, examination of the order of blocking<br>potency of a series of amiloride analogs indicates both<br>channels display identical potency sequences (Lane et<br>al., 1992; Ruesch et al., 1994). In contrast, other tra potency of a series of amiloride analogs indicates both channels display identical potency sequences (Lane et al., 1992; Ruesch et al., 1994). In contrast, other transport pathways that are blocked by amiloride analogs, in channels display identical potency sequences (Lane et al., 1992; Ruesch et al., 1994). In contrast, other transport pathways that are blocked by amiloride analogs, including the epithelial Na<sup>+</sup> channel, show different ana al., 1992; Ruesch et al., 1994). In contrast, other transport pathways that are blocked by amiloride analogs, including the epithelial  $Na<sup>+</sup>$  channel, show different analog potency sequences (table 1). Therefore sequen port pathways that are blocked by amiloride analogs<br>including the epithelial  $Na^+$  channel, show differen<br>analog potency sequences (table 1). Therefore sequence<br>fingerprinting with amiloride analogs can compensate<br>for ami including the epithelial  $Na<sup>+</sup>$  channel, show different<br>analog potency sequences (table 1). Therefore sequence<br>fingerprinting with amiloride analogs can compensate<br>for amiloride's low specificity. For example, table 1 analog potency sequences (table 1). Therefore sequence<br>fingerprinting with amiloride analogs can compensate<br>for amiloride's low specificity. For example, table 1 indi-<br>cates that amiloride and only one appropriate analog<br>n fingerprinting with amiloride analogs can compensate<br>for amiloride's low specificity. For example, table 1 indi-<br>cates that amiloride and only one appropriate analog<br>need be tested to implicate MG channels over other<br>suspe r amiloride's low specificity. For example, table 1 indites that amiloride and only one appropriate analog<br>eed be tested to implicate MG channels over other<br>spected transporters in a specific cellular function.<br>Examination indicates that the binding sites may be structurally re-<br>lated. For example, examination of the order of blocking<br>potency of a series of amiloride analogs indicates both<br>channels display identical potency sequences (Lane

cates that amiloride and only one appropriate analog<br>need be tested to implicate MG channels over other<br>suspected transporters in a specific cellular function.<br>Examination of the structure-activity relation in table<br>1 indi have detected to implicate MG channels over other<br>suspected transporters in a specific cellular function.<br>Examination of the structure-activity relation in table<br>1 indicates that analog potency in both the oocyte and<br>hair suspected transporters in a specific cellular function.<br>Examination of the structure-activity relation in table<br>1 indicates that analog potency in both the oocyte and<br>hair cell can be increased by adding hydrophobic side<br>c Examination of the structure-activity relation in table 1 indicates that analog potency in both the occyte and hair cell can be increased by adding hydrophobic side chains to the amiloride core structure (Lane et al., 1992 1 indicates that analog potency in both the oocyte and hair cell can be increased by adding hydrophobic sichains to the amiloride core structure (Lane et al., 199 Ruesch et al., 1994). However, the hair cell studies is dic





**<sup>a</sup>** Dimethyla.mioride (DMA), hexamethyleneamiloride (HMA), 6-iodide-2-methoxy-5-nitrobenzamil (I-NMBA), bromohexamethylene**amiloride (BrHMA), 5-(N-propyl-N-butyl)-dichlorobenzamil (PBDCB).**

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indicate the amiloride binding sites are located within file<br>
sterically restricted hydrophobic pockets. The most po-St Example 236<br>indicate the amiloride binding sites are located within<br>sterically restricted hydrophobic pockets. The most po-<br>tent amiloride analog that has been found to date is 6-HAMILL AND N<br>indicate the amiloride binding sites are located within fi<br>sterically restricted hydrophobic pockets. The most po-<br>stent amiloride analog that has been found to date is 6-<br>iodide-2-methoxy-5-nitrobenzamil (I-N indicate the amiloride binding sites are located within fibre sterically restricted hydrophobic pockets. The most potent amiloride analog that has been found to date is 6-<br>iodide-2-methoxy-5-nitrobenzamil (I-NMBA), which blocks the hair cell MG channel with an IC<sub>50</sub> of  $\sim$ 2  $\mu$ M.<br>However, this drug may be even more potent when mea-<br>sured in the absence of external divalent cations (see tent amiloride analog that has been found to date is 6-<br>iodide-2-methoxy-5-nitrobenzamil (I-NMBA), which de<br>blocks the hair cell MG channel with an  $IC_{50}$  of  $\sim$ 2  $\mu$ M. nu<br>However, this drug may be even more potent whe iodide-2-methoxy-<br>blocks the hair cel<br>However, this dru<br>sured in the abse<br>Section III.A.1.b).<br>d. SUMMARY. A ocks the hair cell MG channel with an  $IC_{50}$  of  $\sim$ 2  $\mu$ M. nurowever, this drug may be even more potent when mea-<br>red in the absence of external divalent cations (see ind<br>ction III.A.1.b).<br>d. SUMMARY. Although amilorid

However, this drug may be even more potent when mea-<br>sured in the absence of external divalent cations (see indicat<br>Section III.A.1.b). analog<br>d. SUMMARY. Although amiloride has not proven a classee<br>highly potent/specific Section III.A.1.b). and discussed in the MG cation III.A.1.b). and discussed in the MG channel blocker, it has provided valuable information regarding one type of MG Hordannel. First, amiloride sensitivity of the MG cation d. SUMMARY. Although amiloride has not proven a class highly potent/specific MG channel blocker, it has provided valuable information regarding one type of MG Ho channel. First, amiloride sensitivity of the MG cation like highly potent/specific MG channel blocker, it has provided valuable information regarding one type of MG channel. First, amiloride sensitivity of the MG cation channel provided the initial clue that this channel may someho vided valuable information regarding one type of MC<br>channel. First, amiloride sensitivity of the MG cation<br>channel provided the initial clue that this channel may<br>somehow be related to the amiloride-sensitive epithelia<br>Na channel. First, amiloride sensitivity of the MG cation<br>channel provided the initial clue that this channel may<br>somehow be related to the amiloride-sensitive epithelial<br>Na<sup>+</sup> channel. This idea has subsequently been rein-<br> channel provided the initial clue that this channel may al., 19%<br>somehow be related to the amiloride-sensitive epithelial of amil<br>Na<sup>+</sup> channel. This idea has subsequently been rein-<br>forced by (a) apparent immunological c somehow be related to the amiloride-sensitive epithelial  $Na^+$  channel. This idea has subsequently been reinforced by  $(a)$  apparent immunological cross-reactivity between the epithelial  $Na^+$  channel and the hair cell MG  $Na<sup>+</sup>$  channel. This idea has subsequently been rein-<br>forced by  $(a)$  apparent immunological cross-reactivity<br>between the epithelial  $Na<sup>+</sup>$  channel and the hair cell MG<br>channel for an antibody raised against the form between the epithelial Na<sup>+</sup> channel and the hair cell MG<br>channel for an antibody raised against the former K<br>(Hackney et al., 1992) and (b) sequence homology be-<br>tween the epithelial Na<sup>+</sup> channel and putative MG the<br>cha channel for an antibody raised against the form<br>(Hackney et al., 1992) and (*b*) sequence homology<br>tween the epithelial Na<sup>+</sup> channel and putative N<br>channel proteins (Canessa et al., 1994). Second, detai<br>analysis of amilo tween the epithelial Na<sup>+</sup> channel and putative MG the channel proteins (Canessa et al., 1994). Second, detailed analysis of amiloride block indicates multiple, voltagesisensitive open channel conformations of the MG cati channel proteins (Canessa et al., 1994). Second, detailed aminoglycosides block the open channel according to a<br>analysis of amiloride block indicates multiple, voltage-<br>sensitive open channel conformations of the MG cation channel proteins (Canessa et al., 1994). Second, detailed<br>analysis of amiloride block indicates multiple, voltage-<br>sensitive open channel conformations of the MG cation<br>channel. This feature must be incorporated into any<br>g analysis of amiloride block indicates multiple, voltage-<br>sensitive open channel conformations of the MG cation<br>channel. This feature must be incorporated into any of<br>gating model of the channel. Third, potency sequence bi<br> sensitive open channel conformations of the MG cation<br>channel. This feature must be incorporated into any<br>gating model of the channel. Third, potency sequence<br>fingerprinting using amiloride analogs provides a way of<br>identi channel. This feature must be incorporated into any of gating model of the channel. Third, potency sequence betting mariloride analogs provides a way of hidentifying MG channel involvement in specific cellular differencess gating model of the channel. Third, potency sequence by fingerprinting using amiloride analogs provides a way of hidentifying MG channel involvement in specific cellular deprocesses. Finally, because all amiloride analogs identifying MG channel involvement in specific cellular<br>processes. Finally, because all amiloride analogs so far<br>tested have proven more potent than amiloride, future<br>screening of the  $\sim$ 1000 available analogs may reveal processes. Finally, because all amiloride analogs so far ocesses. Finally, because all amiloride analogs so fare sted have proven more potent than amiloride, future reening of the  $\sim$ 1000 available analogs may reveal en more potent/specific MG channel blockers.<br>2. Aminoglycosid tested have proven more potent than amiloride, future sta<br>screening of the  $\sim$ 1000 available analogs may reveal lect<br>even more potent/specific MG channel blockers. and<br>2. Aminoglycoside antibiotics. Antibiotics of the am

even more potent/specific MG channel blockers.<br>
2. Aminoglycoside antibiotics. Antibiotics of the ami-<br>
noglycoside family (e.g., gentamicin, neomycin and<br>
streptomycin) also block MG cation channels in hair<br>
cells (Kroese 2. Aminoglycoside antibiotics. Antibiotics of the aminoglycoside family (e.g., gentamicin, neomycin and streptomycin) also block MG cation channels in hair cells (Kroese et al., 1989) and skeletal muscle (Sokabe et al., 19 noglycoside family (e.g., gentamicin, neomycin and<br>streptomycin) also block MG cation channels in hair<br>cells (Kroese et al., 1989) and skeletal muscle (Sokabe et<br>al., 1993). However, compared with amiloride, less de-<br>taile streptomycin) also block MG cation channels in ha<br>cells (Kroese et al., 1989) and skeletal muscle (Sokabe<br>al., 1993). However, compared with amiloride, less d<br>tailed information exists on their mechanism of actio<br>ionic int cells (Kroese et al., 1989) and skeletal muscle (Sokabe et has al., 1993). However, compared with amiloride, less de-<br>tailed information exists on their mechanism of action, and<br>ionic interactions and structure-activity re all, 1993). However, compared with anhioride, less de-<br>tailed information exists on their mechanism of action, are<br>ionic interactions and structure-activity requirements.<br>Aminoglycosides consist of two or more amino sugars ionic interactions and structure-activity requirements.<br>Aminoglycosides consist of two or more amino sugars in<br>glycosidic linkage to a hexose nucleus, and most have<br>several positive charges because each sugar may have<br>up t Aminoglycosides consist of two or more amino sugars in<br>glycosidic linkage to a hexose nucleus, and most have<br>several positive charges because each sugar may have<br>up to two positively charged amino residues (Daniels,<br>1978). glycosidic linkage to a hexose nucleus, and most have volse<br>veral positive charges because each sugar may have dep<br>to two positively charged amino residues (Daniels, be<br>1978). In contrast to amiloride analogs, aminoglycosi several positive charges because each sugar may have<br>up to two positively charged amino residues (Daniels,<br>1978). In contrast to amiloride analogs, aminoglycosides<br>are quite soluble  $(> 500 \text{ mM})$  in aqueous solution, whic up to two positively charged amino residues (Daniels, 1978). In contrast to amiloride analogs, aminoglycosides are quite soluble ( $> 500$  mM) in aqueous solution, which from a practical standpoint, makes them more convenie 1978). In contrast to amiloride analogs, aminoglycosides pare quite soluble  $(> 500 \text{ mM})$  in aqueous solution, which (S<br>from a practical standpoint, makes them more convenient also for experimental use (e.g., see Jaramill are quite soluble  $(>500 \text{ mM})$  in aqueous solution, which (Sokabe et al., 1993; and see table 2). Aminoglycosides<br>from a practical standpoint, makes them more convenient also block a variety of other MS processes (see Sec from a practical standpoint, makes them more convenient also<br>for experimental use (e.g., see Jaramillo and Hudspeth,  $\text{III.1}$ <br>1991). In terms of MG channel block, most attention has tand<br>focused on actions on hair cells for experimental use (e.g., see Jaramillo and Hudspe<br>1991). In terms of MG channel block, most attention l<br>focused on actions on hair cells because chronic exposite<br>to aminoglycosides causes hair cell death, resulting<br>clin 1991). In terms of MG channel block, most attention has tag<br>focused on actions on hair cells because chronic exposure<br>to aminoglycosides causes hair cell death, resulting in<br>clinically significant and irreversible hearing focused on actions on hair cells because chronic exposure cell<br>to aminoglycosides causes hair cell death, resulting in cha<br>clinically significant and irreversible hearing impair- (Git<br>ment (Rybak, 1986). Although the exact clinically significant and irreversible hearing impair-<br>ment (Rybak, 1986). Although the exact mechanism of<br>antibiotic ototoxicity is unknown, one possibility is an<br>action involving the MG channel (Denk et al., 1992). ment (Rybak, 1986). Although the exact mechanism of antibiotic ototoxicity is unknown, one possibility is an action involving the MG channel (Denk et al., 1992). The first acute studies of aminoglycoside action were on the

antibiotic ototoxicity is unknown, one possibility is a<br>action involving the MG channel (Denk et al., 1992).<br>The first acute studies of aminoglycoside action wer<br>on the hair cells of the amphibian lateral line organ<br>where action involving the MG channel (Denk et al., 1992).<br>The first acute studies of aminoglycoside action were<br>on the hair cells of the amphibian lateral line organ,<br>where gentamicin was shown to cause a reversible, dose-<br>depe

between the epithelial Na<sup>+</sup> channel and the hair cell MG rents approach zero with hyperpolarization (e.g., see<br>channel for an antibody raised against the former Kimitsuki and Ohmori, 1993) instead of approaching a<br>(Hackn even more potent/specific MG channel blockers. aptation in the hair cell (Howard et al., 1988; Hudspeth<br>2. Aminoglycoside antibiotics. Antibiotics of the ami-<br>nod Gillespie, 1994), and the availability of drugs that<br>noglyc fiber activity (Kroese and Van den Bercken, 1980, 1982). MCBRIDE<br>
fiber activity (Kroese and Van den Bercken, 1980, 1982).<br>
Subsequently, voltage-clamp studies of frog vestibular<br>
hair cells indicated a rapid (< 100  $\mu$ sec), voltage-depen-MCBRIDE<br>fiber activity (Kroese and Van den Bercken, 1980, 1<br>Subsequently, voltage-clamp studies of frog vesti<br>hair cells indicated a rapid ( $< 100$   $\mu$ sec), voltage-d<br>dent block of the MG currents by gentamicin a fiber activity (Kroese and Van den Bercken, 1980, 1982).<br>Subsequently, voltage-clamp studies of frog vestibular<br>hair cells indicated a rapid ( $\leq 100 \ \mu$ sec), voltage-depen-<br>dent block of the MG currents by gentamicin an fiber activity (Kroese and Van den Bercken, 1980, 1982).<br>Subsequently, voltage-clamp studies of frog vestibular<br>hair cells indicated a rapid ( $< 100 \ \mu$ sec), voltage-depen-<br>dent block of the MG currents by gentamicin and Subsequently, voltage-clamp studies of frog vestibular<br>hair cells indicated a rapid  $(< 100 \mu sec$ ), voltage-depen-<br>dent block of the MG currents by gentamicin and a<br>number of other aminoglycoside antibiotics (Kroese et<br>al., hair cells indicated a rapid  $(< 100 \mu \text{sec})$ , voltage-dependent block of the MG currents by gentamicin and a number of other aminoglycoside antibiotics (Kroese et al., 1989; and see table 2). Comparison of tables 1 and 2 i dent block of the MG currents by gentamicin and a<br>number of other aminoglycoside antibiotics (Kroese et<br>al., 1989; and see table 2). Comparison of tables 1 and 2<br>indicates the potency of aminoglycosides and amiloride<br>analo number of other aminoglycoside antibiotics (Kroese et al., 1989; and see table 2). Comparison of tables 1 and 2 indicates the potency of aminoglycosides and amiloride analogs are comparable. In addition, block by both cla al., 1989; and see table 2). Comparison of tables 1 and 2 indicates the potency of aminoglycosides and amiloride analogs are comparable. In addition, block by both classes of drugs is decreased by both depolarization or e indicates the potency of aminoglycosides and amiloride<br>analogs are comparable. In addition, block by both<br>classes of drugs is decreased by both depolarization or<br>external  $Ca^{2+}$  (Kroese et al., 1989; Lane et al., 1993).<br> analogs are comparable. In addition, block by both classes of drugs is decreased by both depolarization or external Ca<sup>2+</sup> (Kroese et al., 1989; Lane et al., 1993). However, despite these similarities, the two drugs most classes of drugs is decreased by both depolarization or external  $Ca^{2+}$  (Kroese et al., 1989); Lane et al., 1993).<br>However, despite these similarities, the two drugs most likely involve different blocking mechanisms (Kro external Ca<sup>2+</sup> (Kroese et al., 1989; Lane et al., 1993).<br>However, despite these similarities, the two drugs most<br>likely involve different blocking mechanisms (Kroese et<br>al., 1989). To begin with, the concentration depende However, despite these similarities, the two drugs most<br>likely involve different blocking mechanisms (Kroese et<br>al., 1989). To begin with, the concentration dependence<br>of aminoglycoside block indicates a Hill coefficient o likely involve different blocking mechanisms (Kroese et al., 1989). To begin with, the concentration dependence of aminoglycoside block indicates a Hill coefficient of 1, rather than the coefficient of 2 seen for amiloride al., 1989). To begin with, the concentration dependence<br>of aminoglycoside block indicates a Hill coefficient of 1,<br>rather than the coefficient of 2 seen for amiloride. Sec-<br>ond, with aminoglycosides, MG conductance and cur of aminoglycoside block indicates a Hill coefficient of 1,<br>rather than the coefficient of 2 seen for amiloride. Sec-<br>ond, with aminoglycosides, MG conductance and cur-<br>rents approach zero with hyperpolarization (e.g., see<br> rather than the coefficient of 2 seen for amiloride. Second, with aminoglycosides, MG conductance and currents approach zero with hyperpolarization (e.g., see<br>Kimitsuki and Ohmori, 1993) instead of approaching a<br>nonzero va ond, with aminoglycosides, MG conductance and currents approach zero with hyperpolarization (e.g., see<br>Kimitsuki and Ohmori, 1993) instead of approaching a<br>nonzero value, as seen with amiloride. Taken together,<br>these obser rents approach zero with hyperpolarization (e.g., see<br>Kimitsuki and Ohmori, 1993) instead of approaching a<br>nonzero value, as seen with amiloride. Taken together,<br>these observations are consistent with the idea that<br>aminogl Kimitsuki and Ohmori, 1993) instead of approaching a<br>nonzero value, as seen with amiloride. Taken together,<br>these observations are consistent with the idea that<br>aminoglycosides block the open channel according to a<br>simple nonzero value, as seen with amiloride. Taken togethe<br>these observations are consistent with the idea the<br>aminoglycosides block the open channel according to<br>simple plug model (see Section III.A.1.a). The voltaq<br>dependence these observations are consistent with the idea the aminoglycosides block the open channel according to simple plug model (see Section III.A.1.a). The voltage dependence of the block indicates that external aminoglycosides aminoglycosides block the open channel according to a<br>simple plug model (see Section III.A.1.a). The voltage<br>dependence of the block indicates that external amin-<br>oglycosides binding site senses 20 to 40% of the mem-<br>brane simple plug model (see Section III.A.1.a). The voltage<br>dependence of the block indicates that external amin-<br>oglycosides binding site senses 20 to 40% of the mem-<br>brane field (Kroese et al., 1989). In addition to blocking<br> dependence of the block indicates that external amin-<br>oglycosides binding site senses 20 to 40% of the mem-<br>brane field (Kroese et al., 1989). In addition to blocking<br>hair cell MG channels, aminoglycosides may also have<br>di oglycosides binding site senses 20 to 40% of the membrane field (Kroese et al., 1989). In addition to blocking<br>hair cell MG channels, aminoglycosides may also have<br>direct effects on the adaptation mechanism that changes<br>th hair cell MG channels, aminoglycosides may also have direct effects on the adaptation mechanism that changes the channel's mechanosensitivity in response to steady state stimulation (Kimitsuki and Ohmori, 1993). A mohair cell MG channels, aminoglycosides may also have<br>direct effects on the adaptation mechanism that changes<br>the channel's mechanosensitivity in response to steady<br>state stimulation (Kimitsuki and Ohmori, 1993). A mo-<br>lecu direct effects on the adaptation mechanism that changes<br>the channel's mechanosensitivity in response to steady<br>state stimulation (Kimitsuki and Ohmori, 1993). A mo-<br>lecular mechanism has been put forward to explain ad-<br>apt the channel's mechanosensitivity in response to steady<br>state stimulation (Kimitsuki and Ohmori, 1993). A mo-<br>lecular mechanism has been put forward to explain ad-<br>aptation in the hair cell (Howard et al., 1988; Hudspeth<br>an state stimulation (Kimitsuki and Ohmori, 1993). A mo-<br>lecular mechanism has been put forward to explain ad-<br>aptation in the hair cell (Howard et al., 1988; Hudspeth<br>and Gillespie, 1994), and the availability of drugs that<br> lecular mechanism has been put forward to explain ad-<br>aptation in the hair cell (Howard et al., 1988; Hudspeth<br>and Gillespie, 1994), and the availability of drugs that<br>affect adaptation should prove useful in analyzing suc aptation in the hair cell (Howard et al., 1988; Hudspeth<br>and Gillespie, 1994), and the availability of drugs that<br>affect adaptation should prove useful in analyzing such<br>mechanisms. Another practical use of aminoglycosides and Gillespie, 1994), and the availability of drugs that affect adaptation should prove useful in analyzing such mechanisms. Another practical use of aminoglycosides has been focal application of gentamicin to localize the affect adaptation should prove useful in analyzing such mechanisms. Another practical use of aminoglycosides has been focal application of gentamicin to localize the MG channels on the tips of the hair cell cilia (Jaramill rather than the coefficient of 2 seen for amiloride. Second, with aminoglycosides, MG conductance and currents approach zero with hyperpolarization (e.g., see Kimitsuki and Ohmori, 1993) instead of approaching a nonzero v

ment (Rybak, 1986). Although the exact mechanism of tracellular  $Ca^{2+}$  in guinea pig ventricular myocytes antibiotic ototoxicity is unknown, one possibility is an (Gannier et al., 1994). Although the aminoglycoside senac has been focal application of gentamicin to localize the MG channels on the tips of the hair cell cilia (Jaramillo and Hudspeth, 1991).<br>Aminoglycosides also block two different types of SA cation channels in chick skeleta MG channels on the tips of the hair cell cilia (Jaram<br>and Hudspeth, 1991).<br>Aminoglycosides also block two different types of<br>cation channels in chick skeletal muscle, namely a 60<br>voltage-independent channel and a 190 pS vo and Hudspeth, 1991).<br>
Aminoglycosides also block two different types of SA<br>
cation channels in chick skeletal muscle, namely a 60 pS<br>
voltage-independent channel and a 190 pS voltage-<br>
dependent channel. These two SA chann Aminoglycosides also block two different types of<br>cation channels in chick skeletal muscle, namely a 60<br>voltage-independent channel and a 190 pS volta<br>dependent channel. These two SA channels can furt<br>be distinguished phar cation channels in chick skeletal muscle, namely a 60 ps<br>voltage-independent channel and a 190 pS voltage<br>dependent channel. These two SA channels can furthe<br>be distinguished pharmacologically by their sequence<br>potency-fin voltage-independent channel and a 190 pS voltage-<br>dependent channel. These two SA channels can further<br>be distinguished pharmacologically by their sequence-<br>potency-fingerprint using various aminoglycosides<br>(Sokabe et al., dependent channel. These two SA channels can further<br>be distinguished pharmacologically by their sequence-<br>potency-fingerprint using various aminoglycosides<br>(Sokabe et al., 1993; and see table 2). Aminoglycosides<br>also bloc be distinguished pharmacologically by their sequence-<br>potency-fingerprint using various aminoglycosides<br>(Sokabe et al., 1993; and see table 2). Aminoglycosides<br>also block a variety of other MS processes (see Section<br>III.A. potency-fingerprint using various aminoglycosides<br>(Sokabe et al., 1993; and see table 2). Aminoglycosides<br>also block a variety of other MS processes (see Section<br>III.A.5), including the slow adapting activity of cat cu-<br>ta (Sokabe et al., 1993; and see table 2). Aminoglycosides<br>also block a variety of other MS processes (see Section<br>III.A.5), including the slow adapting activity of cat cu-<br>taneous mechanoreceptors (Baumann et al., 1988), hai also block a variety of other MS processes (see Section III.A.5), including the slow adapting activity of cat cutaneous mechanoreceptors (Baumann et al., 1988), hair cell activity in squid statocysts (Williamson, 1990), me III.A.5), including the slow adapting activity of cat cutaneous mechanoreceptors (Baumann et al., 1988), hair cell activity in squid statocysts (Williamson, 1990), mechanically induced nematocyte discharge in hydrozoans ( taneous mechanoreceptors (Baumann et al., 1988), hair<br>cell activity in squid statocysts (Williamson, 1990), me-<br>chanically induced nematocyte discharge in hydrozoans<br>(Gitter et al., 1993) and stretch-induced increase in i cell activity in squid statocysts (Williamson, 1990), mechanically induced nematocyte discharge in hydrozoans<br>(Gitter et al., 1993) and stretch-induced increase in in-<br>tracellular Ca<sup>2+</sup> in guinea pig ventricular myocytes<br> chanically induced nematocyte discharge in hydrozoans<br>
(Gitter et al., 1993) and stretch-induced increase in in-<br>
tracellular  $Ca^{2+}$  in guinea pig ventricular myocytes<br>
(Gannier et al., 1994). Although the aminoglycoside (Gitter et al., 1993) and stretch-induced increase in in-<br>tracellular  $Ca^{2+}$  in guinea pig ventricular myocytes<br>(Gannier et al., 1994). Although the aminoglycoside sen-<br>sitivity of these processes points to an underlying tracellular  $Ca^{2+}$  in guinea pig ventricular myocytes (Gannier et al., 1994). Although the aminoglycoside sensitivity of these processes points to an underlying MG channel mechanism, a complication in interpretation exis (Gannier et al., 1994). Although the aminoglycoside sen<br>sitivity of these processes points to an underlying MC<br>channel mechanism, a complication in interpretation<br>exists because aminoglycosides, like amiloride analogs<br>lac sitivity of these processes points to an underlying MG<br>channel mechanism, a complication in interpretation<br>exists because aminoglycosides, like amiloride analogs,<br>lack specificity and have been shown to also block volt-<br>a

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ounce the case is a complete that the complete of the activated K<sup>+</sup> channels (Nomura et al., 1991) and adenosine triphosphate-sensitive channels (Lin et al., 1993) as well as increasing desensitization of acetylcholine activated  $K^+$  channels (Nomura et al., 1991) and adenosine triphosphate-sensitive channels (Lin et al., 1993)<br>as well as increasing desensitization of acetylcholine<br>receptor channels (Okamoto et al., 1991). activated K<sup>+</sup> channels (Nomura et al., 199<br>osine triphosphate-sensitive channels (Lin<br>as well as increasing desensitization of a<br>receptor channels (Okamoto et al., 1991).<br>3. Gadolinium. Gadolinium (Gd<sup>3+</sup>) is th tivated K<sup>-</sup> channels (Nomura et al., 1991) and aden<br>ine triphosphate-sensitive channels (Lin et al., 1993<br>well as increasing desensitization of acetylcholine<br>ceptor channels (Okamoto et al., 1991).<br>3. *Gadolinium*. Gadoli

osine triphosphate-sensitive channels (Lin et al., 1993) Gd<br>as well as increasing desensitization of acetylcholine point<br>receptor channels (Okamoto et al., 1991). To rouse of MG channels and is often used Pice<br>monly used as well as increasing desensitization of acetylcholine point of the proceptor channels (Okamoto et al., 1991). The most com-<br>3. Gadolinium. Gadolinium (Gd<sup>3+</sup>) is the most com-<br>monly used blocker of MG channels and is oft receptor channels (Okamoto et al., 1991).<br>
3. Gadolinium. Gadolinium ( $Gd^{3+}$ ) is the most con<br>
monly used blocker of MG channels and is often use<br>
as a pharmacological tool for testing the putative ro<br>
of MG channels in 3. Gadolinium. Gadolinium  $(Gd^{3+})$  is the most com-<br>monly used blocker of MG channels and is often used<br>has a pharmacological tool for testing the putative role<br>the of MG channels in various MG processes. It is a mem-<br>iti monly used blocker of MG channels and is often used<br>as a pharmacological tool for testing the putative role<br>of MG channels in various MG processes. It is a mem-<br>ber of the lanthanide series, which is composed of the<br>15 ele as a pharmacological tool for testing the putative role these of MG channels in various MG processes. It is a mem-<br>ting ber of the lanthanide series, which is composed of the and 15 elements, inclusively, between lanthanu of MG channels in various MG processes. It is a mem-<br>
iting  $Ca^{2+}$ -permeable MG channels (see also Edwards<br>
ber of the lanthanide series, which is composed of the<br>
15 elements, inclusively, between lanthanum (La, confirm ber of the lanthanide series, which is composed of the<br>15 elements, inclusively, between lanthanum (La, contomic number 57, ionic radius 1.061 Å) and lutetium cu<br>(Lu, atomic number 71, ionic radius 0.85 Å), with Gd les<br>in 15 elements, inclusively, between lanthanum (La,<br>atomic number 57, ionic radius 1.061 Å) and lutetium<br>(Lu, atomic number 71, ionic radius 0.85 Å), with Gd<br>in the middle (atomic number 64, ionic radius 0.938<br>Å). All the la (Lu, atomic number 71, ionic radius 0.85 Å), with Gd<br>in the middle (atomic number 64, ionic radius 0.938<br>Å). All the lanthanides are trivalent ions in aqueous<br>solution and have proven useful in biochemical stud-<br>ies becau in the middle (atomic number 64, ionic radius 0.938 but also in fungi (Zhou et al., 1991), bacteria (Berrier et  $\hat{A}$ ). All the lanthanides are trivalent ions in aqueous al., 1992; Martinac, 1992; Cui et al., 1995; Hase in the middle (atomic number 64, ionic radius 0.<br>
Å). All the lanthanides are trivalent ions in aque<br>
solution and have proven useful in biochemical st<br>
ies because of their remarkable similarity to  $Ca^{2}$ <br>
terms of size A). All the lanthanides are trivalent ions in aqueous solution and have proven useful in biochemical studies because of their remarkable similarity to  $Ca^{2+}$  in terms of size (ionic radius 0.99 Å), bonding, coordination solution and have proven u<br>ies because of their remark<br>terms of size (ionic radius (<br>tion geometry and donor<br>1973; Evans, 1990).

ported that  $Gd^{3+}$  (10 to 250  $\mu$ M) blocked both thigmot-Millet and Pickard were the first to focus attention  $Gd^{3+}$  as a possible MG channel blocker when they ported that  $Gd^{3+}$  (10 to 250  $\mu$ M) blocked both thigm ropism and geotropism in plants, whereas similar c Millet and Pickard were the first to focus attention on Gd<sup>3+</sup> as a possible MG channel blocker when they reported that Gd<sup>3+</sup> (10 to 250  $\mu$ M) blocked both thigmotropism and geotropism in plants, whereas similar concent Millet and Pickard were the first to focus attention on  $Gd^{3+}$  as a possible MG channel blocker when they reported that  $Gd^{3+}$  (10 to 250  $\mu$ M) blocked both thigmotropism and geotropism in plants, whereas similar con Gd<sup>3+</sup> as a possible MG channel blocker when they re-<br>ported that Gd<sup>3+</sup> (10 to 250  $\mu$ M) blocked both thigmot-<br>ropism and geotropism in plants, whereas similar con-<br>centrations of La<sup>3+</sup> were without effect (Millet and<br> ported that  $Gd^{3+}$  (10 to 250  $\mu$ M) blocked both thigmorpism and geotropism in plants, whereas similar co<br>centrations of La<sup>3+</sup> were without effect (Millet an<br>Pickard, 1988). They hypothesized that  $Gd^{3+}$  blocker<br>the centrations of  $La^{3+}$  were without effect (Millet and Pickard, 1988). They hypothesized that  $Gd^{3+}$  blocked these mechanosensitive processes by specifically inhibiting  $Ca^{2+}$ -permeable MG channels (see also Edwards and Pickard, 1987). Subsequent patch clamp studies confirmed that  $Gd^{3+}$  did indeed block single MG channel currents in not only plant cells (Alexandre and Lassalles, 1991; Ding and Pickard, 1993a; Garrill et al., 1993). les, 1991; Ding and Pickard, 1993a; Garrill et al., 1993)<br>but also in fungi (Zhou et al., 1991), bacteria (Berrier et<br>al., 1992; Martinac, 1992; Cui et al., 1995; Hase et al.,<br>1995) and a variety of animal cells (see table al., 1992; Martinac, 1992; Cui et al., 1995; Hase et al., 1995) and a variety of animal cells (see table 3). In particular, Yang and Sachs (1989) showed that 10  $\mu$ M Gd<sup>3+</sup> in solutions perfused onto outside-out patches 1995) and a variety of animal cells (see table 3). In particular, Yang and Sachs (1989) showed that 10  $\mu$ M Gd<sup>3+</sup> in solutions perfused onto outside-out patches of *Xenopus* occytes completely and reversibly blocked MG

238 HAMILL ANISSEM HAMILL ANISSEM<br>study, much higher concentrations (i.e.,  $> 10 \times$ ) of ei-<br>ther La<sup>3+</sup> or Lu<sup>3+</sup> were required to cause MG channel 238<br>study, much higher concentrations (i.e.,  $> 10 \times$ ) of ei-<br>ther La<sup>3+</sup> or Lu<sup>3+</sup> were required to cause MG channel<br>block. block. ady, much higher concentrations (i.e.,  $> 10 \times$ ) of<br>er La<sup>3+</sup> or Lu<sup>3+</sup> were required to cause MG channels.<br>ock.<br>Generally, Gd<sup>3+</sup> blocks MG channels in the concention range of 1 to 100  $\mu$ M, independently of eith

study, much higher concentrations (i.e.,  $> 10 \times$ ) of ei-<br>ther La<sup>3+</sup> or Lu<sup>3+</sup> were required to cause MG channel<br>block.<br>Generally, Gd<sup>3+</sup> blocks MG channels in the concen-<br>tration range of 1 to 100  $\mu$ M, independently o ther La<sup>3+</sup> or Lu<sup>3+</sup> were required to cause MG channel neblock. Moreover, the conductance or ion selectivity of either single channel conductance or ion selectivity of the 19 MG channel (table 3). However, there are exce block.<br>
Generally, Gd<sup>3+</sup> blocks MG channels in the concentration range of 1 to 100  $\mu$ M, independently of either<br>
their single channel conductance or ion selectivity of the<br>
MG channel (table 3). However, there are exce Generally, Gd<sup>3+</sup> blocks MG channels in the concentration range of 1 to 100  $\mu$ M, independently of either their single channel conductance or ion selectivity of the MG channel (table 3). However, there are exceptions. Fo tration range of 1 to 100  $\mu$ M, independently of either SA<br>their single channel conductance or ion selectivity of the 199-<br>MG channel (table 3). However, there are exceptions. (c.f.,<br>For instance, in one study of *Escher* their single channel conductance or ion selectivity of the MG channel (table 3). However, there are exceptions.<br>For instance, in one study of *Escherichia coli* (*E. coli*), Gd<sup>3+</sup> in lower concentrations (20  $\mu$ M) was s MG channel (table 3). However, there are exceptions. (c.f.<br>For instance, in one study of *Escherichia coli* (*E. coli*), app<br>Gd<sup>3+</sup> in lower concentrations (20  $\mu$ M) was shown to in a<br>*increase* the activity of a 350 pS Gd<sup>3+</sup> in lower concentrations (20  $\mu$ M) was shown to *increase* the activity of a 350 pS and a 1100 pS channel but inhibit their activity in higher concentrations (> 20  $\mu$ M) (Cui et al., 1995). Similar concentration-d  $Gd^{3+}$  in lower concentrations (20  $\mu$ M) was shown to in atri-<br>increase the activity of a 350 pS and a 1100 pS channel channel<br>but inhibit their activity in higher concentrations (> 20 cytes ( $\mu$ M) (Cui et al., 1995). increase the activity of a 350 pS and a 1100 pS channel channel but inhibit their activity in higher concentrations ( $>20$  cyt  $\mu$ M) (Cui et al., 1995). Similar concentration-dependent can excitatory and inhibitory effec but inhibit their activity in higher concentrations ( $>20$   $\mu$ M) (Cui et al., 1995). Similar concentration-dependent excitatory and inhibitory effects were reported for MG cation channel activity in onion protoplasts by  $\mu$ M) (Cui et al., 1995). Similar concentration-dependent cexcitatory and inhibitory effects were reported for MG scation channel activity in onion protoplasts by Ding and Pickard (1993a). However, as noted by these auth excitatory and inhibitory effects were reported for MC<br>cation channel activity in onion protoplasts by Ding and<br>Pickard (1993a). However, as noted by these author:<br>(Ding and Pickard, 1993a), these mixed Gd<sup>3+</sup> effect:<br>see cation channel activity in onion protoplasts by Ding and ph<br>Pickard (1993a). However, as noted by these authors N,<br>(Ding and Pickard, 1993a), these mixed  $Gd^{3+}$  effects se<br>seen at low concentrations (0.1 to 2  $\mu$ M) are

MCBRIDE<br>to block larger conductance (300 to 2300 pS) MG chan-<br>nels without affecting lower conductance (100 to 220 ps MCBRIDE<br>to block larger conductance (300 to 2300 pS) MG chan-<br>nels without affecting lower conductance (100 to 220 pS)<br>MG channels (Berrier et al., 1992). Other exceptions MCBRIDE<br>to block larger conductance (300 to 2300 pS) MG channels without affecting lower conductance (100 to 220 pS)<br>MG channels (Berrier et al., 1992). Other exceptions<br>include the relatively low potency  $(\sim 1 \text{ mM})$  bloc to block larger conductance (300 to 2300 pS) MG channels without affecting lower conductance (100 to 220 pS) MG channels (Berrier et al., 1992). Other exceptions include the relatively low potency ( $\sim$ 1 mM) block of an S nels without affecting lower conductance (100 to 220 pS)<br>MG channels (Berrier et al., 1992). Other exceptions<br>include the relatively low potency ( $\sim$ 1 mM) block of an<br>SA K<sup>+</sup> channel in human myelinated nerve (Quastoff,<br> MG channels (Berrier et al., 1992). Other exceptions MG channels (Berrier et al., 1992). Other exceptions<br>include the relatively low potency  $(-1 \text{ mM})$  block of an<br>SA K<sup>+</sup> channel in human myelinated nerve (Quastoff,<br>1994) and a cation MG channel in one strain of yeast<br>(c.f. include the relatively low potency  $(-1 \text{ mM})$  block of an SA K<sup>+</sup> channel in human myelinated nerve (Quastoff, 1994) and a cation MG channel in one strain of yeast (c.f., Zhou and Kung, 1992; Zhou et al., 1991) and its app SA  $K^+$  channel in human myelinated nerve (Quastoff, 1994) and a cation MG channel in one strain of yeast (c.f., Zhou and Kung, 1992; Zhou et al., 1991) and its apparent ineffectiveness in blocking SA cation channels in 1994) and a cation MG channel in one strain of ye (c.f., Zhou and Kung, 1992; Zhou et al., 1991) and apparent ineffectiveness in blocking SA cation chann<br>in atrial heart muscle (Kim, 1993) as well as SA channels in astrocy (c.f., Zhou and Kung, 1992; Zhou et al., 1991) and<br>apparent ineffectiveness in blocking SA cation chann<br>in atrial heart muscle (Kim, 1993) as well as SA l<br>channels in astrocytes (Yang and Sachs, 1989), lympl<br>cytes (Schlict in atrial heart muscle (Kim, 1993) as well as SA K<sup>+</sup><br>channels in astrocytes (Yang and Sachs, 1989), lympho-<br>cytes (Schlicter and Sakellaropoulos, 1994) and mollus-<br>can neurons (Small and Morris, 1995). However, in some<br>st in atrial heart muscle (Kim, 1993) as well as SA K<sup>+</sup><br>channels in astrocytes (Yang and Sachs, 1989), lympho-<br>cytes (Schlicter and Sakellaropoulos, 1994) and mollus-<br>can neurons (Small and Morris, 1995). However, in some<br>s channels in astrocytes (Yang and Sachs, 1989), lymp<br>cytes (Schlicter and Sakellaropoulos, 1994) and moll<br>can neurons (Small and Morris, 1995). However, in so<br>studies, the presence of anions such as bicarbonate :<br>phosphate cytes (Schlicter and Sakellaropoulos, 1994) and mollus-<br>can neurons (Small and Morris, 1995). However, in some<br>studies, the presence of anions such as bicarbonate and<br>phosphate or the  $Ca^{2+}$  chelator, ethylene glycol-bis can neurons (Small and Morris, 1995). However, in some studies, the presence of anions such as bicarbonate and phosphate or the  $Ca^{2+}$  chelator, ethylene glycol-bis-<br>N,N'-tetracetic acid (EGTA), may contribute to the obs studies, the presence of anions such as bicarbonate a<br>phosphate or the  $Ca^{2+}$  chelator, ethylene glycol-b<br>N,N'-tetraacetic acid (EGTA), may contribute to the e<br>served low potencies. These chemicals interact with<br>chelate N,N'-tetraacetic acid (EGTA), may contribute to the observed low potencies. These chemicals interact with or chelate  $Gd^{3+}$  and therefore change its effective concentration (Boland et al., 1991).

Gd<sup>3+</sup> was shown tration (Boland et<br>TABLE 3<br>*Gadolinium block of MG and other channels*<br>Channel ordust Blocking

Species cell type	Ion selectivity	Channel conduct. (pS)	Blocking concent. [JM]	Reference(s)
<b>MG</b> channels				
E. coli	nonselective	300-2300	100	Berrier et al., 1992
E. coli	nonselective	350 and 1100	100	Cui et al., 1995
Saccharomyces (yeast)	nonselective	40	10	Gustin et al., 1988
Schizosacchar (yeast)	cation	180	1000	Zhou and Kung, 1992
Uromyces (fungi)	cation	600	50	Zhou et al., 1991
Hyphae (fungi)	cation		100	Garrill et al., 1993
Red beet vacuole	cation	70	10	Alexandre and Lasalles, 1991
Onion protoplast	cation	35	10	Ding and Pickard, 1993
Necturus kidney	cation	18	20	Filipovic and Sackin, 1991
Xenopus oocyte	cation	50	10	Yang and Sachs, 1989
Xenopus kidney	cation	70	10	Kawahara and Matsuzaki, 1993
Bone cell line	cation	40	20	Duncan et al., 1992
Guinea pig bladder	cation	80	20	Wellner and Isenberg, 1993; 1995
Mouse skeletal muscle	cation	20–50	>10	Franco and Lansman, 1990
Mouse skeletal muscle	cation (SI)	$20 - 50$	>10	Franco et al., 1991
Rat hepatoma cells	cation	40	50	Bear and Li. 1991
Rat supraoptic neurons	cation	$-30$	100	Oliet and Bourque, 1994
Mouse BC3H1 muscle	cation	30	100	Hamill and McBride, 1993
Rat cardiocytes	cation	42	$\mathbf{1}$	Sandoshima et al., 1992
Chick cardiocytes	cation	25 and 50	20	Ruknudin et al., 1993
<b>Chick cardiocytes</b>	$K^+$	100 and 200	20	Ruknudin et al., 1993
Human demyelinated axon	$K^+$	52	1000	Quasthoff, 1994
E. coli	anion	100-250	No effect 100	Berrier et al., 1992
Rat astrocyte	$K^+$	70	No effect 10	Yang and Sachs, 1989
Mouse Ehrlich ascites	cation	$15 - 40$	No effect 20	Christensen and Hoffmann, 1992
Rat atrial cells	cation	20	No effect 100 <sup>*</sup>	Kim, 1993
Rat atrial cells	$K^+$	50-100	No effect 100	Kim et al., 1995
Snail (Lymnaea) neur.	$K^+$	44	No effect 100 <sup>*</sup>	Small and Morris, 1995
<b>OTHER CHANNELS</b>				
Species, cell type	Channel type		[µM]	Reference
Guinea pig ventricul. myocytes	$Ca2+$ (L-type)		10	Lacampagne et al., 1994
Rat pituitary	$Ca2+$ (L-type)		$0.2$	Biagi and Enyeart, 1990
Rat pituitary	$Ca2+$ (T-type)		$2.5\,$	Biagi and Enveart, 1990
Xenopus myelinated nerve	$K^+$ (delayed rec.)		100	Elinder and Arhem, 1994
Xenopus myelinated nerve	$Na+$ (voltage-gated)		100	Elinder and Arhem, 1994
E. coli	Colicin A. N		30,100	Bonhivers et al., 1995
Bryonica dioica (plant)		Ca <sup>2+</sup> -release channel ER membrane	10	Kluesener et al., 1995

**a EGTA** present with Gd<sup>3+</sup>.<br>All channels are SA unless indicated SI.

PHARMACOLOGICAL REVIEWS

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PHARMACOLOGY OF MECHANOGATED<br>a. MECHANISM OF GD<sup>3+</sup> ACTION. To date, no detailed 1994<br>mechanism for Gd<sup>3+</sup> block of any MG channel has been of<br>determined. One reason for this, at least for SA chan-of PHARMACOLOGY OF MECHANISM OF GD<sup>3+</sup> ACTION. To date, no detaile<br>mechanism for  $Gd^{3+}$  block of any MG channel has bee<br>determined. One reason for this, at least for SA chan-<br>nels, may be that  $Gd^{3+}$  action is complex an a. MECHANISM OF GD<sup>3+</sup> ACTION. To date, no detailed 19<br>mechanism for Gd<sup>3+</sup> block of any MG channel has been of<br>determined. One reason for this, at least for SA chan-of<br>nels, may be that Gd<sup>3+</sup> action is complex and most a. MECHANISM OF GD<sup>3+</sup> ACTION. To date, no detailed 1<br>mechanism for Gd<sup>3+</sup> block of any MG channel has been<br>determined. One reason for this, at least for SA chan-<br>nels, may be that Gd<sup>3+</sup> action is complex and most likely mechanism for  $Gd^{3+}$  block of any MG channel has bee<br>determined. One reason for this, at least for SA channels, may be that  $Gd^{3+}$  action is complex and most like<br>has multiple mechanisms and sites of action dependin<br>u nels, may be that  $Gd^{3+}$  action is complex and most likely di<br>has multiple mechanisms and sites of action depending in<br>upon its concentration. In addition to any specific inter-<br>actions with membrane channel proteins, has multiple mechanisms and sites of action depending<br>upon its concentration. In addition to any specific inter-<br>actions with membrane channel proteins,  $Gd^{3+}$ , as well<br>as other lanthanides, has been shown to exhibit st upon its concentration. In addition to any specific inter-<br>actions with membrane channel proteins,  $Gd^{3+}$ , as well<br>as other lanthanides, has been shown to exhibit strong<br>interactions with lipid bilayers. For example, la as other lanthanides, has been shown to exhibit strong interactions with lipid bilayers. For example, lanthanides bind strongly to both charged and neutral bilayers (Lehrmann and Seelig, 1994). Furthermore, difas other lanthanides, has been shown to exhibit strong<br>interactions with lipid bilayers. For example, lan-<br>thanides bind strongly to both charged and neutral bi-<br>layers (Lehrmann and Seelig, 1994). Furthermore, dif-<br>ferent interactions with lipid bilayers. For example, lanthanides bind strongly to both charged and neutral bilayers (Lehrmann and Seelig, 1994). Furthermore, differential scanning calorimetric and freeze-fracture studies have sh thanides bind strongly to both charged and neutral bi-<br>layers (Lehrmann and Seelig, 1994). Furthermore, dif-<br>ferential scanning calorimetric and freeze-fracture<br>studies have shown that lanthanides are capable of in-<br>creasi layers (Lehrmann and Seelig, 1994). Furthermore, dif-<br>ferential scanning calorimetric and freeze-fracture d<br>studies have shown that lanthanides are capable of in-<br>creasing phase transition temperatures, decreasing is<br>membr ferential scanning calorimetric and freeze-fracture displays no voltage dependence, the rate of unblocking<br>studies have shown that lanthanides are capable of in-<br>creasing phase transition temperatures, decreasing is drive studies have shown that lanthanides are capable of increasing phase transition temperatures, decreasing<br>membrane fluidity and promoting phase separations of<br>domains and membrane dipole potentials (Li et al.<br>1994; Yu et al. creasing phase transition temperatures, decreasing is<br>membrane fluidity and promoting phase separations or<br>domains and membrane dipole potentials (Li et al., ch<br>1994; Yu et al., 1996). Such effects may alter MG chan-<br>cal a membrane fluidity and promoting phase separations or<br>domains and membrane dipole potentials (Li et al., cl<br>1994; Yu et al., 1996). Such effects may alter MG chan-<br>nel activity by changing the physical environment of the<br>se domains and membrane dipole potentials (Li et al., 1994; Yu et al., 1996). Such effects may alter MG channel activity by changing the physical environment of the membrane channel protein (Yu et al., 1996). In relation to t 1994; Yu et al., 1996). Such effects may alter MG changel and nearly the physical environment of the membrane channel protein (Yu et al., 1996). In relation these ideas, temperature studies of MG channel tivity in plant ce membrane channel protein (Yu et al., 1996). In relation<br>to these ideas, temperature studies of MG channel ac-<br>tivity in plant cells indicate a membrane phase transi-<br>tion that affects MG channel activity (Ding and Pickard, 1993b). these ideas, temperature studies of MG channel ac-<br>
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about).<br>
The most detailed analysis of  $Gd^{3+}$ 

tivity in plant cells indicate a membrane phase transition that affects MG channel activity (Ding and Pickard, 1993b).<br>The most detailed analysis of Gd<sup>3+</sup> block has been carried out on the *Xenopus* oocyte SA cation chann tion that affects MG channel activity (Ding and Pickard, 1993b).<br>
The most detailed analysis of  $Gd^{3+}$  block has been<br>
carried out on the *Xenopus* oocyte SA cation channel<br>
(Yang and Sachs, 1989). The properties of the 1993b). contract the most detailed analysis of  $Gd^{3+}$  block has been  $Ca^{2+}$  carried out on the *Xenopus* occyte SA cation channel (Tag) (Yang and Sachs, 1989). The properties of the various Fran  $Gd^{3+}$  effects on thi The most detailed analysis of  $Gd^{3+}$  block has been<br>carried out on the *Xenopus* occyte SA cation channel<br>(Yang and Sachs, 1989). The properties of the various<br> $Gd^{3+}$  effects on this channel and the extremely narrow<br>c carried out on the *Xenopus* oocyte SA cation channel (Yang and Sachs, 1989). The properties of the varior Gd<sup>3+</sup> effects on this channel and the extremely narriconcentration range (5 to 10  $\mu$ M) over which they occeem t (Yang and Sachs, 1989). The properties of the various  $Gd^{3+}$  effects on this channel and the extremely narrow concentration range (5 to 10  $\mu$ M) over which they occuse a com-<br>seem to rule out a simple open channel bloc  $Gd^{3+}$  effects on this channel and the extremely narrow concentration range (5 to 10  $\mu$ M) over which they occur seem to rule out a simple open channel block mechanism. Instead, Yang and Sachs (1989) proposed a combina concentration range (5 to 10  $\mu$ M) over which they occents are to rule out a simple open channel block mech mism. Instead, Yang and Sachs (1989) proposed a co bination of three different mechanisms that are evide at diff seem to rule out a simple open channel block mechanism. Instead, Yang and Sachs (1989) proposed a combination of three different mechanisms that are evident at different Gd<sup>3+</sup> concentrations. First, at low concentrations mism. Instead, Yang and Sachs (1989) proposed a com-<br>bination of three different mechanisms that are evident metal<br>at different Gd<sup>3+</sup> concentrations. First, at low concen-<br>trations (1 to 5  $\mu$ M), the Gd<sup>3+</sup> reduced sing bination of three different mechanisms that are evident nat different  $Gd^{3+}$  concentrations. First, at low concentrations (1 to 5  $\mu$ M), the  $Gd^{3+}$  reduced single channel pourrent amplitude, seen as an almost paralle current amplitude, seen as an almost parallel shift of the single channel current-voltage curve along the voltage axis, was proposed to be caused by  $Gd^{3+}$  screening of negative surface charges in or near the vestibule axis, was proposed to be caused by  $Gd^{3+}$  screening of single channel current-voltage curve along the voltage axis, was proposed to be caused by  $Gd^{3+}$  screening of negative surface charges in or near the vestibule of the channel. Second, also at low concentrations, the obs axis, was proposed to be caused by  $Gd^{3+}$  screening of negative surface charges in or near the vestibule of the channel. Second, also at low concentrations, the observed voltage-independent reduction in open channel lif negative surface charges in or near the vestibule of the channel. Second, also at low concentrations, the observed voltage-independent reduction in open channelifetime was proposed to be caused by  $Gd^{3+}$  interactine wit channel. Second, also at low concentrations, the ob-<br>served voltage-independent reduction in open channel Tm<br>lifetime was proposed to be caused by  $Gd^{3+}$  interacting equ<br>with an external allosteric site (i.e., outside t served voltage-independent reduction in open channel<br>lifetime was proposed to be caused by  $Gd^{3+}$  interacting<br>with an external allosteric site (i.e., outside the mem-<br>brane field) that caused transition of the channel t with an external allosteric site (i.e., outside the membrane field) that caused transition of the channel to a short-lived closed state. Finally, at 10  $\mu$ M but not 5  $\mu$ M, channel activity completely disappeared. This with an external allosteric site (i.e., outside the mem-<br>brane field) that caused transition of the channel to a<br>short-lived closed state. Finally, at 10  $\mu$ M but not 5  $\mu$ M,<br>channel activity completely disappeared. Thi brane field) that caused transition of the channel to a 1<br>short-lived closed state. Finally, at 10  $\mu$ M but not 5  $\mu$ M,<br>channel activity completely disappeared. This last effect<br>was believed to occur because of a Gd<sup>3+</sup> short-lived closed state. Finally, at 10  $\mu$ M but not 5  $\mu$ M, channel activity completely disappeared. This last effect was believed to occur because of a Gd<sup>3+</sup>-induced, highly has cooperative transition of the channel channel activity completely disappeared. This last effect<br>was believed to occur because of a  $Gd^{3+}$ -induced, highly<br>cooperative transition of the channel to a long-lived<br>closed state. Such highly cooperative behavior wo was believed to occur because of a  $Gd^{3+}$ -induced, highly has cooperative transition of the channel to a long-lived ble closed state. Such highly cooperative behavior would be ble consistent with  $Gd^{3+}$ -induced shifts cooperative trans<br>closed state. Such<br>consistent with Gor<br>or promotion of p<br>discussed above.<br>Although most beed state. Such highly cooperative behavior would has<br>istent with  $Gd^{3+}$ -induced shifts in phase transition<br>promotion of phase domains in the lipid bilayer, a<br>scussed above.<br>Although most  $Gd^{3+}$  studies have been on

or promotion of phase domains in the lipid bilayer, as <br>discussed above.<br>Although most  $Gd^{3+}$  studies have been on SA chan-<br>hels, there is at least one detailed report describing N<br> $Gd^{3+}$  block of the so-called SI cat discussed above. 19<br> *(mdx)* muscle ( $\text{Gd}^{3+}$  studies have been on SA chan-<br>
hels, there is at least one detailed report describing Na<br>  $\text{Gd}^{3+}$  block of the so-called SI cation channel in mouse pe<br>
(*mdx*) muscle Although most  $Gd^{3+}$  studies have been on SA channels, there is at least one detailed report describing  $Gd^{3+}$  block of the so-called SI cation channel in mouse  $(mdx)$  muscle (Franco et al., 1991). This study found, as nels, there is at least one detailed report describing  $Gd^{3+}$  block of the so-called SI cation channel in mous  $(mdx)$  muscle (Franco et al., 1991). This study found, a with the SA cation channel, that  $Gd^{3+}$  block can  $Gd^{3+}$  block of the so-called SI cation channel in mouse  $(mdx)$  muscle (Franco et al., 1991). This study found, as with the SA cation channel, that  $Gd^{3+}$  block can occur with no shift in the mechanosensitivity (i.e.,

PHARMACOLOGY OF MECHANOGATED MEMBRANE ION CHANNELS 239<br>a. MECHANISM OF GD<sup>3+</sup> ACTION. To date, no detailed 1991; Yang and Sachs, 1989). Nevertheless, comparison mechanism for  $Gd^{3+}$  block of any MG channel has been of the voltage- and concentration-dependent properties determined. One reason for this, at least for SA chan-of  $Gd^{3+}$  block of SI and SA channels indicates notabl nels, may be that  $Gd^{3+}$  action is complex and most likely differences. In particular, the block of the SI channel<br>has multiple mechanisms and sites of action depending involves brief, yet resolvable, channel closures w ED MEMBRANE ION CHANNELS<br>1991; Yang and Sachs, 1989). Nevertheless, comparison<br>of the voltage- and concentration-dependent properties ED MEMBRANE ION CHANNELS<br>1991; Yang and Sachs, 1989). Nevertheless, comparison<br>of the voltage- and concentration-dependent properties<br>of Gd<sup>3+</sup> block of SI and SA channels indicates notable ED MEMBRANE ION CHANNELS 239<br>1991; Yang and Sachs, 1989). Nevertheless, comparison<br>of the voltage- and concentration-dependent properties<br>of  $Gd^{3+}$  block of SI and SA channels indicates notable<br>differences. In particula 1991; Yang and Sachs, 1989). Nevertheless, comparison<br>of the voltage- and concentration-dependent properties<br>of  $Gd^{3+}$  block of SI and SA channels indicates notable<br>differences. In particular, the block of the SI channe 1991; Yang and Sachs, 1989). Nevertheless, comparison<br>of the voltage- and concentration-dependent properties<br>of  $Gd^{3+}$  block of SI and SA channels indicates notable<br>differences. In particular, the block of the SI channe of the voltage- and concentration-dependent proper<br>of  $Gd^{3+}$  block of SI and SA channels indicates nota<br>differences. In particular, the block of the SI chan<br>involves brief, yet resolvable, channel closures with<br>change i of  $Gd^{3+}$  block of SI and SA channels indicates notable differences. In particular, the block of the SI channel involves brief, yet resolvable, channel closures with no change in single channel current amplitude. Furthe differences. In particular, the block of the SI channel<br>involves brief, yet resolvable, channel closures with no<br>change in single channel current amplitude. Further-<br>more, the voltage and concentration dependence of the<br>op involves brief, yet resolvable, channel closures with no<br>change in single channel current amplitude. Further-<br>more, the voltage and concentration dependence of the<br>open-close transitions indicates a blocking mechanism<br>con change in single channel current amplitude. Furthermore, the voltage and concentration dependence of the open-close transitions indicates a blocking mechanism consistent with  $Gd^{3+}$  being an open pore, permeant blocker. more, the voltage and concentration dependence of the open-close transitions indicates a blocking mechanism consistent with  $Gd^{3+}$  being an open pore, permeant blocker. To be specific, although the blocking rate (i.e., open-close transitions indicates a blocking mechanism<br>consistent with  $Gd^{3+}$  being an open pore, permeant<br>blocker. To be specific, although the blocking rate (i.e.,<br> $Gd^{3+}$  entry into the channel) is diffusion-limited blocker. To be specific, although the blocking rate (i.e.,  $Gd^{3+}$  entry into the channel) is diffusion-limited and displays no voltage dependence, the rate of unblocking increases with hyperpolarization, presumably as blocker. To be specific, althought displays no voltage dependence displays no voltage dependence increases with hyperpolarization is driven through the channel. The differences in  $Gd^{3+}$  blow  $H^{3+}$  entry into the channel) is diffusion-limited and<br>splays no voltage dependence, the rate of unblocking<br>creases with hyperpolarization, presumably as  $Gd^{3+}$ <br>driven through the channel.<br>The differences in  $Gd^{3+}$ 

at different  $Gd^{3+}$  concentrations. First, at low concen-<br>trations (1 to 5  $\mu$ M), the  $Gd^{3+}$  reduced single channel physical basis for  $Gd^{3+}$ 's higher potency compared with<br>current amplitude, seen as an almost para displays no voltage dependence, the rate of unblocking<br>increases with hyperpolarization, presumably as  $Gd^{3+}$ <br>is driven through the channel.<br>The differences in  $Gd^{3+}$  block of SI and SA cation<br>channels may reflect rea increases with hyperpolarization, presumably as  $Gd^{3+}$ <br>is driven through the channel.<br>The differences in  $Gd^{3+}$  block of SI and SA cation<br>channels may reflect real differences in the nature of<br> $Gd^{3+}$  interactions wi is driven through the channel.<br>The differences in  $Gd^{3+}$  block of SI and SA cation<br>channels may reflect real differences in the nature<br> $Gd^{3+}$  interactions with the two channels. Howeve<br>strict comparison between the tw channels may reflect real differences in the nature of  $Gd^{3+}$  interactions with the two channels. However, strict comparison between the two studies is complicated because of the different ionic conditions. In the SI ca channels may reflect real differences in the nature of  $Gd^{3+}$  interactions with the two channels. However strict comparison between the two studies is complicated because of the different ionic conditions. In the Scase,  $Gd^{3+}$  interactions with the two channels. However,<br>strict comparison between the two studies is compli-<br>cated because of the different ionic conditions. In the SI<br>case,  $Gd^{3+}$  block was measured in the presence of di strict comparison between the two studies is complicated because of the different ionic conditions. In the SI case,  $Gd^{3+}$  block was measured in the presence of divalent cations (2 mM  $Ca^{2+}$  and 1 mM  $Mg^{2+}$ ) but in t cated because of the different ionic conditions. In the SI<br>case,  $Gd^{3+}$  block was measured in the presence of diva-<br>lent cations (2 mM  $Ca^{2+}$  and 1 mM  $Mg^{2+}$ ) but in their<br>absence in the SA case. This difference undo case,  $Gd^{3+}$  block was measured in the presence of diva-<br>lent cations (2 mM  $Ca^{2+}$  and 1 mM  $Mg^{2+}$ ) but in their<br>absence in the SA case. This difference undoubtedly<br>contributes to the different blocking effects becau lent cations  $(2 \text{ mM } Ca^{2+} \text{ and } 1 \text{ mM } Mg^{2+})$  but in their absence in the SA case. This difference undoubtedly contributes to the different blocking effects because  $Ca^{2+}$  also permeates and blocks both channel types (Tag absence in the SA case. This difference undoubtedly<br>contributes to the different blocking effects because<br> $Ca^{2+}$  also permeates and blocks both channel types<br>(Taglietti and Toselli, 1988; Yang and Sachs, 1989;<br>Franco et contributes to the different blocking effects because  $Ca^{2+}$  also permeates and blocks both channel types (Taglietti and Toselli, 1988; Yang and Sachs, 1989; Franco et al., 1991; Lane et al., 1993). Clearly, more detaile  $Ca^{2+}$  also permeates and blocks both channel types<br>(Taglietti and Toselli, 1988; Yang and Sachs, 1989;<br>Franco et al., 1991; Lane et al., 1993). Clearly, more<br>detailed experiments on  $Gd^{3+}$  action under similar re-<br>cor Franco et al., 1991; Lane et al., 1993). Clearly, more<br>detailed experiments on  $Gd^{3+}$  action under similar re-<br>cording conditions would be helpful. Furthermore, a<br>more systematic study of the blocking effect of the othe Franco et al., 1991; Lane et al., 1993). Clearly, more<br>detailed experiments on  $Gd^{3+}$  action under similar re-<br>cording conditions would be helpful. Furthermore, a<br>more systematic study of the blocking effect of the othe detailed experiments on  $Gd^{3+}$  action under similar cording conditions would be helpful. Furthermore, more systematic study of the blocking effect of the oth 15 lanthanides of SA and SI channels may provide means of dis cording conditions would be helpful. Furthermore, a<br>more systematic study of the blocking effect of the other<br>15 lanthanides of SA and SI channels may provide a<br>means of dissecting or distinguishing different mecha-<br>nisms more systematic study of the blocking effect of the other 15 lanthanides of SA and SI channels may provide a means of dissecting or distinguishing different mechanisms and sites of action. For example, one possible physic 15 lanthanides of SA and SI channels may provide a<br>means of dissecting or distinguishing different mecha-<br>nisms and sites of action. For example, one possible<br>physical basis for Gd<sup>3+</sup>'s higher potency compared with<br>other means of dissecting or distinguishing different mechanisms and sites of action. For example, one possible physical basis for  $Gd^{3+s}$  higher potency compared with other lanthanides is the "gadolinium break," a term that r misms and sites of action. For example, one possible<br>physical basis for  $Gd^{3+s}$ s higher potency compared with<br>other lanthanides is the "gadolinium break," a term that<br>refers to the drastic change in the stability of orga The differences in Gd<sup>3+</sup> block of SI and SA cation<br>
channels may reflect real differences in the nature of<br>
Gd<sup>3+</sup> interactions with the two studies is compli-<br>
cated because of the different ionic conditions. In the SI<br> other lanthanides is the "gadolinium break," a term that refers to the drastic change in the stability of organic is complexes that occurs around the middle of the lanthanide series (Nieboer, 1975). On the other hand, it refers to the drastic change in the stability of organic ion<br>complexes that occurs around the middle of the lan-<br>thanide series (Nieboer, 1975). On the other hand, it is<br>interesting that in one systematic study of lanthan complexes that occurs around the middle of the lan-<br>thanide series (Nieboer, 1975). On the other hand, it is<br>interesting that in one systematic study of lanthanides,<br> $Tm^{3+}$ ,  $Er^{3+}$ ,  $Dy^{3+}$   $Tb^{3+}$ ,  $Eu^{3+}$  were foun thanide series (Nieboer, 1975). On the other hand, it is<br>interesting that in one systematic study of lanthanides,<br>Tm<sup>3+</sup>, Er<sup>3+</sup>, Dy<sup>3+</sup> Tb<sup>3+</sup>, Eu<sup>3+</sup> were found to be as<br>equally potent as Gd<sup>3+</sup> in blocking the touch-ind 1993). equally potent as  $Gd^{3+}$  in blocking the touch-induced<br>action potential of the plant *Chara* (Staves and Wayne,<br>1993).<br>b.  $GD^{3+}$  BLOCK OF NON-MG CHANNELS. Although  $Gd^{3+}$ <br>was initially thought to be selective for MG action potential of the plant Chara (Staves and Wayne,

consistent with Gd<sup>3+</sup>-induced shifts in phase transitions nels (Biagi and Enyeart, 1990; Boland et al., 1991;<br>or promotion of phase domains in the lipid bilayer, as Docherty, 1988; Song et al., 1992; Lacampagne et al.,<br>d action potential of the plant *Chara* (Staves and Wayne, 1993).<br>
b.  $GD^{3+}$  BLOCK OF NON-MG CHANNELS. Although  $Gd^{3+}$ <br>
was initially thought to be selective for MG channels, it<br>
has subsequently been shown to be a parti 1993).<br>b. GD<sup>3+</sup> BLOCK OF NON-MG CHANNELS. Although Gd<sup>3+</sup><br>was initially thought to be selective for MG channels, it<br>has subsequently been shown to be a particularly potent<br>blocker of voltage-gated L-type Ca<sup>2+</sup> channels b.  $GD^{3+}$  BLOCK OF NON-MG CHANNELS. Although  $Gd^3$  was initially thought to be selective for MG channels, has subsequently been shown to be a particularly poter blocker of voltage-gated L-type  $Ca^{2+}$  channels (complet was initially thought to be selective for MG channels, it<br>has subsequently been shown to be a particularly potent<br>blocker of voltage-gated L-type  $Ca^{2+}$  channels (complete<br>block with 0.2  $\mu$ M) as well as T- and N-type has subsequently been shown to be a particularly potent<br>blocker of voltage-gated L-type  $Ca^{2+}$  channels (complete<br>block with  $0.2 \mu M$ ) as well as T- and N-type  $Ca^{2+}$  chan-<br>nels (Biagi and Enyeart, 1990; Boland et al., blocker of voltage-gated L-type Ca<sup>2+</sup> channels (complete<br>block with 0.2  $\mu$ M) as well as T- and N-type Ca<sup>2+</sup> chan-<br>nels (Biagi and Enyeart, 1990; Boland et al., 1991;<br>Docherty, 1988; Song et al., 1992; Lacampagne et al block with 0.2  $\mu$ M) as well as T- and N-type Ca<sup>2+</sup> channels (Biagi and Enyeart, 1990; Boland et al., 1991; Docherty, 1988; Song et al., 1992; Lacampagne et al., 1994; Romano-Silva et al., 1994). Furthermore, it also bl nels (Biagi and Enyeart, 1990; Boland et al., 1<br>Docherty, 1988; Song et al., 1992; Lacampagne e<br>1994; Romano-Silva et al., 1994). Furthermore, it<br>blocks, although less potently (~100  $\mu$ M), voltage- $\mu$ Na<sup>+</sup> channels and Docherty, 1988; Song et al., 1992; Lacampagne et al., 1994; Romano-Silva et al., 1994). Furthermore, it also blocks, although less potently  $(\sim 100 \ \mu)$ , voltage-gated Na<sup>+</sup> channels and K<sup>+</sup> channels as well as voltage-i 1994; Romano-Silva et al., 1994). Furthermore, it also<br>blocks, although less potently  $(\sim 100 \ \mu$ M), voltage-gated<br>Na<sup>+</sup> channels and K<sup>+</sup> channels as well as voltage-inde-<br>pendent leak channels in myelinated nerves (Elin blocks, although less potently  $(\sim 100 \mu)$ , voltage-gated Na<sup>+</sup> channels and K<sup>+</sup> channels as well as voltage-independent leak channels in myelinated nerves (Elinder and Arhem, 1994a). A multisite mechanism of block simil Na<sup>+</sup> channels and K<sup>+</sup> channels as well as voltage-inde-<br>pendent leak channels in myelinated nerves (Elinder<br>and Arhem, 1994a). A multisite mechanism of block<br>similar to that of Yang and Sachs has been proposed for<br> $Gd^{3$ and Arhem, 1994a). A multisite mechanism of block<br>similar to that of Yang and Sachs has been proposed for<br> $Gd^{3+}$  block of voltage-gated Na<sup>+</sup> and K<sup>+</sup> channels<br>(Elinder and Arhem, 1994b). On the other hand, a de-

240 **HAMILL AND MC**<br>tailed analysis of the block of L-type  $Ca^{2+}$  channels by c.<br> $Gd^{3+}$  and other lanthanides indicates a mechanism sim-ogy EXTE and the block of L-type Ca<sup>2+</sup> channels by<br>Gd<sup>3+</sup> and other lanthanides indicates a mechanism sim-<br>ilar to that used to explain Gd<sup>3+</sup> block of the SI channel <sup>HAMILL</sup> AN<br>tailed analysis of the block of L-type  $Ca^{2+}$  channels by<br> $Gd^{3+}$  and other lanthanides indicates a mechanism sim-<br>ilar to that used to explain  $Gd^{3+}$  block of the SI channel<br>(Lansman, 1990). tailed analysis of the block of L-type  $Ca^{2+}$  channels by  $Gd^{3+}$  and other lanthanides indicates a mechanism sim-<br>ilar to that used to explain  $Gd^{3+}$  block of the SI channel channel (Lansman, 1990).<br>c. SUMMARY.  $Gd^{3$ 

 $Gd^{3+}$  and other lanthanides indicates a mechanism similar to that used to explain  $Gd^{3+}$  block of the SI channel (Lansman, 1990).<br>
c. SUMMARY.  $Gd^{3+}$  is a potent blocker of a wide variety of MG channels and, as pre ilar to that used to explain  $Gd^{3+}$  block of the SI channel<br>
(Lansman, 1990).<br>
c. SUMMARY.  $Gd^{3+}$  is a potent blocker of a wide variety<br>
of MG channels and, as predicted by Millet and Pickard,<br>
has proven to be the in (Lansman, 1990). also<br>c. SUMMARY.  $Gd^{3+}$  is a potent blocker of a wide variety<br>of MG channels and, as predicted by Millet and Pickard, sen<br>has proven to be the inhibitor of choice for testing the<br>tive putative role of M c. SUMMARY.  $Gd^{3+}$  is a potent blocker of a wide variety analogy, one might expect that SA K<sup>+</sup> channels would be of MG channels and, as predicted by Millet and Pickard, sensitive to the various toxins and drugs that ac of MG channels and, as predicted by Millet and Pickard<br>has proven to be the inhibitor of choice for testing the<br>putative role of MG channels in MG processes, not only<br>in plants, but in a wide range of animal cells (see tab has proven to be the inhibitor of choice for testing the tive putative role of MG channels in MG processes, not only blue in plants, but in a wide range of animal cells (see table in 4). Its action, at least on the SA cati putative role of MG channels in MG processes, not only his plants, but in a wide range of animal cells (see table is 4). Its action, at least on the SA cation channel, is complex, and more detailed studies taking advantage in plants, but in a wide range of animal cells (see ta)<br>4). Its action, at least on the SA cation channel, is co<br>plex, and more detailed studies taking advantage of t<br>other lanthanides and their known physical chemis<br>shoul 4). Its action, at least on the SA cation channel, plex, and more detailed studies taking advantage other lanthanides and their known physical channolation should be helpful in distinguishing different misms and sites (i.e ex, and more detailed studies taking advantage of the time lanthanides and their known physical chemistry chould be helpful in distinguishing different mechasisms and sites (i.e., lipid or protein) of action. (F4. Other bl

other lanthanides and their known physical chemistry characterized blockers in distinguishing different mechanisms and sites (i.e., lipid or protein) of action. (F.<br>4. Other blockers. In this section, we list a number of 1 should be helpful in distinguishing different mechanisms and sites (i.e., lipid or protein) of action.<br>4. Other blockers. In this section, we list a number of less characterized blockers of MG channels. Some of the drugs l nisms and sites (i.e., lipid or protein) of action.<br>4. Other blockers. In this section, we list a number of<br>less characterized blockers of MG channels. Some of the<br>drugs listed are better known as blockers of other volt-<br>a

less characterized blockers of MG channels. Some of the drugs listed are better known as blockers of other voltage- and transmitter-gated channels.<br>
a. NA<sup>+</sup> CHANNEL BLOCKERS. Tetrodotoxin (TTX) is best known for its abil drugs listed are better known as blockers of other volt-<br>age- and transmitter-gated channels. <br>a. NA<sup>+</sup> CHANNEL BLOCKERS. Tetrodotoxin (TTX) is best<br>channel of the ability to block the voltage-gated Na<sup>+</sup><br>channel. However, age- and transmitter-gated channels.<br>
a. NA<sup>+</sup> CHANNEL BLOCKERS. Tetrodotoxin (TTX) is best<br>
known for its ability to block the voltage-gated Na<sup>+</sup><br>
channel. However, whereas some studies of the Pacinian<br>
corpuscle indicat a. NA<sup>+</sup> CHANNEL BLOCKERS. Tetrodotoxin (TTX) is best channel. However, whereas some studies of the Pacinian Morpuscle indicate that TTX only blocks the action potential, other studies indicate it may also reduce the nome known for its ability to block the voltage-gated Na<sup>+</sup><br>channel. However, whereas some studies of the Pacinian<br>corpuscle indicate that TTX only blocks the action po-<br>tential, other studies indicate it may also reduce the<br>me channel. However, whereas some studies of the Pacinian Rorpuscle indicate that TTX only blocks the action potential, other studies indicate it may also reduce the reduction occurs because function occurs because of direct corpuscle indicate that TTX only blocks the action potential, other studies indicate it may also reduce the mechanoreceptor potential (see Bell et al., 1994). It remains unresolved whether this reduction occurs because of mechanoreceptor potential (see Bell et al., 1994). It remains unresolved whether this reduction occurs because<br>of direct block of MG channels or block of voltage-gated<br>channels that may contribute to the receptor potential mechanoreceptor potential (see Bell et al., 1994). It re-<br>
mains unresolved whether this reduction occurs because Sty.<br>
of direct block of MG channels or block of voltage-gated TE.<br>
channels that may contribute to the rece mains unresolved whether this reduction occurs because Sise of direct block of MG channels or block of voltage-gated The channels that may contribute to the receptor potential. (In At least in chick cardiomyoctes, TTX does of direct block of MG channels or block of voltage-gated channels that may contribute to the receptor potential. (At least in chick cardiomyoctes, TTX does block a 25-pS 45A cation channel without affecting four other clas channels that may contribute to the receptor potential.<br>At least in chick cardiomyoctes, TTX does block a 25-pS<br>SA cation channel without affecting four other classes of<br>SA channels also expressed in the myocyte (Ruknudin At least in chick cardiomyoctes, TTX does block a 25-pS<br>SA cation channel without affecting four other classes of<br>SA channels also expressed in the myocyte (Ruknudin et<br>al., 1993). Whereas TTX has no effect on the micropho SA cation channel without affecting four other classes of<br>SA channels also expressed in the myocyte (Ruknudin et<br>al., 1993). Whereas TTX has no effect on the microphonic<br>potential recorded from goldfish saccula, procaine, SA channels also expressed in the myocyte (Ruknudin et al., 1993). Whereas TTX has no effect on the microphonic potential recorded from goldfish saccula, procaine, another Na<sup>+</sup> channel blocker, produces a partial (35%) r al., 1993). Whereas TTX has no effect on the microphonic capotential recorded from goldfish saccula, procaine, an-<br>other Na<sup>+</sup> channel blocker, produces a partial (35%) areduction at a concentration of  $2 \times 10^{-3}$  g/ml (M other Na<sup>+</sup> channel blocker, produces a partial (35%) reduction at a concentration of  $2 \times 10^{-3}$  g/ml (Matsuura et al., 1971). In a quite different preparation, the ciliated protozoan, 1 mM procaine blocks the mechanorec other Na<sup>+</sup> channel blocker, produces a partial (35%) and vertebrate hair cells (Crawford et al., 1991). De-<br>reduction at a concentration of  $2 \times 10^{-3}$  g/ml (Matsuura tailed analysis of this Ca<sup>2+</sup> block by Taglietti and et al., 1971). In a quite different preparation, the ciliated (1988) indicates a permeant ion block mechanism in protozoan, 1 mM procaine blocks the mechanoreceptor which  $Ca^{2+}$ , like Na<sup>+</sup> and K<sup>+</sup>, enters and binds to et al., 1971). In a quite different preparation, the ciliated<br>protozoan, 1 mM procaine blocks the mechanoreceptor<br> $K^+$  current (Deitmer, 1992). However, further down the<br>evolutionary scale, 0.5 mM procaine activates the a protozoan, 1 mM procaine blocks the mechanoreceptor  $K^+$  current (Deitmer, 1992). However, further down the evolutionary scale, 0.5 mM procaine activates the anion MG channel in  $E$ .  $coli$  (see Section III, B.1, and table to screen procaine action on other MG channels.<br>b.  $CA^{2+}$  CHANNEL BLOCKERS. As indicated above, amiloolutionary scale,  $0.5$  mM procaine activates the anid G channel in *E. coli* (see Section III, B.1, and table iven these divergent effects, it would seem worthwhis erreen procaine action on other MG channels.<br>b.  $CA^{2+}$ 

MG channel in *E. coli* (see Section III, B.1, and table 5).<br>Given these divergent effects, it would seem worthwhile<br>to screen procaine action on other MG channels.<br>b.  $CA^{2+}$  CHANNEL BLOCKERS. As indicated above, amilo-<br> Given these divergent effects, it would seem worthwhile<br>to screen procaine action on other MG channels.<br>b.  $CA^{2+}$  CHANNEL BLOCKERS. As indicated above, amilo-<br>ride, aminoglycosides and  $Gd^{3+}$  all block  $Ca^{2+}$  channels to screen procaine action on other MG channels.<br>b.  $CA^{2+}$  CHANNEL BLOCKERS. As indicated above, amilo-<br>ride, aminoglycosides and  $Gd^{3+}$  all block  $Ca^{2+}$  channels<br>as well as MG channels. This complicates functional<br>stu b.  $CA^{2+}$  CHANNEL BLOCKERS. As indicated above, aminde, aminoglycosides and  $Gd^{3+}$  all block  $Ca^{2+}$  channel as MG channels. This complicates function studies, because reports indicate that the L-type Cachannel may be as well as MG channels. This complicates functional nels is reduced to near zero when external pH is reduced<br>studies, because reports indicate that the L-type  $Ca^{2+}$  from 7.2 to 4.5 in onion cell epidermis (Ding et al., as well as MG channels. This complicates functional netudies, because reports indicate that the L-type  $Ca^{2+}$  free channel may be mechanosensitive as well as voltage-<br>sensitive (Langton, 1993; Ben-Tabou et al., 1994). On studies, because reports indicate that the L-type Ca<sup>2-</sup><br>channel may be mechanosensitive as well as voltage<br>sensitive (Langton, 1993; Ben-Tabou et al., 1994). On<br>strategy to discriminate its role has been to test more<br>spe channel may be mechanosensitive as well as voltage-<br>sensitive (Langton, 1993; Ben-Tabou et al., 1994). One<br>strategy to discriminate its role has been to test more<br>specific  $Ca^{2+}$  channel blockers such as dihydropyridines sensitive (Langton, 1993; Ben-Tabou et al., 1994). Or<br>strategy to discriminate its role has been to test more<br>specific  $Ca^{2+}$  channel blockers such as dihydropyridine<br>(see Naruse and Sokabe, 1993). However, some cautio<br>i strategy to discriminate its role has been to test more M<br>specific  $Ca^{2+}$  channel blockers such as dihydropyridines ti<br>(see Naruse and Sokabe, 1993). However, some caution c<br>is required with this approach because such  $Ca$ (see Naruse and Sokabe, 1993). However, some caution<br>is required with this approach because such  $Ca^{2+}$  chan-<br>nel blockers also affect MG channel activities, including<br>diltiazem, which blocks the 25-pS SA, TTX-sensitive<br> (see Naruse and Sokabe, 1993). However, some caution<br>is required with this approach because such  $Ca^{2+}$  chan-<br>nel blockers also affect MG channel activities, including<br>diltiazem, which blocks the 25-pS SA, TTX-sensitive<br> is required with this approach because such  $Ca^{2+}$  channel blockers also affect MG channel activities, including diltiazem, which blocks the 25-pS SA, TTX-sensitive cation channel in chick cardiomyoctes (Rukhudin et al., nel blockers also affect MG channel activities, includin<br>diltiazem, which blocks the 25-pS SA, TTX-sensitiv<br>cation channel in chick cardiomyoctes (Ruknudin et al<br>1993). Other known Ca<sup>2+</sup> blockers, including Co<sup>2+</sup><br>La<sup>3+</sup> diltiazem, which blocks the<br>cation channel in chick cardio<br>1993). Other known  $Ca^{2+}$  b<br> $La^{3+}$ , heptanol and octanol, bl<br>in hair cells (Ohmori, 1985).

CBRIDE<br>C. K<sup>+</sup> CHANNEL BLOCKERS. To date, blocker pharm<sub>i</sub><br>y has been mostly focused on the SA cation-selee MCBRIDE<br>
c.  $K^+$  CHANNEL BLOCKERS. To date, blocker pharmacology has been mostly focused on the SA cation-selective<br>
channel, and the major blockers of this channel have MCBRIDE<br>c. K<sup>+</sup> CHANNEL BLOCKERS. To date, blocker pharmacol-<br>ogy has been mostly focused on the SA cation-selective<br>channel, and the major blockers of this channel have<br>also been shown to act on  $Na^+$  and  $Ca^{2+}$  channel c.  $K^+$  CHANNEL BLOCKERS. To date, blocker pharmacology has been mostly focused on the SA cation-selective channel, and the major blockers of this channel have also been shown to act on Na<sup>+</sup> and Ca<sup>2+</sup> channels. By anal c.  $K^+$  CHANNEL BLOCKERS. To date, blocker pharmacology has been mostly focused on the SA cation-selective channel, and the major blockers of this channel have also been shown to act on Na<sup>+</sup> and Ca<sup>2+</sup> channels. By anal ogy has been mostly focused on the SA cation-selective channel, and the major blockers of this channel have also been shown to act on Na<sup>+</sup> and Ca<sup>2+</sup> channels. E analogy, one might expect that SA K<sup>+</sup> channels would k se channel, and the major blockers of this channel have<br>also been shown to act on  $Na^+$  and  $Ca^{2+}$  channels. By<br>analogy, one might expect that SA K<sup>+</sup> channels would be<br>sensitive to the various toxins and drugs that act sel also been shown to act on Na<sup>+</sup> and Ca<sup>2+</sup> channels. By<br>analogy, one might expect that SA K<sup>+</sup> channels would be<br>sensitive to the various toxins and drugs that act selec-<br>tively on K<sup>+</sup> channels. Indeed, a number of K<sup>+</sup> analogy, one might expect that SA  $K^+$  channels would be sensitive to the various toxins and drugs that act selectively on  $K^+$  channels. Indeed, a number of  $K^+$  channel blockers do act on SA  $K^+$  channels but appear tively on  $K^+$  channels. Indeed, a number of  $K^+$  channel<br>blockers do act on SA  $K^+$  channels but appear to be<br>ineffective against the SA cation channels (Morris,<br>1990). However, in general, these blockers are of relablockers do act on SA  $K^+$  channels but appear to be blockers do act on SA K<sup>+</sup> channels but appear to be ineffective against the SA cation channels (Morris, 1990). However, in general, these blockers are of relatively low potency and overall low specificity for K<sup>+</sup> channe ineffective against the SA cation channels (Morris, 1990). However, in general, these blockers are of relatively low potency and overall low specificity for K<sup>+</sup> channels. For example, the SA K<sup>+</sup> channel in frog renal pr 1990). However, in general, these blockers are of rela-<br>tively low potency and overall low specificity for K<sup>+</sup><br>channels. For example, the SA K<sup>+</sup> channel in frog renal<br>proximal tubule can be blocked by external Ba<sup>2+</sup> (5 (Filipovic and Sackin, 1991; Cemerikic and Sackin, 1993), whereas the SA K<sup>+</sup> channel in molluscan neurons is blocked by external tetraethylammonium (TEA) ( $K_a$  of channels. For example, the SA K<sup>+</sup> channel in frog renal<br>proximal tubule can be blocked by external Ba<sup>2+</sup> (5 mM)<br>(Filipovic and Sackin, 1991; Cemerikic and Sackin,<br>1993), whereas the SA K<sup>+</sup> channel in molluscan neurons<br> proximal tubule can be blocked by external Ba<sup>2+</sup> (5 mM)<br>(Filipovic and Sackin, 1991; Cemerikic and Sackin,<br>1993), whereas the SA K<sup>+</sup> channel in molluscan neurons<br>is blocked by external tetraethylammonium (TEA)(K<sub>d</sub> of<br>1 (Filipovic and Sackin, 1991; Cemerikic and Sackin, 1993), whereas the SA K<sup>+</sup> channel in molluscan neurons is blocked by external tetraethylammonium (TEA) ( $K_d$  of 10 mM) and quinidine ( $K_d = 0.8$  mM) but unaffected by eit 1993), whereas the SA K<sup>+</sup> channel in molluscan neurons<br>is blocked by external tetraethylammonium (TEA) (K<sub>d</sub> of<br>10 mM) and quinidine (K<sub>d</sub> = 0.8 mM) but unaffected by<br>either of these internally. Also ineffective on the l is blocked by external tetraethylammonium (TEA) ( $K_d$  of 10 mM) and quinidine ( $K_d = 0.8$  mM) but unaffected by either of these internally. Also ineffective on the latter channel when applied externally are  $Ba^{2+}$  (50 mM) either of these internally. Also ineffective on the latter channel when applied externally are  $Ba^{2+}$  (50 mM), apamin (1  $\mu$ M) and 4-aminopyridine (10 mM) (Small and Morris, 1995). In contrast,  $Ba^{2+}$  (2 mM) blocks the either of these internally. Also ineffective on the latt<br>channel when applied externally are  $Ba^{2+}$  (50 ml<br>apamin (1  $\mu$ M) and 4-aminopyridine (10 mM) (Small a<br>Morris, 1995). In contrast,  $Ba^{2+}$  (2 mM) blocks the SA I<br> channel when applied externally are  $Ba^{2+}$  (50 mM),<br>apamin (1  $\mu$ M) and 4-aminopyridine (10 mM) (Small and<br>Morris, 1995). In contrast,  $Ba^{2+}$  (2 mM) blocks the SA K<sup>+</sup><br>channels in rat brain neurons, but external TEA, 4 apamin (1  $\mu$ M) and 4-aminopyridine (10 mM) (Small and<br>Morris, 1995). In contrast,  $Ba^{2+}$  (2 mM) blocks the SA K<sup>+</sup><br>channels in rat brain neurons, but external TEA, 4-ami-<br>nopyridine or quinidine apparently does not (Ki channels in rat brain neurons, but external TEA, 4-ami-<br>nopyridine or quinidine apparently does not (Kim et al.,<br>1995). On the other hand, in the ciliated protozoan,<br>*Stylonychia*, external 4-aminopyridine (0.5 mM) and<br>TEA channels in rat brain neurons, but external TEA, 4-ami-<br>nopyridine or quinidine apparently does not (Kim et al.,<br>1995). On the other hand, in the ciliated protozoan,<br>Stylonychia, external 4-aminopyridine (0.5 mM) and<br>TEA ( nopyridine or quinidine apparently does not (Kim et al., 1995). On the other hand, in the ciliated protozoan,  $Stylonychia$ , external 4-aminopyridine (0.5 mM) and TEA (1 mM) but not  $Cs^+$  block the MG K<sup>+</sup> current (Deitmer, 199 Stylonychia, external 4-aminopyridine (0.1<br>TEA (1 mM) but not Cs<sup>+</sup> block the MG<br>(Deitmer, 1992). Neither external TEA (4-aminopyridine (1 mM) blocks the MG cation<br>crayfish stretch receptor (Erxleben, 1989).<br>d. CALCIUM IO EA (1 mM) but not Cs<sup>+</sup> block the MG K<sup>+</sup> current<br>
eitmer, 1992). Neither external TEA (1 mM) nor<br>
aminopyridine (1 mM) blocks the MG cation channel in<br>
ayfish stretch receptor (Erxleben, 1989).<br>
d. CALCIUM IONS. Ca<sup>2+</sup> h 1993), whereas the SA K<sup>+</sup> channel in molluscan neurons<br>
is blocked by external tetrachly lammonium (TEA) (K<sub>4</sub> of 10 mM) and quinidine (K<sub>4</sub> = 0.8 mM) but unaffected by<br>
either of these internally. Also ineffective on th

(Deitmer, 1992). Neither external TEA (1 mM) nor<br>4-aminopyridine (1 mM) blocks the MG cation channel in<br>crayfish stretch receptor (Erxleben, 1989).<br>d. CALCIUM IONS. Ca<sup>2+</sup> has been shown to block MG<br>cation channels in *Xen* 4-aminopyridine (1 mM) blocks the MG cation channel in<br>crayfish stretch receptor (Erxleben, 1989).<br>d. CALCIUM IONS.  $Ca^{2+}$  has been shown to block MG<br>cation channels in *Xenopus* oocytes (Taglietti and<br>Toselli, 1988; Yan crayfish stretch receptor (Erxleben, 1989).<br>d. CALCIUM IONS.  $Ca^{2+}$  has been shown to block MG<br>cation channels in *Xenopus* oocytes (Taglietti and<br>Toselli, 1988; Yang and Sachs, 1989; Lane et al., 1993)<br>and vertebrate ha d. CALCIUM IONS.  $Ca^{2+}$  has been shown to block MG<br>cation channels in *Xenopus* oocytes (Taglietti and<br>Toselli, 1988; Yang and Sachs, 1989; Lane et al., 1993)<br>and vertebrate hair cells (Crawford et al., 1991). De-<br>tailed Toselli, 1988; Yang and Sachs, 1989; Lane et al., 1993)<br>and vertebrate hair cells (Crawford et al., 1991). De-<br>tailed analysis of this Ca<sup>2+</sup> block by Taglietti and Toselli<br>(1988) indicates a permeant ion block mechanism and vertebrate hair cells (Crawford et al., 1991). Detailed analysis of this  $Ca^{2+}$  block by Taglietti and Toselli (1988) indicates a permeant ion block mechanism in which  $Ca^{2+}$ , like Na<sup>+</sup> and K<sup>+</sup>, enters and binds t tailed analysis of this  $Ca^{2+}$  block by Taglietti and Toselli<br>(1988) indicates a permeant ion block mechanism in<br>which  $Ca^{2+}$ , like Na<sup>+</sup> and K<sup>+</sup>, enters and binds to the<br>channel but displays a much smaller  $K_d$  (50  $\$ (1988) indicates a permeant ion block mechanism in<br>which  $Ca^{2+}$ , like Na<sup>+</sup> and K<sup>+</sup>, enters and binds to the<br>channel but displays a much smaller K<sub>d</sub> (50  $\mu$ M) and<br>much longer occupancy time (400 nsec) compared with<br>Na which  $Ca^{2+}$ , like Na<sup>+</sup> and K<sup>+</sup>, enters and binds to th<br>channel but displays a much smaller K<sub>d</sub> (50  $\mu$ M) an<br>much longer occupancy time (400 nsec) compared with<br>Na<sup>+</sup> (2 mM and 20 nsec) or K<sup>+</sup> (3.2 mM and 12 nsec). channel but displays a much smaller  $K_d$  (50  $\mu$ M) a much longer occupancy time (400 nsec) compared w Na<sup>+</sup> (2 mM and 20 nsec) or K<sup>+</sup> (3.2 mM and 12 nsec). Thigher affinity for Ca<sup>2+</sup> results in greater channel oc pancy much longer occupancy time (400 nsec) compared wit<br>Na<sup>+</sup> (2 mM and 20 nsec) or  $K^+$  (3.2 mM and 12 nsec). Th<br>higher affinity for  $Ca^{2+}$  results in greater channel occupancy so that inward flow of Na<sup>+</sup> and  $K^+$  is comp

higher affinity for  $Ca^{2+}$  results in greater channel occupancy so that inward flow of  $Na^+$  and  $K^+$  is competitively inhibited.<br>
e. PROTONS. The open probability of SA cation channels is reduced to near zero when exte pancy so that inward flow of  $Na^+$  and  $K^+$  is competitively inhibited.<br>
e. PROTONS. The open probability of SA cation chan-<br>
rels is reduced to near zero when external pH is reduced<br>
from 7.2 to 4.5 in onion cell epider tively inhibited.<br>
e. PROTONS. The open probability of SA cation chan-<br>
relation 8.2 to 4.5 in onion cell epidermis (Ding et al., 1993)<br>
and from 7.2 to 5.8 in *E. coli* (Cui et al., 1995). In *E. coli*,<br>
acidic pH was als e. PROTONS. The open probability of SA cation channels is reduced to near zero when external pH is reduced from 7.2 to 4.5 in onion cell epidermis (Ding et al., 1993) and from 7.2 to 5.8 in  $E$ . coli (Cui et al., 1995). I nels is reduced to near zero when external pH is reduced<br>from 7.2 to 4.5 in onion cell epidermis (Ding et al., 1993)<br>and from 7.2 to 5.8 in E. coli (Cui et al., 1995). In E. coli,<br>acidic pH was also shown to reduce the sen from 7.2 to 4.5 in onion cell epidermis (Ding et al., 1993)<br>and from 7.2 to 5.8 in  $E.$  coli (Cui et al., 1995). In  $E.$  coli,<br>acidic pH was also shown to reduce the sensitivity of the<br>MG channel (i.e., shifted the pressu and from 7.2 to 5.8 in  $E.$  coli (Cui et al., 1995). In  $E.$  coli, acidic pH was also shown to reduce the sensitivity of the MG channel (i.e., shifted the pressure-response curve to the right). The mechanism of the acid e acidic pH was also shown to reduce the sensitivity of t<br>MG channel (i.e., shifted the pressure-response curve<br>the right). The mechanism of the acid effects on M<br>channel gating remains unknown but may be due<br>protonation of MG channel (i.e., shifted the pressure-response curve to<br>the right). The mechanism of the acid effects on MG<br>channel gating remains unknown but may be due to<br>protonation of amino groups or a proton-induced confor-<br>mation c the right). The mechanism of the acid effects on M<br>channel gating remains unknown but may be due<br>protonation of amino groups or a proton-induced confi<br>mation change (Cui et al., 1995). In the case of plan<br>the pH effect has channel gating remains unknown but may be due to<br>protonation of amino groups or a proton-induced confor-<br>mation change (Cui et al., 1995). In the case of plants,<br>the pH effect has been proposed to underlie the inhibi-<br>tory protonation of amino groups or a proton-induced conformation change (Cui et al., 1995). In the case of plants,<br>the pH effect has been proposed to underlie the inhibitory effect of acid soil syndrome on plant root tip growt mation change (Cui et al., 1995). In the case of plants,<br>the pH effect has been proposed to underlie the inhibi-<br>tory effect of acid soil syndrome on plant root tip growth<br>(Ding et al., 1993). In contrast to the strong in the pH effect has been proposed to underlie the inhibitory effect of acid soil syndrome on plant root tip growth (Ding et al., 1993). In contrast to the strong inhibitory effects of acid pH, alkaline pH up to 8.6 has only



PHARMACOLOGICAL REVIEW!

# PHARMACOLOGY **OF MECHANOGATED MEMBRANE ION** CHANNELS <sup>241</sup>







# **242 HAMILL AND MCBRIDE** TABLE 4 *continued*

242			<b>HAMILL AND MCBRIDE</b>				
		<b>TABLE 4 continued</b>					
Process <b>Stimulation used</b>	Cell type	$Gd^{3+}$	Amilor.	Amino- glycoside	Conc. tested $\mu$ M except when in ( )	Reference(s)	
Actin polymerization	Human fibroblasts	N			10	Pender and McCulloch, 1991	
Hypertrophy	Rat cardiac myocytes	N			50	Sadoshima and Izumo, 1993	
Genes activation	Rat cardiac myocytes	N			10	Sadoshima et al., 1992	
Strain-activated							
Depolarization	Rat osteosarcoma cells	Y			10	Duncan and Hruska, 1994	
<b>Specialized mechanosensory</b>							
receptors							
Pressure-induced							
Baroreceptor discharge	Rat arterial	N			400	Andresen and Yang, 1992	
Baroreceptor discharge	Rabbit carotid	Y			10	Hajduczok et al., 1994	
Stretch-induced							
Depolarization	Frog muscle spindles	Y	Y		$(1 \text{ mM}, 1 \text{ mM})$	Ito et al., 1990	
Depolarization	Crayfish stretch receptor	Y			400	Swerup et al., 1991	
Touch-induced							
Calcium increase	Rat nodose sensory neurons	Y			10	Sharma et al., 1995	
Depolarization	Cat cutaneous			Y	(i.v. 2.5)	Baumann et al., 1988	
	mechanoreceptors				mg/min)		
Depolarization	Squid statocyst			Y	$(10 \text{ mM})$	Williamson, 1990	
Cation inward current	Rat nodose sensory neurons	Y			20	Cunningham et al., 1995	
Cation inward current Voltage-induced	Rat supraortic neurons	Y			100	Oliet and Bourque, 1994	
Hair cell motion	Guinea pig outer hair cells	Y			500	Santos-Sacchi, 1991	
Muscle							
Stretch-induced							
Force development	Guinea pig papillary muscle	Y			10	Lab et al., 1994	
Contracture	Rat uterine smooth muscle	Y	N		100, 3000	Kasai et al., 1995	
<b>Arrhythmias</b>	Canine ventricular muscle	Y			10	Hansen et al., 1990	
Depolarization	Canine ventricular muscle	Y			10	Stacy et al., 1992	
Depolarization	Guinea pig urinary bladder myocytes	Y			40	Wellner and Isenberg, 1994	
Peptide secretion	Rat atrial myocytes	Y			5-80	Laine et al., 1994	
<b>Transmitter release</b>	Frog neuromuscular junction	N			100	Chen and Grinnell, 1995	
<b>Plants and some lower</b> invertebrates							
Touch-induced action potential	Chara corallina	Y			0.0001	<b>Staves and Wayne, 1993</b>	
Touch-induced tendril coiling	Byronia dioica	Y			10,000	Kluesener et al., 1995	
$Ca2+$ efflux from ER vesicles	Byronia dioica	Y			20		
Gravity-induced							
Thigmotropism	Zea mays	Y			10	Millet and Pickard, 1988	
Orthogeotropism	Zea mays	Y			250	Millet and Pickard, 1988	
Tip growth	Saprolegnia ferax (Fungi)	$\mathbf Y$			100	Garrill et al., 1993	
Rise in $[Ca^{2+}]_i$	Fungi growing tip	Y			100	Garrill et al., 1993	
Wind-induced							
Rise in $[Ca^{2+}]_i$	Nicotiana plumbaginifolia	${\bf N}$			$(10 \text{ mM})$	Knight et al., 1992	
Touch-induced							
Nematocyte discharge	Hydra vulgaris			Y	50	Gitter et al., 1993	
Nematocyte discharge	Cnidaria (Coelenterates)	Y			1	Salleo et al., 1994a,b	

However, for the SA cation channel in chick skeletal<br>muscle, raising pH from 7.4 to 10 significantly increases However, for the SA cation channel in chick skeletal<br>muscle, raising pH from 7.4 to 10 significantly *increases*<br>the channel's stretch sensitivity as well as its voltage However, for the SA cation channel in chick skeletal results. The channel's stretch sensitivity as well as its voltage sensitivity without affecting single channel conductance  $\mu$ However, for the SA cation channel in chick skeletal<br>muscle, raising pH from 7.4 to 10 significantly *increases*<br>the channel's stretch sensitivity as well as its voltage<br>sensitivity without affecting single channel conduct muscle, raising pH from 7.4 to 10 significantly increases<br>the channel's stretch sensitivity as well as its voltage<br>sensitivity without affecting single channel conductance<br>(Guharay and Sachs, 1985). These last effects were muscle, raising pH from 7.4 to 10 significantly *increas*<br>the channel's stretch sensitivity as well as its volta<br>sensitivity without affecting single channel conductan<br>(Guharay and Sachs, 1985). These last effects were pr<br> the channel's stretch sensitivity as well as its voltage f<br>sensitivity without affecting single channel conductance  $\mu$ M<br>(Guharay and Sachs, 1985). These last effects were pro-<br>me posed to occur because a titratable site

responsible for controlling voltage and stretch sensitiv-<br>ity (Guharay and Sachs, 1985). responsible for controlling voltag<br>ity (Guharay and Sachs, 1985).<br>f. ALUMINUM IONS. Aluminum

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sponsible for controlling voltage and stretch sensitiv-<br>  $\frac{1}{2}$  (Guharay and Sachs, 1985).<br>
f. ALUMINUM IONS. Aluminum ions  $(A1^{3+})$  (10 to 100<br>
(a) also inhibit the SA Ca<sup>2+</sup> channel in the plasma responsible for controlling voltage and stretch sensitiv-<br>ity (Guharay and Sachs, 1985).<br>f. ALUMINUM IONS. Aluminum ions  $(A1^{3+})$  (10 to 100<br> $\mu$ M) also inhibit the SA Ca<sup>2+</sup> channel in the plasma<br>membrane of onion cells. responsible for controlling voltage and stretch sensitiv-<br>ity (Guharay and Sachs, 1985).<br>f. ALUMINUM IONS. Aluminum ions  $(A1^{3+})$  (10 to 100<br> $\mu$ M) also inhibit the SA Ca<sup>2+</sup> channel in the plasma<br>membrane of onion cells. ity (Guharay and Sachs, 1985).<br>
f. ALUMINUM IONS. Aluminum ions  $(A1^{3+})$  (10 to 100<br>  $\mu$ M) also inhibit the SA Ca<sup>2+</sup> channel in the plasma<br>
membrane of onion cells. This inhibition might also con-<br>
tribute to acid soil f. ALUMINUM IONS. Aluminum ions (Al $\mu$ M) also inhibit the SA Ca<sup>2+</sup> channel<br>membrane of onion cells. This inhibition is<br>tribute to acid soil syndrome because lo<br>free Al<sup>3+</sup> in the soil (Ding et al., 1993).

PHARMACOLOGY OF MECHANOGATED<br>g. TUBOCURARINE. (+)-Tubocurarine (TC) and other activisquarternary amines (gallamine, decamethonium and effectively depress (TC:  $IC_{50} = 19 \mu$ M) the add **PHARMACOLOGY OF MECHANOGATED**<br>g. TUBOCURARINE. (+)-Tubocurarine (TC) and other ac<br>bisquarternary amines (gallamine, decamethonium and eff<br>succylcholine) selectively depress (TC:  $IC_{50} = 19 \mu M$ ) the ad<br>mechanoreceptor cur g. TUBOCURARINE.  $(+)$ -Tubocurarine (TC) and other<br>bisquarternary amines (gallamine, decamethonium and<br>succylcholine) selectively depress (TC:  $IC_{50} = 19 \mu M$ ) the<br>mechanoreceptor current of the ciliate protozoan *Stentor*<br> g. TUBOCURARINE. (+)-Tubocurarine (TC) and other according potential and reflaction and effectively depress (TC:  $IC_{50} = 19 \mu M$ ) the admechancreceptor current of the ciliate protozoan *Stentor* itic coeruleus without affe bisquarternary amines (gallamine, decamethonium and<br>succylcholine) selectively depress (TC:  $IC_{50} = 19 \mu M$ ) the<br>mechanoreceptor current of the ciliate protozoan *Stentor*<br>coeruleus without affecting the resting potential succylcholine) selectively depress (TC:  $IC_{50} = 19 \mu$ M) the<br>mechanoreceptor current of the ciliate protozoan *Stentor*<br>coeruleus without affecting the resting potential and the<br>action potential (Wood, 1985). The mechanore mechanoreceptor current of the ciliate protozoan *Stento*<br>coeruleus without affecting the resting potential and th<br>action potential (Wood, 1985). The mechanoreceptor curent, in the absence of TC, is increased by depolariza coeruleus without affecting the resting potential and<br>action potential (Wood, 1985). The mechanoreceptor<br>rent, in the absence of TC, is increased by depolariza<br>(i.e., MG channel open probability increases with d<br>larization action potential (Wood, 1985). The mechanoreceptor current, in the absence of TC, is increased by depolarization<br>(i.e., MG channel open probability increases with depolarization), whereas TC block is relieved by depolariza rent, in the absence of TC, is increased by depolarizat<br>(i.e., MG channel open probability increases with de<br>larization), whereas TC block is relieved by depolari<br>tion. To explain these observations, Wood (1985) p<br>posed th (i.e., MG channel open probability increases with depo-<br>larization), whereas TC block is relieved by depolariza-<br>tion. To explain these observations, Wood (1985) pro-<br>throwsed that the MG channel can exist in two voltagelarization), whereas TC block is relieved by depolarization. To explain these observations, Wood (1985) proposed that the MG channel can exist in two voltage-<br>dependent closed conformations (R and U) and one open<br>conformat tion. To explain these observations, Wood (1985) posed that the MG channel can exist in two volts dependent closed conformations (R and U) and one of conformation. One of the closed conformations (R), p dominates at depola posed that the MG channel can exist in two voltage-<br>dependent closed conformations (R and U) and one open<br>conformation. One of the closed conformations (R), pre-<br>dominates at depolarized potentials and can be mechan-<br>icall dependent closed conformations (R and U) and one open<br>conformation. One of the closed conformations (R), pre-<br>dominates at depolarized potentials and can-be mechan-<br>ically activated to open. The other closed conformation<br>( conformation. One of the closed conformations (R), pre-<br>dominates at depolarized potentials and can be mechan-<br>ically activated to open. The other closed conformation sp<br>(U), predominates at hyperpolarized potentials and c dominates at depolarized potentials and can be mechan-<br>ically activated to open. The other closed conformation span the plasma membrane (Wang et al., 1993; Ingber,<br>(U), predominates at hyperpolarized potentials and can-<br>no ically activated to open. The other closed conformation (U), predominates at hyperpolarized potentials and cannot be opened by mechanical stimulation. TC blocks the channel by selectively binding to the U form and thus pre (U), predominates at hyperpolarized potentials and cannot be opened by mechanical stimulation. TC blocks the channel by selectively binding to the U form and thus prevents the channel from being mechanically activated. Thi channel by selectively binding to the U form and thus<br>prevents the channel from being mechanically activated.<br>This model is similar to the conformation model pro-<br>posed for amiloride block of the MG channel in *Xenopus*<br>oc channel by selectively binding to the U form and thus<br>prevents the channel from being mechanically activated.<br>This model is similar to the conformation model pro-<br>posed for amiloride block of the MG channel in *Xenopus*<br>oo prevents the channel from being mechanically activated This model is similar to the conformation model proposed for amiloride block of the MG channel in *Xenopu* oocytes (Lane et al., 1991), except the oocyte model propose This model is similar to the conformation model proposed for amiloride block of the MG channel in *Xenopus* cocytes (Lane et al., 1991), except the oocyte model proposes two open conformations. In both cases, drug binding posed for amiloride block<br>oocytes (Lane et al., 1991)<br>poses two open conformat<br>ing occurs to the conform<br>hyperpolarized potentials<br>h. HALOTHANE AND OTI poses two open conformations. In both cases, drug bind-<br>ing occurs to the conformation that predominates at<br>hyperpolarized potentials.<br>h. HALOTHANE AND OTHER INHALATION ANESTHETICS. b<br>Halothane reduces the mechanoreceptor

ing occurs to the conformation that predominates at pre-<br>hyperpolarized potentials. the<br>h. HALOTHANE AND OTHER INHALATION ANESTHETICS. be<br>Halothane reduces the mechanoreceptor potential of and<br>crustacean stretch receptors: hyperpolarized potentials. The mechanism of the mechanism of the mechanism of the mechanism of this block may involve in Na<sup>+</sup> channels. The mechanism of this block may involve beffects on cable properties because neither h. HALOTHANE AND OTHER INHALATION ANESTHETICS. be<br>Halothane reduces the mechanoreceptor potential of arcustacean stretch receptors: TTX was present to block in<br>Na<sup>+</sup> channels. The mechanism of this block may involve be<br>eff Halothane reduces the mechanoreceptor potential of crustacean stretch receptors: TTX was present to block Na<sup>+</sup> channels. The mechanism of this block may involve effects on cable properties because neither the time course crustacean stretch receptors: TTX was present to block<br>Na<sup>+</sup> channels. The mechanism of this block may involve<br>effects on cable properties because neither the time<br>course nor amplitude of the mechanoreceptor curren<br>appeare  $Na<sup>+</sup>$  channels. The mechanism of this block may involve effects on cable properties because neither the time course nor amplitude of the mechanoreceptor curren appeared to be altered (see fig. 8 in Swerup and Ryd qvis effects on cable properties because neither the tim<br>course nor amplitude of the mechanoreceptor curren<br>appeared to be altered (see fig. 8 in Swerup and Ryd<br>qvist, 1985). In a whole lung preparation halothane<br>enflurane and appeared to be altered (see fig. 8 in Swerup and Ryd-100 qvist, 1985). In a whole lung preparation halothane, intenflurane and isoflurane were shown to raise the pressure threshold for recruitment of slowly adapting tice s qvist, 1985). In a whole lung preparation halothane,<br>enflurane and isoflurane were shown to raise the pres-<br>sure threshold for recruitment of slowly adapting<br>stretch receptors in the tracheobronchial system and<br>inhibit pul enflurane and isoflurane were shown to raise the pressure threshold for recruitment of slowly adapting titles that the exact mechanism of pulmonary irritant receptors (Nishino et al., both 1994). Again, in this situation, inhibit pulmonary irritant receptors (Nishino et al., 1994). Again, in this situation, the exact mechanism of drug action remains unknown.<br>i. QUININE. Quinine, a cinchona alkaloid used for the treatment of malaria, is know retch receptors in the tracheobronchial system and periodic pulmonary irritant receptors (Nishino et al., be 94). Again, in this situation, the exact mechanism of clarity action remains unknown.<br>i. QUININE. Quinine, a cinc

inhibit pulmonary irritant receptors (Nishino et al., 1994). Again, in this situation, the exact mechanism of drug action remains unknown.<br>
i. QUININE. Quinine, a cinchona alkaloid used for the treatment of malaria, is kno 1994). Again, in this situation, the exact mechanism of drug action remains unknown.<br>
i. QUININE. Quinine, a cinchona alkaloid used for the treatment of malaria, is known to induce a reversible hearing loss in mammals in m drug action remains unknown.<br>
i. QUININE. Quinine, a cinchona alkaloid used for the<br>
treatment of malaria, is known to induce a reversible<br>
hearing loss in mammals in millimolar concentrations<br>
(see references cited in Mat i. QUININE. Quinine, a cinchona alkaloid used for t<br>treatment of malaria, is known to induce a reversib<br>hearing loss in mammals in millimolar concentratio<br>(see references cited in Matsuura et al., 1971). Quini<br>causes an ir treatment of malaria, is known to induce a reversible<br>hearing loss in mammals in millimolar concentrations<br>(see references cited in Matsuura et al., 1971). Quinine<br>causes an irreversible suppression of microphonic poten-<br>t hearing loss in mammals in millimolar concentrations 19<br>(see references cited in Matsuura et al., 1971). Quinine lincauses an irreversible suppression of microphonic poten-<br>tials recorded from fish saccular hair cells (Mat (see references cited in Matsuura et al., 1971). Quinine 1 causes an irreversible suppression of microphonic potentials recorded from fish saccular hair cells (Matsuura et al., 1971) and an apparent increase in stiffness causes an irreversible suppression of microphonic poten-<br>tials recorded from fish saccular hair cells (Matsuura et and distal sensory neuropathy, indicated by early de-<br>al., 1971) and an apparent increase in stiffness of t tials recorded from fish saccular hair cells (Matsuura et al., 1971) and an apparent increase in stiffness of the hair bundle of the fish lateral line organ (Van Netten et al., 1994). These results are similar to the effec al., 1971) and an apparent increase in<br>hair bundle of the fish lateral line organ<br>al., 1994). These results are similar to<br>aminoglycosides on hair cells and may in<br>blockage of the MG channel by quinine.<br>j. FATTY ACIDS. A g

al., 1994). These results are similar to the effects of phanonoglycosides on hair cells and may indicate a direct action of blockage of the MG channel by quinine.<br>
i. FATTY ACIDS. A group of positively charged (medium and aminoglycosides on hair cells and may indicate a direct<br>blockage of the MG channel by quinine.<br>i. FATTY ACIDS. A group of positively charged (medium<br>at to long chain) fatty acid analogs (table 5) has been shown has<br>to sup blockage of the MG channel by quinine.<br>
j. FATTY ACIDS. A group of positively charged (medium<br>
to long chain) fatty acid analogs (table 5) has been shown<br>
to suppress a SA K<sup>+</sup> channel in toad gastric smooth<br>
muscle (Petr j. FATTY ACIDS. A group of positively charged (medium an to long chain) fatty acid analogs (table 5) has been shown has to suppress a SA  $K^+$  channel in toad gastric smooth acsumuscle (Petrou et al., 1994). In contrast, to long chain) fatty acid analogs (table 5) has been shown hair to suppress a SA  $K^+$  channel in toad gastric smooth actimuscle (Petrou et al., 1994). In contrast, negatively we charged (medium to long chain) fatty acids to suppress a SA  $K^+$  channel in toad gastric smooth action. In our own studies to test this proposed action,<br>muscle (Petrou et al., 1994). In contrast, negatively we have found that, at up to 100  $\mu$ M, neither cisplati

PHARMACOLOGY OF MECHANOGATED MEMBRANE ION CHANNELS 243<br>g. TUBOCURARINE. (+)-Tubocurarine (TC) and other acids, whether positively or negatively charged, have no<br>bisquarternary amines (gallamine, decamethonium and effect on EXTED MEMBRANE ION CHANNELS<br>acids, whether positively or negatively charged, have no ED MEMBRANE ION CHANNELS 243<br>acids, whether positively or negatively charged, have no<br>effect on the channel activity (Petrou et al., 1994). In<br>addition to the fatty acids, the naturally occurring pos-ED MEMBRANE ION CHANNELS 243<br>acids, whether positively or negatively charged, have no<br>effect on the channel activity (Petrou et al., 1994). In<br>addition to the fatty acids, the naturally occurring pos-<br>itively charged amino acids, whether positively or negatively charged, have no<br>effect on the channel activity (Petrou et al., 1994). In<br>addition to the fatty acids, the naturally occurring pos-<br>itively charged amino alcohol, sphingosine, also s acids, whether positively or negatively charged, have neffect on the channel activity (Petrou et al., 1994). In addition to the fatty acids, the naturally occurring positively charged amino alcohol, sphingosine, also sup p effect on the channel activity (Petrou et al., 1994). In<br>addition to the fatty acids, the naturally occurring pos-<br>itively charged amino alcohol, sphingosine, also sup-<br>presses channel activity. These positively charged co addition to the fatty acids, the naturally occurring positively charged amino alcohol, sphingosine, also suppresses channel activity. These positively charged compounds do not appear to act as open channel blockers because itively charged amino alcohol, sphingosine, also suppresses channel activity. These positively charged compounds do not appear to act as open channel blockers because they do not reduce either channel open time or single c presses channel activity. These positively charged compounds do not appear to act as open channel blockers<br>because they do not reduce either channel open time or<br>single channel conductance (Petrou et al., 1994). In-<br>stead, pounds do not appear to act as open channel blockers<br>because they do not reduce either channel open time or<br>single channel conductance (Petrou et al., 1994). In-<br>stead, their inhibitory actions has been proposed to arise<br>t single channel conductance (Petrou et al., 1994). Instead, their inhibitory actions has been proposed to arise<br>through an allosteric mechanism (Petrou et al., 1994).<br>k. INTEGRIN-BLOCKING PEPTIDES AND ANTIBODIES. A spe-

appeared to be altered (see fig. 8 in Swerup and Ryd- 100  $\mu$ M Gd<sup>3+</sup> and may involve either MG release of qvist, 1985). In a whole lung preparation halothane, internal Ca<sup>2+</sup> or shift in Ca<sup>2+</sup> sensitivity of the releas single channel conductance (Petrou et al., 1994). Instead, their inhibitory actions has been proposed to arise<br>through an allosteric mechanism (Petrou et al., 1994).<br>k. INTEGRIN-BLOCKING PEPTIDES AND ANTIBODIES. A spe-<br>cif stead, their inhibitory actions has been proposed to arise<br>through an allosteric mechanism (Petrou et al., 1994).<br>k. INTEGRIN-BLOCKING PEPTIDES AND ANTIBODIES. A spe-<br>cific model of mechanotransduction proposes that me-<br>ch through an allosteric mechanism (Petrou et al., 1994).<br>
k. INTEGRIN-BLOCKING PEPTIDES AND ANTIBODIES. A spe-<br>
cific model of mechanotransduction proposes that me-<br>
chanical energy distorting the extracellular matrix is<br>
fo k. INTEGRIN-BLOCKING PEPTIDES AND ANTIBODIES. A specific model of mechanotransduction proposes that mechanical energy distorting the extracellular matrix is focused through to the cytoskeleton via integrins that span the p chanical energy distorting the extracellular matrix is focused through to the cytoskeleton via integrins that fogens the plasma membrane (Wang et al., 1993; Ingber, 1993). In this model, one would expect that agents, such chanical energy distorting the extracellular matrix is<br>focused through to the cytoskeleton via integrins that<br>span the plasma membrane (Wang et al., 1993; Ingber,<br>1993). In this model, one would expect that agents, such<br>as biocused through to the cytosketeton via integrins that<br>span the plasma membrane (Wang et al., 1993; Ingber,<br>1993). In this model, one would expect that agents, such<br>as blocking peptides or antibodies, that inhibit integri span the plasma membrane (Wang et al., 1993; Ingber, 1993). In this model, one would expect that agents, such as blocking peptides or antibodies, that inhibit integrin binding to extracellular matrix proteins would reduce 1993). In this model, one would expect that agents, such<br>as blocking peptides or antibodies, that inhibit integrin<br>binding to extracellular matrix proteins would reduce or<br>block mechanosensitivity. Two studies, although no as blocking peptides or antibodies, that inhibit integrin<br>binding to extracellular matrix proteins would reduce or<br>block mechanosensitivity. Two studies, although not di-<br>rectly on MG channels, lend support to this idea. I binding to extracellular matrix proteins would reduce of block mechanosensitivity. Two studies, although not denote rectly on MG channels, lend support to this idea. In on study (Wayne et al., 1992), it has been demonstrat block mechanosensitivity. Two studies, although not directly on MG channels, lend support to this idea. In one<br>study (Wayne et al., 1992), it has been demonstrated<br>that the integrin blocking peptide Arg-Gly-Asp-Ser<br>(RGDS) rectly on MG channels, lend support to this idea. In one<br>study (Wayne et al., 1992), it has been demonstrated<br>that the integrin blocking peptide Arg-Gly-Asp-Ser<br>(RGDS) inhibits both the gravitational and hydrostatic<br>press study (Wayne et al., 1992), it has been demonstrated<br>that the integrin blocking peptide Arg-Gly-Asp-Ser<br>(RGDS) inhibits both the gravitational and hydrostatic<br>pressure-induced polarity of cytoplasmic streaming in<br>the plan  $(RGDS)$  inhibits both the gravitational and hydrostatic pressure-induced polarity of cytoplasmic streaming in the plant *Chara*. Both processes have been proposed to be mediated by MG channels. In another study (Chen and G (RGDS) inhibits both the gravitational and hydrostatic<br>pressure-induced polarity of cytoplasmic streaming in<br>the plant *Chara*. Both processes have been proposed to<br>be mediated by MG channels. In another study (Chen<br>and G pressure-induced polarity of cytoplasmic streaming in<br>the plant *Chara*. Both processes have been proposed to<br>be mediated by MG channels. In another study (Cher<br>and Grinnell, 1995), it has been demonstrated that the<br>integr the plant *Chara*. Both processes have been proposed to be mediated by MG channels. In another study (Chen and Grinnell, 1995), it has been demonstrated that the integrin-blocking peptide RGD, as well as integrin anti-bodi bodies, suppress stretch-induced release of transmitter<br>from frog nerve terminals. Stretch-induced release still<br>occurs in the absence of external  $Ca^{2+}$ , is not blocked by and Grinnell, 1995), it has been demonstrated that the<br>integrin-blocking peptide RGD, as well as integrin anti-<br>bodies, suppress stretch-induced release of transmitter<br>from frog nerve terminals. Stretch-induced release st integrin-blocking peptide RGD, as well as integrin anti-<br>bodies, suppress stretch-induced release of transmitter<br>from frog nerve terminals. Stretch-induced release still<br>occurs in the absence of external  $Ca^{2+}$ , is not b bodies, suppress stretch-induced release of transmitter<br>from frog nerve terminals. Stretch-induced release still<br>occurs in the absence of external  $Ca^{2+}$ , is not blocked by<br>100  $\mu$ M  $Gd^{3+}$  and may involve either MG re from frog nerve terminals. Stretch-induced release stilence of external  $Ca^{2+}$ , is not blocked b 100  $\mu$ M  $Gd^{3+}$  and may involve either MG release cinternal  $Ca^{2+}$  or shift in  $Ca^{2+}$  sensitivity of the release proce occurs in the absence of external  $Ca^{2+}$ , is not blocked by 100  $\mu$ M  $Gd^{3+}$  and may involve either MG release of internal  $Ca^{2+}$  or shift in  $Ca^{2+}$  sensitivity of the release process. Unfortunately, for patch clamp 100  $\mu$ M  $Gd^{3+}$  and may involve either MG release of internal  $Ca^{2+}$  or shift in  $Ca^{2+}$  sensitivity of the release process. Unfortunately, for patch clamp studies, a practical problem in testing integrin function usi internal  $Ca^{2+}$  or shift in  $Ca^{2+}$  sensitivity of the release<br>process. Unfortunately, for patch clamp studies, a prac-<br>tical problem in testing integrin function using blocking<br>peptides is that the extracellular matrix clamped. peptides is that the extracellular matrix must typically<br>be removed before the plasma membrane can be patch<br>clamped.<br>1. CISPLATIN. Cisplatin is the major antineoplastic<br>agent used to treat solid tumors such as ovarian, tes

aminoglycosides on hair cells and may indicate a direct acts by blocking the MG channel in hair cells in a man-<br>blockage of the MG channel by quinine.<br>j. FATTY ACIDS. A group of positively charged (medium and Johnstone, 19 peptides is that the extracellular matrix must typical<br>be removed before the plasma membrane can be pat<br>clamped.<br>1. CISPLATIN. Cisplatin is the major antineoplast<br>agent used to treat solid tumors such as ovarian, test<br>ular be removed before the plasma membrane can be patch<br>clamped.<br>1. CISPLATIN. Cisplatin is the major antineoplastic<br>agent used to treat solid tumors such as ovarian, testic-<br>ular and bladder cancers (Rosenberg, 1985; Seymour,<br> clamped.<br>
1. CISPLATIN. Cisplatin is the major antineoplasti<br>
agent used to treat solid tumors such as ovarian, testic<br>
ular and bladder cancers (Rosenberg, 1985; Seymou<br>
1993). Unfortunately, cisplatin has a number of dos l. CISPLATIN. Cisplatin is the major antineoplass<br>agent used to treat solid tumors such as ovarian, test<br>ular and bladder cancers (Rosenberg, 1985; Seymou<br>1993). Unfortunately, cisplatin has a number of dos<br>limiting side e agent used to treat solid tumors such as ovarian, testic-<br>ular and bladder cancers (Rosenberg, 1985; Seymour,<br>1993). Unfortunately, cisplatin has a number of dose-<br>limiting side effects that include ototoxicity with conseular and bladder cancers (Rosenberg, 1985; Seymour, 1993). Unfortunately, cisplatin has a number of dose-<br>limiting side effects that include ototoxicity with consequent hearing loss (see McAlpine and Johnstone, 1990)<br>and d 1993). Unfortunately, cisplatin has a number of dose-<br>limiting side effects that include ototoxicity with conse-<br>quent hearing loss (see McAlpine and Johnstone, 1990)<br>and distal sensory neuropathy, indicated by early de-<br>c limiting side effects that include ototoxicity with consequent hearing loss (see McAlpine and Johnstone, 199<br>and distal sensory neuropathy, indicated by early c<br>creased vibratory sensibility (Thompson et al., 198<br>Based on quent hearing loss (see McAlpine and Johnstone, 1990)<br>and distal sensory neuropathy, indicated by early de-<br>creased vibratory sensibility (Thompson et al., 1985).<br>Based on acute studies on guinea pig cochlear micro-<br>phonic and distal sensory neuropathy, indicated by early decreased vibratory sensibility (Thompson et al., 1985<br>Based on acute studies on guinea pig cochlear microphonic potentials, it has been proposed that cisplati<br>acts by bloc creased vibratory sensibility (Thompson et al., 1985).<br>Based on acute studies on guinea pig cochlear micro-<br>phonic potentials, it has been proposed that cisplatin<br>acts by blocking the MG channel in hair cells in a man-<br>ner Based on acute studies on guinea pig cochlear micro-<br>phonic potentials, it has been proposed that cisplatin<br>acts by blocking the MG channel in hair cells in a man-<br>ner analogous to aminoglycoside antibiotics (McAlpine<br>and phonic potentials, it has been proposed that cisplatin<br>acts by blocking the MG channel in hair cells in a man-<br>ner analogous to aminoglycoside antibiotics (McAlpine<br>and Johnstone, 1990). However, voltage clamp studies of<br>h acts by blocking the MG channel in hair cells in a man-<br>ner analogous to aminoglycoside antibiotics (McAlpine<br>and Johnstone, 1990). However, voltage clamp studies of<br>hair cells have not been carried out to confirm this<br>ac ner analogous to aminoglycoside antibiotics (McAlpine and Johnstone, 1990). However, voltage clamp studies of hair cells have not been carried out to confirm this action. In our own studies to test this proposed action, w and Johnstone, 1990). However, voltage clamp studies of hair cells have not been carried out to confirm this action. In our own studies to test this proposed action, we have found that, at up to  $100 \mu$ M, neither cisplati nor transplatin blocks the MG cation channel in Xenoservations).

# <sup>244</sup> **HAMILL AND MCBRIDE**



**<sup>a</sup>** A, activate; NE, no effect; I, inhibit.

m. TARANTULA SPIDER *(GRAMMOSTOLA SPATULATA)* A, activate; NE, no effect; I, inhibit.<br>
m. TARANTULA SPIDER (GRAMMOSTOLA SPATULATA) 1996).<br>
VENOM. Preliminary reports indicate that the venom neurol<br>
from the tarantula spider (Grammostola spatulata) (GS) compo from the tarantula spider, the tarantula spider *(GRAMMOSTOLA SPATULATA)*<br>
From the tarantula spider *(Grammostola spatulata)* (GS) c<br>
blocks SA channel currents in *Xenopus* oocytes and chick 1 m. TARANTULA SPIDER (*GRAMMOSTOLA SPATULATA*) 19:<br>VENOM. Preliminary reports indicate that the venom nee<br>from the tarantula spider (*Grammostola spatulata*) (GS) cor<br>blocks SA channel currents in *Xenopus* oocytes and chic m. TARANTULA SPIDER (GRAMMOSTOLA SPATULATA) 1<br>VENOM. Preliminary reports indicate that the venom<br>from the tarantula spider (Grammostola spatulata) (GS) c<br>blocks SA channel currents in Xenopus oocytes and chick 1<br>heart cell vENOM. Preliminary reports indicate that the venom<br>from the tarantula spider (*Grammostola spatulata*) (GS)<br>blocks SA channel currents in *Xenopus* occytes and chick<br>heart cells (Niggell et al., 1996). GS venom also block from the tarantula spider (*Grammostola spatulata*) (GS) con<br>blocks SA channel currents in *Xenopus* oocytes and chick lar<br>heart cells (Niggell et al., 1996). GS venom also blocks nel<br>the hypotonic swelling-induced elevat blocks SA channel currents in *Xenopus* occytes and chick<br>heart cells (Niggell et al., 1996). GS venom also blocks net<br>the hypotonic swelling-induced elevation of intracellular<br> $Ca^{2+}$  (sensed with Fura-2) in GH3 cells pr heart cells (Niggell et al., 1996). GS venom also blocks nelset<br>the hypotonic swelling-induced elevation of intracellular n.<br>Ca<sup>2+</sup> (sensed with Fura-2) in GH3 cells proposed to be colce<br>mediated by SA cation channels (Ch the hypotonic swelling-induced elevation of intracellular n. CC  $a^{2+}$  (sensed with Fura-2) in GH3 cells proposed to be colchic mediated by SA cation channels (Chen et al., 1996). The crotub blocking concentrations of ve  $Ca^{2+}$  (sensed with Fura-2) in GH3 cells proposed to be colomediated by SA cation channels (Chen et al., 1996). The croblocking concentrations of venom used were 1000 to due 15,000 times dilutions in saline. Identificati mediated by SA cation channels (Chen et al., 1996). The blocking concentrations of venom used were 1000 115,000 times dilutions in saline. Identification of the M<br>channel active components of the venom has yet to b<br>made. C blocking concentrations of venom used were 1000 to dues 15,000 times dilutions in saline. Identification of the MG (C channel active components of the venom has yet to be damade. Concerning the venom's specificity for MG

nitrophenol and the study on rat hippocampal and  $\frac{1}{2}$  and  $\frac{1}{2}$  and  $\frac{1}{2}$  and 1996). However, in another study on rat hippocampal<br>neurons, it has been shown that a purified GS venom<br>component (w-grammotoxin) does block in the micromo-1996). However, in another study on rat hippocam<br>neurons, it has been shown that a purified GS ven<br>component (w-grammotoxin) does block in the micron<br>lar range N-, P- and Q-type but not L-type  $Ca^{2+}$  ch 1996). However, in another study on rat hippocamponeurons, it has been shown that a purified GS venom component  $(w$ -grammotoxin) does block in the micrometer and Q-type but not L-type  $Ca^{2+}$  channels (Piser et al., 1995) 1996). However, in another study on rat hippocampal<br>neurons, it has been shown that a purified GS venom<br>component (*w*-grammotoxin) does block in the micromo-<br>lar range N-, P- and Q-type but not L-type  $Ca^{2+}$  chan-<br>nels

channel active components of the venom has yet to be domesticus (Erler, 1983), respectively. The concentra-<br>made. Concerning the venom's specificity for MG chan-<br>nels, it was demonstrated in GH3 cells that the crude hours component (*w*-grammotoxin) does block in the micromo-<br>lar range N-, P- and Q-type but not L-type  $Ca^{2+}$  chan-<br>nels (Piser et al., 1995).<br>n. COLCHICINE AND VINBLASTINE. The antimiotic drugs,<br>colchicine and vinblastine, w nar range N-, F- and Q-type but not L-type Ca<br>mels (Piser et al., 1995).<br>n. COLCHICINE AND VINBLASTINE. The antimiotic drugs,<br>colchicine and vinblastine, which act by disrupting mi-<br>crotubules (Borgers et al., 1975), aboli colchicine and vinblastine, which act by disrupting microtubules (Borgers et al., 1975), abolish mechanotrans-<br>duction in the nematode *Caenorhabditis elegans*<br>(Chalfie and Thomson, 1982) and the cricket *Acheta* colchicine and vinblastine, which act by disrupting<br>crotubules (Borgers et al., 1975), abolish mechanotri<br>duction in the nematode *Caenorhabditis eleg*<br>(Chalfie and Thomson, 1982) and the cricket *Act*<br>*domesticus* (Erler, crotubules (Borgers et al., 1975), abolish mechanotrans-<br>duction in the nematode *Caenorhabditis elegans*<br>(Chalfie and Thomson, 1982) and the cricket *Acheta*<br>domesticus (Erler, 1983), respectively. The concentra-<br>tions an duction in the nematode *Caenorhabditis elegans*<br>(Chalfie and Thomson, 1982) and the cricket *Acheta*<br>*domesticus* (Erler, 1983), respectively. The concentra-<br>tions and incubation times used were 0.5 to 1mM for 12<br>hours fo (Chalfie and Thomson, 1982) and the cricket *Acheta domesticus* (Erler, 1983), respectively. The concentrations and incubation times used were 0.5 to  $1 \text{mM}$  for 12 hours for colchicine and 10  $\text{mM}$  for up to 21 hour

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PHARMACOLOGICAL REVIEWS

**PHARMACOLOGY OF MECHANOGATED MEMBRANE ION CHANNELS** <sup>245</sup>

PHARMACOLOGY OF MECHANOG.<br>
ture that is disrupted is proposed to be part of a su-<br>
pramolecular complex that underlies touch sensitivity PHARMACOLOGY OF MECHANOGAT<br>ture that is disrupted is proposed to be part of a su-<br>pramolecular complex that underlies touch sensitivity<br>(Thurm et al., 1983; Huang et al., 1995; for review see PHARMACOLOGY OF MECHANOGATED<br>
ture that is disrupted is proposed to be part of a su-<br>
complex that underlies touch sensitivity Kii<br>
(Thurm et al., 1983; Huang et al., 1995; for review see signall and McBride, 1996b). In co ture that is disrupted is proposed to be part of a su-<br>pramolecular complex that underlies touch sensitivity K<br>(Thurm et al., 1983; Huang et al., 1995; for review see si<br>Hamill and McBride, 1996b). In contrast to the block ture that is disrupted is proposed to be part of a su-<br>pramolecular complex that underlies touch sensitivity<br>(Thurm et al., 1983; Huang et al., 1995; for review see<br>Hamill and McBride, 1996b). In contrast to the blocking<br>e pramolecular complex that underlies touch sensitivity K<br>(Thurm et al., 1983; Huang et al., 1995; for review see si<br>Hamill and McBride, 1996b). In contrast to the blocking si<br>effects of these drugs on lower invertebrates, n (Thurm et al., 1983; Huang et al., 1995; for review see Hamill and McBride, 1996b). In contrast to the blocking effects of these drugs on lower invertebrates, neither colchicine nor vinblastine reduces MG channel activity Hamill and McBride, 1996b). In contrast to the blockine effects of these drugs on lower invertebrates, neith<br>colchicine nor vinblastine reduces MG channel activit<br>in chick skeletal muscle (see Sachs, 1988) or in Xenopu<br>occ effects of these drugs on lower invertebrates, neither colchicine nor vinblastine reduces MG channel activity in chick skeletal muscle (see Sachs, 1988) or in *Xenopus* oocytes (OPH and DWM unpublished observations). This colchicine nor vinblastine reduces MG channel activity<br>in chick skeletal muscle (see Sachs, 1988) or in *Xenopus*<br>oocytes (OPH and DWM unpublished observations).<br>This lack of sensitivity in the oocyte may indicate that<br>oth in chick skeletal muscle (see Sachs, 1988) or in *Xenopus* Can cocytes (OPH and DWM unpublished observations). 19 This lack of sensitivity in the occyte may indicate that For ther types of non-microtubule cytoskeletal stru This lack of sensitivity in the oocyte may indicate that<br>other types of non-microtubule cytoskeletal structures<br>can focus mechanical energy onto MG channels (see<br>Sachs, 1988; Hamill and McBride, 1995a).<br>5. Blocker sensitiv is lack of sensitivity in the oocyte may indicate that<br>her types of non-microtubule cytoskeletal structures<br>n focus mechanical energy onto MG channels (see<br>chs, 1988; Hamill and McBride, 1995a).<br>5. Blocker sensitivity of m

other types of non-microtubule cytoskeletal structures<br>can focus mechanical energy onto MG channels (see<br>Sachs, 1988; Hamill and McBride, 1995a).<br>5. Blocker sensitivity of mechanosensitive processes.<br>Table 4 lists the wide can focus mechanical energy onto MG channels (see<br>Sachs, 1988; Hamill and McBride, 1995a).<br>5. *Blocker sensitivity of mechanosensitive processes*.<br>Table 4 lists the wide variety of mechanosensitive processes that have bee cesses that have been tested at the tissue or whole cell<br>level for MG channel blocker sensitivity. Clearly,  $Gd^{3+}$ <br>has proven the most popular agent in such studies. A 5. Blocker sensitivity of mechanosensitive processes. ingly, G<br>Table 4 lists the wide variety of mechanosensitive procause a<br>cesses that have been tested at the tissue or whole cell Gd<sup>3+</sup> b<br>level for MG channel blocker s Table 4 lists the wide variety of mechanosensitive processes that have been tested at the tissue or whole cell Gd level for MG channel blocker sensitivity. Clearly,  $Gd^{3+}$  me has proven the most popular agent in such st cesses that have been tested at the tissue or whole cell  $G$ <br>level for MG channel blocker sensitivity. Clearly,  $Gd^{3+}$ <br>has proven the most popular agent in such studies. A<br>likely reason for this is that  $Gd^{3+}$  causes level for MG channel blocker sensitivity. Clearly,  $Gd^{3+}$  has proven the most popular agent in such studies. A likely reason for this is that  $Gd^{3+}$  causes a complete and voltage-independent block (i.e., "knock out" e has proven the most popular agent in such studies. A<br>likely reason for this is that  $Gd^{3+}$  causes a complete and a r<br>voltage-independent block (i.e., "knock out" effect) of hyp<br>many types of SA channels, often at relati likely reason for this is that  $Gd^{3+}$  causes a complete and voltage-independent block (i.e., "knock out" effect) of many types of SA channels, often at relatively low concentrations (1 to 20  $\mu$ M). In contrast, amilori voltage-independent block (i.e., "knock out" effect) of many types of SA channels, often at relatively low concentrations (1 to 20  $\mu$ M). In contrast, amiloride and aminoglycosides only produce a partial and highly volta many types of SA channels, often at relatively low concentrations (1 to 20  $\mu$ M). In contrast, amiloride and maninoglycosides only produce a partial and highly volt-<br>age-dependent block, even with relatively high drug co centrations (1 to 20  $\mu$ M). In contrast, amiloride and meaninoglycosides only produce a partial and highly voltage-dependent block, even with relatively high drug concentrations (1 to 2 mM). However, even if Gd<sup>3+</sup>'s act aminoglycosides only produce a partial and highly volt-<br>age-dependent block, even with relatively high drug con-<br>centrations (1 to 2 mM). However, even if  $Gd^{3+}$ 's action is cal re<br>all-or-none, additional control experi age-dependent block, even with relatively high drug concentrations (1 to 2 mM). However, even if  $Gd^{3+}$ 's action is call-or-none, additional control experiments should be process. For example, a false in channel role in centrations (1 to 2 mM). However, even if  $Gd^{3+s}$  action all-or-none, additional control experiments should carried out before either accepting or rejecting an  $\Lambda$  channel role in a specific process. For example, a fa p all-or-none, additional control experiments should be carried out before either accepting or rejecting an MG channel role in a specific process. For example, a false positive could arise if the process involved a voltageg carried out before either accepting or rejecting an MG into<br>channel role in a specific process. For example, a false ind<br>positive could arise if the process involved a voltage-<br>gated Ca<sup>2+</sup> channel or another process that channel role in a specific process. For example, a false<br>positive could arise if the process involved a voltage-<br>gated Ca<sup>2+</sup> channel or another process that was Gd<sup>3+</sup><br>blocked. Conversely, a false negative may arise if a gated Ca<sup>2+</sup> channel or another process that was  $Gd^{3+}$  blocked. Conversely, a false negative may arise if an underlying MG channel is  $Gd^{3+}$  insensitive (see table 3). Notwithstanding these caveats, the breadth of ph blocked. Conversely, a false negative may arise if an underlying MG channel is  $Gd^{3+}$  insensitive (see table 3). Notwithstanding these caveats, the breadth of physiologically important mechanosensitive processes that di underlying MG channel is  $Gd^{3+}$  insensitive (see table 3). underlying MG channel is  $Gd^{3+}$  insensitive (see table 3<br>Notwithstanding these caveats, the breadth of physic<br>logically important mechanosensitive processes that di<br>play, at the tissue and/or whole cell level, the same Notwithstanding these caveats, the breadth of physlogically important mechanosensitive processes that c<br>play, at the tissue and/or whole cell level, the same Gosensitivity and ionic requirements as single MG chanels record play, at the tissue and/or whole cell level, the same  $Gd^{3+}$  sequent net water influx. In this regard,  $Gd^{3+}$  also sensitivity and ionic requirements as single MG chan-<br>nels recorded in the membrane patch is highly im play, at the tissue and/or whole cell level, the same  $Gd^{3+}$  sequents:<br>
sensitivity and ionic requirements as single MG chan-<br>
hold nels recorded in the membrane patch is highly impres-<br>
(Ch<br>
sive. Presumably, it is the sensitivity and ionic requirements as single MG channels recorded in the membrane patch is highly impressive. Presumably, it is the functional versatility of MG channels that underlies their ubiquitous expression in cells channels that underlies their ubiquitous expression in c. GROWTH AND DEVELOPMENTAL EVENTS. It is plausible cells spanning the full evolutionary spectrum. Other that as cells grow in size, develop and divide that mechannota sive. Presumably, it is the functional versatility of MG channels that underlies their ubiquitous expression in cells spanning the full evolutionary spectrum. Other notable highlights, trends and exceptions indicated in t

cells spanning the full evolutionary spectrum. Other that notable highlights, trends and exceptions indicated in ical table 4 are discussed below (see Section III.A.5.a-f). chan a MECHANICALLY INDUCED ELEVATION OF INTERNA notable highlights, trends and exceptions indicated in table 4 are discussed below (see Section III.A.5.a-f).<br>a. MECHANICALLY INDUCED ELEVATION OF INTERNAL  $CA^{2+}$ .<br>Internal  $Ca^{2+}$  is well recognized as a second-messenge table 4 are discussed below (see Section III.A.5.a-f). channot a. MECHANICALLY INDUCED ELEVATION OF INTERNAL  $CA^{2+}$ . trimulation  $Ca^{2+}$  is well recognized as a second-messenger in cause elevation of a stimulation that c a. MECHANICALLY INDUCED ELEVATION OF INTERNAL  $CA^{2+}$ .<br>Internal  $Ca^{2+}$  is well recognized as a second-messenger in<br>a wide range of cellular processes. In table 4, the various<br>forms of mechanical stimulation that cause el Internal Ca<sup>2+</sup> is well recognized as a second-messenger in cell<br>a wide range of cellular processes. In table 4, the various express of mechanical stimulation that cause elevation of str<br> $[Ca^{2+}$ <sub>i</sub>, in various cell types a wide range of cellular processes. In table 4, the various<br>forms of mechanical stimulation that cause elevation of<br> $[Ca^{2+}]$ <sub>i</sub> in various cell types are listed. In general,  $[Ca^{2+}]$ <sub>i</sub><br>elevation may come about from one o forms of mechanical stimulation that cause elevation of  $[Ca^{2+}]_i$  in various cell types are listed. In general,  $[Ca^{2+}]_i$  elevation may come about from one or a combination of the following mechanisms: increased  $Ca^{2+}$  $[Ca^{2+}]_i$  in various cell types are listed. In general,  $[Ca^{2+}]_i$  erained elevation may come about from one or a combination of the *Xe* following mechanisms: increased  $Ca^{2+}$  influx from the external solution; decreas elevation may come about from one or a combination of the *Xe*<br>following mechanisms: increased  $Ca^{2+}$  influx from the ex-<br>ternal solution; decreased  $Ca^{2+}$  efflux from the cell and/or blo<br>increased  $Ca^{2+}$  mobilization following mechanisms: increased  $Ca^{2+}$  influx from the ex-<br>ternal solution; decreased  $Ca^{2+}$  efflux from the cell and/or<br>increased  $Ca^{2+}$  mobilization from internal stores. In many a c<br>of the cases listed in table 4, t increased Ca<sup>2+</sup> mobilization from internal stores. In many a critical role in oocyte maturation, fertilization or embry-<br>of the cases listed in table 4, the MS  $[Ca^{2+}]$ , increase is ogenesis (see Wilkinson et al., 1996a, blocked by  $Gd^{3+}$ . This is consistent with a Ca<sup>2+</sup> influx via sible role in oocyte growth and differentiation has not been  $Gd^{3+}$ -sensitive SA cation channels (Sigurdson et al., 1992; excluded. The proposal that SA c of the cases listed in table 4, the MS  $[Ca^{2+}]$ , increase is oge blocked by  $Gd^{3+}$ . This is consistent with a  $Ca^{2+}$  influx via sible  $Gd^{3+}$ -sensitive SA cation channels (Sigurdson et al., 1992; excelliver and Chase blocked by  $Gd^{3+}$ . This is consistent with a  $Ca^{2+}$  influx  $Gd^{3+}$ -sensitive SA cation channels (Sigurdson et al., 19. Oliver and Chase, 1992; Naruse and Sokabe, 1993; Hara et al., 1993; Sharma et al., 1995). However,  $Gd^{3+}$ -sensitive SA cation channels (Sigurdson et al., 1992;<br>Oliver and Chase, 1992; Naruse and Sokabe, 1993; Harada<br>et al., 1993; Sharma et al., 1995). However, there is also<br>pharmacological evidence for L-type  $Ca^{2+}$ 

ED MEMBRANE ION CHANNELS<br>Carty and O'Neil, 1991; Boitano et al., 1994; Mooren and<br>Kinne, 1994, but see Naruse and Sokabe, 1993), which is ED MEMBRANE ION CHANNELS<br>Carty and O'Neil, 1991; Boitano et al., 1994; Mooren and<br>Kinne, 1994, but see Naruse and Sokabe, 1993), which is<br>significant given the recently demonstrated mechanosen-SED MEMBRANE ION CHANNELS<br>Carty and O'Neil, 1991; Boitano et al., 1994; Mooren<br>Kinne, 1994, but see Naruse and Sokabe, 1993), whi<br>significant given the recently demonstrated mechanositivity of this channel (Ben Tabou et al Carty and O'Neil, 1991; Boitano et al., 1994; Mooren and<br>Kinne, 1994, but see Naruse and Sokabe, 1993), which is<br>significant given the recently demonstrated mechanosen-<br>sitivity of this channel (Ben Tabou et al., 1994; Lan Carty and O'Neil, 1991; Boitano et al., 1994; Mooren and Kinne, 1994, but see Naruse and Sokabe, 1993), which is significant given the recently demonstrated mechanosensitivity of this channel (Ben Tabou et al., 1994; Lang Kinne, 1994, but see Naruse and Sokabe, 1993), which is<br>significant given the recently demonstrated mechanosen-<br>sitivity of this channel (Ben Tabou et al., 1994; Langton,<br>1993). In cases in which the mechanically induced significant given the recently demonstrated mechanosensitivity of this channel (Ben Tabou et al., 1994; Langton, 1993). In cases in which the mechanically induced increase in  $[Ca^{2+}]$ , occurs via release from internal st sitivity of this channel (Ben Tabou et al., 1994; Langton, 1993). In cases in which the mechanically induced increase in  $[Ca^{2+}l_i$  occurs via release from internal stores, external  $Ca^{2+}$  is not necessary (Boitano et al 1993). In cases in which the mechanically induced increase<br>in  $[Ca^{2+}]_i$  occurs via release from internal stores, external<br> $Ca^{2+}$  is not necessary (Boitano et al., 1994; Charles et al.,<br>1991; Demer et al., 1993; but see in  $[Ca^{2+}]$  occurs via release from internal stores, external  $Ca^{2+}$  is not necessary (Boitano et al., 1994; Charles et al., 1991; Demer et al., 1993; but see Sigurdson et al., 1992). For example, in airway epithelial ce  $Ca^{2+}$  is not necessary (Boitano et al., 1994; Charles et al., 1991; Demer et al., 1993; but see Sigurdson et al., 1992).<br>For example, in airway epithelial cells, internal  $Ca^{2+}$  release is proposed to be mediated by a 1991; Demer et al., 1993; but see Sigurdson et al., 199<br>For example, in airway epithelial cells, internal Ca<sup>2+</sup><br>lease is proposed to be mediated by a mechanosensit<br>phospholipase C that modulates, via IP<sub>3</sub>, Ca<sup>2+</sup> rele<br>f For example, in airway epithelial cells, internal  $Ca^{2+}$  re-<br>lease is proposed to be mediated by a mechanosensitive<br>phospholipase C that modulates, via  $IP_3$ ,  $Ca^{2+}$  release<br>from internal  $Ca^{2+}$  stores (Boitano et al., lease is proposed to be mediated by a mechanosensitive<br>phospholipase C that modulates, via  $IP_3$ ,  $Ca^{2+}$  release<br>from internal  $Ca^{2+}$  stores (Boitano et al., 1994). Interest-<br>ingly,  $Gd^{3+}$  addition, in the absence of phospholipase C that modulates, via  $IP_3$ ,  $Ca^{2+}$  release<br>from internal  $Ca^{2+}$  stores (Boitano et al., 1994). Interest-<br>ingly,  $Gd^{3+}$  addition, in the absence of external  $Ca^{2+}$ , can<br>cause a larger MS increase in  $[Ca$ membrane (Boitano et al., 1994). Interest-<br>ingly,  $Gd^{3+}$  addition, in the absence of external  $Ca^{2+}$ , can<br>cause a larger MS increase in  $[Ca^{2+}]}_i$ , presumably because<br> $Gd^{3+}$  blocks  $Ca^{2+}$  efflux via MG channels in

Gd<sup>3+</sup> blocks Ca<sup>2+</sup> efflux via MG channels in the plasma<br>membrane (Boitano et al., 1994). Nany cell types show<br>a regulatory volume decrease (RVD) when swollen in<br>hypotonic solutions. Table 4 lists examples of RVD that<br>ca hypotonic solutions. Table 4 lists examples of RVD that membrane (Boitano et al., 1994).<br>b. VOLUME REGULATORY EVENTS. Many cell types show<br>a regulatory volume decrease (RVD) when swollen in<br>hypotonic solutions. Table 4 lists examples of RVD that<br>can be blocked by low (10  $\mu$ M b. VOLUME REGULATORY EVENTS. Many cell types show<br>a regulatory volume decrease (RVD) when swollen in<br>hypotonic solutions. Table 4 lists examples of RVD that<br>can be blocked by low (10  $\mu$ M) Gd<sup>3+</sup>. In general, RVD is<br>medi a regulatory volume decrease (RVD) when swollen in<br>hypotonic solutions. Table 4 lists examples of RVD that<br>can be blocked by low  $(10 \ \mu\text{m}) \text{ Gd}^{3+}$ . In general, RVD is<br>mediated by an increase in K<sup>+</sup> and Cl<sup>-</sup> efflux hypotonic solutions. Table 4 lists examples of RVD tha<br>can be blocked by low  $(10 \ \mu\text{M}) \text{Gd}^{3+}$ . In general, RVD i<br>mediated by an increase in K<sup>+</sup> and Cl<sup>-</sup> efflux and con<br>sequent net water efflux and may involve eit can be blocked by low (10  $\mu$ M) Gd<sup>3+</sup>. In general, RVD is<br>mediated by an increase in K<sup>+</sup> and Cl<sup>-</sup> efflux and con-<br>sequent net water efflux and may involve either Ca<sup>2+</sup>-<br>dependent or Ca<sup>2+</sup>-independent mechanisms (for mediated by an increase in  $K^+$  and  $Cl^-$  efflux and consequent net water efflux and may involve either  $Ca^{2+}$ -<br>dependent or  $Ca^{2+}$ -independent mechanisms (for critical review see Foskett, 1994). Therefore,  $Gd^{3+}$  cou sequent net water efflux and may involve either  $Ca^{2+}$ -<br>dependent or  $Ca^{2+}$ -independent mechanisms (for criti-<br>cal review see Foskett, 1994). Therefore,  $Gd^{3+}$  could<br>presumably block RVD either by blocking  $Ca^{2+}$  inf dependent or Ca<sup>2+</sup>-independent mechanisms (for critical review see Foskett, 1994). Therefore,  $Gd^{3+}$  could<br>presumably block RVD either by blocking  $Ca^{2+}$  influx<br>into the cell (e.g., via a SA cation channel), thereby<br>i cal review see Foskett, 1994). Therefore,  $Gd^{3+}$  could<br>presumably block RVD either by blocking  $Ca^{2+}$  influx<br>into the cell (e.g., via a SA cation channel), thereby<br>indirectly blocking  $K^+_{(Ca)}$  and/or  $Cl_{(Ca)}$  channels presumably block RVD either by blocking  $Ca^{2+}$  influx<br>into the cell (e.g., via a SA cation channel), thereby<br>indirectly blocking  $K^+_{(Ca)}$  and/or  $Cl^-_{(Ca)}$  channels (table<br>4) or by directly blocking swelling-activated  $K^$ into the cell (e.g., via a SA cation channel), thereby<br>indirectly blocking  $K^+_{(Ca)}$  and/or  $Cl^-_{(Ca)}$  channels (table<br>4) or by directly blocking swelling-activated  $K^+$  and/or<br> $Cl^-$  channels (Deutsch and Lee, 1988; Berrier indirectly blocking  $K^+(C_a)$  and/or  $Cl^-(C_a)$  channels (table 4) or by directly blocking swelling-activated  $K^+$  and/or  $Cl^-$  channels (Deutsch and Lee, 1988; Berrier et al., 1992; Medrano and Gruenstein, 1993; Ackerman et 4) or by directly blocking swelling-activated  $K^+$  and/or  $Cl^-$  channels (Deutsch and Lee, 1988; Berrier et al., 1992; Medrano and Gruenstein, 1993; Ackerman et al., 1994). Many cells also show a regulatory volume increas Cl<sup>-</sup> channels (Deutsch and Lee, 1988; Berrier et al., 1992; Medrano and Gruenstein, 1993; Ackerman et al., 1994). Many cells also show a regulatory volume increase (RVI) when shrunken in hypertonic solution. RVI may aris 1994). Many cells also show a regulatory volume increase (RVI) when shrunken in hypertonic solution. RVI may arise through net influx of  $Na^+$  and  $Cl^-$  and consequent net water influx. In this regard,  $Gd^{3+}$  also blocks crease (RVI) when shrunken in hypertonic solution. RVI<br>may arise through net influx of Na<sup>+</sup> and Cl<sup>-</sup> and con-<br>sequent net water influx. In this regard,  $Gd^{3+}$  also<br>blocks a cation channel activated by osmotic shrinkag sequent net water influx. In this regard,  $Gd^{3+}$  also blocks a cation channel activated by osmotic shrinks<br>(Chan and Nelson, 1992), although it remains unclear<br>this stage whether the channel is MG.<br>c. GROWTH AND DEVELOPMENTAL EVENTS. It is plausi<br>that as cells grow in size, d

(Chan and Nelson, 1992), although it remains unclear at<br>this stage whether the channel is MG.<br>c. GROWTH AND DEVELOPMENTAL EVENTS. It is plausible<br>that as cells grow in size, develop and divide that mechan-<br>ical signals pl this stage whether the channel is MG.<br>
c. GROWTH AND DEVELOPMENTAL EVENTS. It is plausible<br>
that as cells grow in size, develop and divide that mechan-<br>
ical signals play a regulatory role. In this regard, MG<br>
channels wou c. GROWTH AND DEVELOPMENTAL EVENTS. It is plausible<br>that as cells grow in size, develop and divide that mechan-<br>ical signals play a regulatory role. In this regard, MG<br>channels would seem attractive candidates to sense and that as cells grow in size, develop and divide that mechanical signals play a regulatory role. In this regard, MG channels would seem attractive candidates to sense and transduce tension changes in the cell membrane durin ical signals play a regulatory role. In this regard, MG channels would seem attractive candidates to sense and transduce tension changes in the cell membrane during cell growth and development. This idea has received some channels would seem attractive candidates to sense at transduce tension changes in the cell membrane durincell growth and development. This idea has received son experimental support in the form of  $Gd^{3+}$  sensitivity st transduce tension changes in the cell membrane during<br>cell growth and development. This idea has received some<br>experimental support in the form of  $Gd^{3+}$  sensitivity of<br>stretch-induced endothelial cell alignment, lung c cell growth and development. This idea has received some experimental support in the form of  $Gd^{3+}$  sensitivity of stretch-induced endothelial cell alignment, lung cell proliferation and myoblast fusion (see table 4). I experimental support in the form of  $Gd^{3+}$  sensitivity of stretch-induced endothelial cell alignment, lung cell proliferation and myoblast fusion (see table 4). In the case of *Xenopus* occytes, which do express a relat stretch-induced endothelial cell alignment, lung cell proliferation and myoblast fusion (see table 4). In the case of *Xenopus* occytes, which do express a relatively high and uniform density of MG channels, the lack of MG eration and myoblast fusion (see table 4). In the case of *Xenopus* oocytes, which do express a relatively high and uniform density of MG channels, the lack of MG channel Xenopus oocytes, which do express a relatively high and<br>uniform density of MG channels, the lack of MG channel<br>blocker sensitivity seems to rule out MG channels playing<br>a critical role in oocyte maturation, fertilization o uniform density of MG channels, the lack of MG channel<br>blocker sensitivity seems to rule out MG channels playing<br>a critical role in oocyte maturation, fertilization or embry-<br>ogenesis (see Wilkinson et al., 1996a, b). Howe blocker sensitivity seems to rule out MG channels playing<br>a critical role in oocyte maturation, fertilization or embry-<br>ogenesis (see Wilkinson et al., 1996a, b). However, a pos-<br>sible role in oocyte growth and differentia a critical role in oocyte maturation, fertilization or emb<br>ogenesis (see Wilkinson et al., 1996a, b). However, a p<br>sible role in oocyte growth and differentiation has not be<br>excluded. The proposal that SA cation channels ogenesis (see Wilkinson et al., 1996a, b). However, a possible role in oocyte growth and differentiation has not been excluded. The proposal that SA cation channels are involved in stretch-induced cardiac hypertrophy (Bust sible role in oocyte growth and differentiation has not been excluded. The proposal that SA cation channels are in volved in stretch-induced cardiac hypertrophy (Busta mante et al., 1991) seems unlikely, given that  $Gd^{3+$ excluded. The proposal that SA<br>volved in stretch-induced card<br>mante et al., 1991) seems unlike<br>not block stretch-induced hypert<br>cytes (Sadoshima et al., 1992).

d. SPECIALIZED MECHANOSENSORY RECEPTORS. An obvi-EXTED MECHANOSENSORY RECEPTORS. An obverse question concerning the various MG channel block-<br>hous question concerning the various MG channel block-<br>ers is whether they also act on specialized mechanor HAMI<br>d. SPECIALIZED MECHANOSENSORY RECEPTORS. An ous question concerning the various MG channel bl<br>ers is whether they also act on specialized mechan<br>ceptors such as those studied by Paintal (1964). In ceptors of the US-2012 CHANOSENSORY RECEPTORS. An obvious question concerning the various MG channel block-<br>lipers is whether they also act on specialized mechanore-<br>ceptors such as those studied by Paintal (1964). In the d. SPECIALIZED MECHANOSENSORY RECEPTORS. An obvious question concerning the various MG channel block-<br>ers is whether they also act on specialized mechanore-<br>ceptors such as those studied by Paintal (1964). In the mease of ous question concerning the various MG channel block-<br>ers is whether they also act on specialized mechanore-<br>ceptors such as those studied by Paintal (1964). In the<br>mease of arterial baroreceptors, although an initial stu ers is whether they also act on specialized mechanore-<br>ceptors such as those studied by Paintal (1964). In the mechan<br>case of arterial baroreceptors, although an initial study the bili<br>indicated little or no Gd<sup>3+</sup> sensit ceptors such as those studied by Paintal (1964). In the mecase of arterial baroreceptors, although an initial study the indicated little or no Gd<sup>3+</sup> sensitivity (Andresen and 199 Yang, 1992), more recent studies indicate case of arterial baroreceptors, although an initial study the indicated little or no  $Gd^{3+}$  sensitivity (Andresen and 19 Yang, 1992), more recent studies indicate that 10  $\mu$ M br  $Gd^{3+}$  is sufficient to block barorec indicated little or no  $Gd^{3+}$  sensitivity (Andresen and Yang, 1992), more recent studies indicate that 10  $\mu$ M  $Gd^{3+}$  is sufficient to block baroreceptor discharge in carotid receptors (Hajduczok et al., 1994) as wel Yang, 1992), more recent studies indicate that 10  $\mu$ M<br>Gd<sup>3+</sup> is sufficient to block baroreceptor discharge in<br>carotid receptors (Hajduczok et al., 1994) as well a<br>mechanotransduction in the nodose sensory neuronichat pr carotid receptors (Hajduczok et al., 1994) as well as<br>mechanotransduction in the nodose sensory neurons<br>that project to the carotid (Sharma et al., 1995; Cun-<br>ningham et al., 1995). In the case of central osmorecep-<br>tion, carotid receptors (Hajduczok et al., 1994) as well as nel<br>mechanotransduction in the nodose sensory neurons et a<br>that project to the carotid (Sharma et al., 1995; Cun-<br>ningham et al., 1995). In the case of central osmorec mechanotransduction in the nodose sensory neurons et a<br>that project to the carotid (Sharma et al., 1995; Cun-<br>ningham et al., 1995). In the case of central osmorecep-<br>have tion, which is important in regulating fluid bala that project to the carotid (Sharma et al., 1995; Cu<br>ningham et al., 1995). In the case of central osmoreccion, which is important in regulating fluid balance a<br>thirst, it has been demonstrated that  $Gd^{3+}$  blocks (IQ<br>= ningham et al., 1995). In the case of central osmoreception, which is important in regulating fluid balance and thirst, it has been demonstrated that  $Gd^{3+}$  blocks (IC<sub>50</sub> = 20  $\mu$ M) the hypertonically induced MG catio tion, which is important in regulating fluid balance an<br>thirst, it has been demonstrated that  $Gd^{3+}$  blocks  $(IC_{\epsilon}$ <br>= 20  $\mu$ M) the hypertonically induced MG cation conductance that underlies osmosensitivity in rat bra thirst, it has been demonstrated that  $Gd^{3+}$  blocks  $(IC_{50}$  (e<br>= 20  $\mu$ M) the hypertonically induced MG cation conduc-<br>tance that underlies osmosensitivity in rat brain su-<br>praoptic neurons (Oliet and Bourque, 1994, 1 = 20  $\mu$ M) the hypertonically induced MG cation conductance that underlies osmosensitivity in rat brain su-<br>praoptic neurons (Oliet and Bourque, 1994, 1996). How-<br>never, in the most recent study, examination of the singl tance that underlies osmosensitivity in rat brain s<br>praoptic neurons (Oliet and Bourque, 1994, 1996). Ho<br>ever, in the most recent study, examination of the sing<br>channel data indicates that  $Gd^{3+}$  only partially block<br>th praoptic neurons (Oliet and Bourque, 1994, 1996). How-<br>ever, in the most recent study, examination of the single<br>channel data indicates that  $Gd^{3+}$  only partially blocked<br>the channel, even at 100  $\mu$ M. Unfortunately, a ever, in the most recent study, examination of the single prochannel data indicates that  $Gd^{3+}$  only partially blocked parties the chelator ethylenediamine-tetraacetic acid (1 mM) in ion the pipette recording solution. channel data indicates that  $Gd^{3+}$  only partially blocked<br>the channel, even at 100  $\mu$ M. Unfortunately, a compli-<br>cating factor in these measurements was the presence of<br>the chelator ethylenediamine-tetraacetic acid (1 the channel, even at 100  $\mu$ M. Unfortunately, a complicating factor in these measurements was the presence of the chelator ethylenediamine-tetraacetic acid (1 mM) in the pipette recording solution. In the case of vertebr cating factor in these measurements was the presence of<br>the chelator ethylenediamine-tetraacetic acid (1 mM) in<br>the pipette recording solution. In the case of vertebrate<br>muscle stretch receptors, relatively high (~1 mM) G the pipette recording solution. In the case of vertebrate<br>muscle stretch receptors, relatively high (~1 mM)  $Gd^{3+}$ <br>or high (2 mM) amiloride concentrations only produce<br>partial block (Ito et al., 1990). Similarly, high ( the pipette recording solution. In the case of vertebrate the muscle stretch receptors, relatively high  $(\sim 1 \text{ mM}) \text{ Gd}^{3+}$  required to block (Ito et al., 1990). Similarly, high  $(400 \ \mu\text{M})$  op  $\text{Gd}^{3+}$  is require muscle stretch receptors, relatively high  $(\sim 1 \text{ mM}) \text{ Gd}^{3+}$ <br>or high (2 mM) amiloride concentrations only produce<br>partial block (Ito et al., 1990). Similarly, high (400  $\mu$ M)<br> $\text{Gd}^{3+}$  is required to block the cray or high  $(2 \text{ mM})$  amiloride concentrations only produce<br>partial block (Ito et al., 1990). Similarly, high  $(400 \ \mu\text{m})$ <br> $Gd^{3+}$  is required to block the crayfish muscle stretch<br>receptor (Swerup et al., 1991). Unfortunat partial block (Ito et al., 1990). Similarly, high (400  $\mu$ M) Gd<sup>3+</sup> is required to block the crayfish muscle stretch receptor (Swerup et al., 1991). Unfortunately, no reports exist on the Gd<sup>3+</sup> sensitivity of specialize  $Gd^{3+}$  is required to block the crayfish muscle stretch between the Gd<sup>3+</sup> sensitivity of specialized cutaneous veckist on the  $Gd^{3+}$  sensitivity of specialized cutaneous vechanoreceptors such as the Pacinian corpuscl receptor (Swerup et al., 1991). Unfortunately, no reporexist on the  $Gd^{3+}$  sensitivity of specialized cutaneou mechanoreceptors such as the Pacinian corpuscle. Finally, although amiloride and aminogly cosides are we est exist on the  $Gd^{3+}$  sensitivity of specialized cutaneous without affecting the slope of the Boltzmann (i.e., stim-<br>mechanoreceptors such as the Pacinian corpuscle. Fi-<br>nuls-response curve). These effects were interprete mechanoreceptors such as the Pacinian corpuscle. Fi-<br>nally, although amiloride and aminoglycosides are well<br>established blockers of mechanotransduction in the verte-<br>amp<br>brate audiovestibular hair cells, there are no publ mally, although amiloride and aminoglycosides are well<br>established blockers of mechanotransduction in the verte-<br>brate audiovestibular hair cells, there are no published<br>animeports on the Gd<sup>3+</sup> sensitivity of mechanotran established blockers of mechanotransduction in the verte-<br>brate audiovestibular hair cells, there are no published<br>reports on the  $Gd^{3+}$  sensitivity of mechanotransduction in<br>this preparation, although high  $Gd^{3+}$  con brate audiovestibular hair cells, there are no published and reports on the  $Gd^{3+}$  sensitivity of mechanotransduction in of this preparation, although high  $Gd^{3+}$  concentrations (500 com  $\mu$ M) have been reported to b reports on the Gd<sup>3+</sup> sensitivity of mechanotransduction in of this preparation, although high  $Gd^{3+}$  concentrations (500 core  $\mu$ M) have been reported to block voltage-dependent outer into thair cell motility (Santos-

hair cell motility (Santos-Sacchi, 1989, 1991; however, see adj<br>Gale and Ashmore, 1994). However how the muscle for SA cation channels in stretch-induced contraction in<br>in smooth muscle (table 4; see also Kirber et al., 19 Gale and Ashmore, 1994).<br>
e. MUSCLE. MG channel blocker sensitivity supports a<br>
role for SA cation channels in stretch-induced contraction<br>
in smooth muscle (table 4; see also Kirber et al., 1988) and<br>
stretch-induced depo e. MUSCLE. MG channel blocker sensitivity supports a<br>role for SA cation channels in stretch-induced contraction<br>in smooth muscle (table 4; see also Kirber et al., 1988) and<br>stretch-induced depolarizations and arrhythmias i le for SA cation channels in stretch-induced contraction<br>smooth muscle (table 4; see also Kirber et al., 1988) and<br>retch-induced depolarizations and arrhythmias in ven-<br>cular muscle (Hansen et al., 1991; Stacy et al., 199

stretch-induced depolarizations and arrhythmias in ven-<br>tricular muscle (Hansen et al., 1991; Stacy et al., 1992). and<br>f. PLANTS. Perhaps the most notable feature of plant the<br>studies is the wide range of  $Gd^{3+}$  concent tricular muscle (Hansen et al., 1991; Stacy et al., 1992).<br>
f. PLANTS. Perhaps the most notable feature of plant<br>
studies is the wide range of  $Gd^{3+}$  concentrations required<br>
to block different processes. For example, w f. PLANTS. Perhaps the most notable feature of plant tistudies is the wide range of  $Gd^{3+}$  concentrations required at to block different processes. For example, whereas only 100 spicomolar  $Gd^{3+}$  is required to block studies is the wide range of  $Gd^{3+}$  conto block different processes. For examp<br>picomolar  $Gd^{3+}$  is required to block the potential in *Chara*, 10 mM  $Gd^{3+}$  (tendril coiling in *Bryonia* (table 4). tion potential in *Chara*, 10 mM  $Gd^{3+}$  only partially blocks<br>tendril coiling in *Bryonia* (table 4).<br>*B. Activators*<br>A diverse group of compounds including lipid metab-<br>olites, free fatty acids, lipids and amphipathic

# **B.** *Activators*

are able to activate certain MG channels. It is believed a<br>
al<br>
B. Activators<br>
A diverse group of compounds including lipid metab-<br>
olites, free fatty acids, lipids and amphipathic molecules<br>
pare able to activate certain MG channels. It is believed<br>
that these compounds themsel B. Activators<br>A diverse group of compounds including lipid metab-<br>olites, free fatty acids, lipids and amphipathic molecules<br>are able to activate certain MG channels. It is believed<br>that these compounds themselves directly A diverse group of compounds including lipid metab-<br>olites, free fatty acids, lipids and amphipathic molecules<br>are able to activate certain MG channels. It is believed<br>that these compounds themselves directly affect channe

metabolites through various enzymatic pathways (e.g., MCBRIDE<br>!metabolites through various enzymatic pathways (e.g.,<br>lipoxygenase or cyclo-oxygenase pathways) that then act<br>on the channel (Meves, 1994). A number of possible MCBRIDE<br>metabolites through various enzymatic pathways (e.g.,<br>lipoxygenase or cyclo-oxygenase pathways) that then act<br>on the channel (Meves, 1994). A number of possible<br>mechanisms have been proposed:  $(a)$  partitioning int metabolites through various enzymatic pathways (e.g., lipoxygenase or cyclo-oxygenase pathways) that then act on the channel (Meves, 1994). A number of possible mechanisms have been proposed: (*a*) partitioning into the bi lipoxygenase or cyclo-oxygenase pathways) that then act<br>on the channel (Meves, 1994). A number of possible<br>mechanisms have been proposed:  $(a)$  partitioning into<br>the bilayer to alter membrane tension (Martinac et al., lipoxygenase or cyclo-oxygenase pathways) that then a<br>on the channel (Meves, 1994). A number of possib<br>mechanisms have been proposed: (a) partitioning in<br>the bilayer to alter membrane tension (Martinac et a<br>1990; Markin an on the channel (Meves, 1994). A number of possible<br>mechanisms have been proposed:  $(a)$  partitioning int<br>the bilayer to alter membrane tension (Martinac et al.<br>1990; Markin and Martinac, 1991),  $(b)$  changing mem-<br>brane def mechanisms have been proposed:  $(a)$  partitioning in<br>the bilayer to alter membrane tension (Martinac et al<br>1990; Markin and Martinac, 1991),  $(b)$  changing men<br>brane deformation energy (Lundbaek and Anderse:<br>1994) or  $(c)$  i the bilayer to alter membrane tension (Martinac et al., 1990; Markin and Martinac, 1991), (b) changing membrane deformation energy (Lundbaek and Andersen, 1994) or (c) interacting with allosteric sites on the channel prote brane deformation energy (Lundbaek and Andersen, 1994) or (c) interacting with allosteric sites on the chan-<br>nel protein (Petrou et al., 1994; Kirber et al., 1992; Kim<br>et al., 1995).<br>*1. Amphipathic molecules.* Amphipathic

 $\mu$ M) have been reported to block voltage-dependent outer into one leaflet increases the membrane tension in the<br>hair cell motility (Santos-Sacchi, 1989, 1991; however, see adjacent leaflet and thereby activates the MG c stretch-induced depolarizations and arrhythmias in ven-<br>tricular muscle (Hansen et al., 1991; Stacy et al., 1992). anosensitivity derives entirely from interactions within<br>f. PLANTS. Perhaps the most notable feature of pl 1994) or  $(c)$  interacting with allosteric sites on the chan-<br>nel protein (Petrou et al., 1994; Kirber et al., 1992; Kim<br>et al., 1995).<br>*1. Amphipathic molecules*. Amphipathic molecules<br>have both hydrophilic and hydrophobi nel protein (Petrou et al., 1994; Kirber et al., 1992; Kim<br>et al., 1995).<br>1. Amphipathic molecules. Amphipathic molecules<br>have both hydrophilic and hydrophobic groups and may<br>be either positive, negative or have no net ele et al., 1995).<br>
1. Amphipathic molecules. Amphipathic molecule<br>
have both hydrophilic and hydrophobic groups and may<br>
be either positive, negative or have no net electric charg<br>
(e.g., chlorpromazine, trinitrophenol and ly 1. Amphipathic molecules. Amphipathic molecules<br>have both hydrophilic and hydrophobic groups and may<br>be either positive, negative or have no net electric charge<br> $(e.g.,$  chlorpromazine, trinitrophenol and lysolecithin,<br>respe have both hydrophilic and hydrophobic groups and mi<br>be either positive, negative or have no net electric char;<br>(e.g., chlorpromazine, trinitrophenol and lysolecithi<br>respectively). Martinac et al. (1990) demonstrated the<br>am (e.g., chlorpromazine, trinitrophenol and lysolecithin, respectively). Martinac et al. (1990) demonstrated that amphipathic molecules, when introduced into the external bathing solution, could reversibly increase the open respectively). Martinac et al. (1990) demonstrated that<br>amphipathic molecules, when introduced into the exter-<br>nal bathing solution, could reversibly increase the open<br>probability of an SA anion channel in *E. coli*. When respectively). Martinac et al. (1990) demonstrated that<br>amphipathic molecules, when introduced into the exter-<br>nal bathing solution, could reversibly increase the open<br>probability of an SA anion channel in E. coli. When a<br> amphipathic molecules, when introduced into the external bathing solution, could reversibly increase the open<br>probability of an SA anion channel in  $E$ . coli. When a<br>particular amphipath, either cationic or anionic, was<br>u probability of an SA anion channel in  $E$ . coli. When a particular amphipath, either cationic or anionic, was used alone, the effects were always stimulatory (i.e., open probability increased). However, cationic and anion probability of an SA anion channel in  $E$ . coli. When particular amphipath, either cationic or anionic, wa used alone, the effects were always stimulatory (i.e. open probability increased). However, cationic and anionic a particular amphipath, either cationic or anionic, was used alone, the effects were always stimulatory (i.e., open probability increased). However, cationic and anionic amphipaths, used in succession, first stimulated, then used alone, the effects were always stimulatory (i.e.<br>open probability increased). However, cationic and an<br>ionic amphipaths, used in succession, first stimulated<br>then neutralized, this stimulatory effect and eventually<br>re open probability increased). However, cationic and an-<br>ionic amphipaths, used in succession, first stimulated,<br>then neutralized, this stimulatory effect and eventually<br>resulted in a stimulatory effect. The effects were typ ionic amphipaths, used in succession, first stimulated,<br>then neutralized, this stimulatory effect and eventually<br>resulted in a stimulatory effect. The effects were typi-<br>cally slow, sometimes taking up to an hour to increa then neutralized, this stimulatory effect and eventually<br>resulted in a stimulatory effect. The effects were typically slow, sometimes taking up to an hour to increase<br>open probability to unity. Amphipaths appeared to act<br> resulted in a stimulatory effect. The effects were typically slow, sometimes taking up to an hour to increase<br>open probability to unity. Amphipaths appeared to act<br>by shifting the sigmoidal stimulus-response relation to<br>th cally slow, sometimes taking up to an hour to increase open probability to unity. Amphipaths appeared to ach by shifting the sigmoidal stimulus-response relation the left so that lower pressures activated the channe withou open probability to unity. Amphipaths appeared to act<br>by shifting the sigmoidal stimulus-response relation to<br>the left so that lower pressures activated the channel<br>without affecting the slope of the Boltzmann (i.e., stim by shifting the sigmoidal stimulus-response relation to<br>the left so that lower pressures activated the channel<br>without affecting the slope of the Boltzmann (i.e., stim-<br>ulus-response curve). These effects were interpreted the left so that lower pressures activated the channel<br>without affecting the slope of the Boltzmann (i.e., stim-<br>ulus-response curve). These effects were interpreted in<br>terms of the bilayer couple hypothesis, in which cati without affecting the slope of the Boltzmann (i.e., stim-<br>ulus-response curve). These effects were interpreted in<br>terms of the bilayer couple hypothesis, in which cationic<br>amphipaths insert into the positive inner monolaye ulus-response curve). These effects were interpreted in<br>terms of the bilayer couple hypothesis, in which cationic<br>amphipaths insert into the positive inner monolayer and<br>anionic species partition into the negative outer le terms of the bilayer couple hypothesis, in which cationic amphipaths insert into the positive inner monolayer and anionic species partition into the negative outer leaflet of the  $E$ .  $coli$  membrane (Sheetz and Singer, 197 amphipaths insert into the positive inner monolayer and<br>anionic species partition into the negative outer leaflet<br>of the E. coli membrane (Sheetz and Singer, 1974). Ac-<br>cording to this hypothesis, the introduction of molec anionic species partition into the negative outer leaflet<br>of the *E*. coli membrane (Sheetz and Singer, 1974). Ac-<br>cording to this hypothesis, the introduction of molecules<br>into one leaflet increases the membrane tension i of the *E. coli* membrane (Sheetz and Singer, 1974). According to this hypothesis, the introduction of molecules into one leaflet increases the membrane tension in the adjacent leaflet and thereby activates the MG channel. cording to this hypothesis, the introduction of molecules<br>into one leaflet increases the membrane tension in the<br>adjacent leaflet and thereby activates the MG channel.<br>However, it remains unclear why neutral amphipaths<br>hav into one leaflet increases the membrane tension in the adjacent leaflet and thereby activates the MG channel.<br>However, it remains unclear why neutral amphipaths have a stimulatory effect unless steric factors also result<br>i adjacent leaflet and thereby activates the MG channel.<br>
However, it remains unclear why neutral amphipaths<br>
have a stimulatory effect unless steric factors also result<br>
in unequal partition within the different monolayers However, it remains unclear why neutral amphipation as the association of the bilayer and model is that mecha-<br>in unequal partition within the different monolaye<br>(Martinac et al., 1990; Markin and Martinac, 1991).<br>notable in unequal partition within the different monolayers in unequal partition within the different monolayers (Martinac et al., 1990; Markin and Martinac, 1991). A notable feature of the bilayer couple model is that mechanosensitivity derives entirely from interactions within t (Martinac et al., 1990; Markin and Martinac, 1991). A notable feature of the bilayer couple model is that mechanosensitivity derives entirely from interactions within the bilayer. This basic idea has received strong suppor notable feature of the bilayer couple model is that mechanosensitivity derives entirely from interactions within<br>the bilayer. This basic idea has received strong support,<br>at least for the  $E. coli$  MG channel, in the form of anosensitivity derives entirely from interactions within<br>the bilayer. This basic idea has received strong support,<br>at least for the  $E.$  coli MG channel, in the form of recent<br>studies showing that mechanosenitivity is ret the bilayer. This basic idea has received strong support, at least for the  $E. coli$  MG channel, in the form of recent studies showing that mechanosenitivity is retained when the MG channel protein, either purified from membr at least for the *E*. *coli* MG channel, in the form of recent studies showing that mechanosenitivity is retained when the MG channel protein, either purified from membranes or in vitro transcribed from the cloned gene, is studies showing that mechanosenitivity is retained<br>when the MG channel protein, either purified from<br>membranes or in vitro transcribed from the cloned gene,<br>is reconstituted into artificial lipid bilayers (Sukharev et<br>al., when the MG channel protein, either purified from<br>membranes or in vitro transcribed from the cloned gen<br>is reconstituted into artificial lipid bilayers (Sukharev<br>al., 1993; 1994). It will be interesting to determin<br>whether membranes or in vitro transcribed from the cloned gene,<br>is reconstituted into artificial lipid bilayers (Sukharev et<br>al., 1993; 1994). It will be interesting to determine<br>whether amphipath sensitivity is retained when chan al., 1993; 1994). It will be interesting to determine<br>whether amphipath sensitivity is retained when chan-<br>nels are reconstituted into bilayers formed from only<br>pure neutral phospholipid.<br>The bilayer couple model contrasts The bilayer state in the bilayers of determine<br>nether amphipath sensitivity is retained when chan-<br>ls are reconstituted into bilayers formed from only<br>re neutral phospholipid.<br>The bilayer couple model contrasts with models

whether amphipath sensitivity is retained when chan-<br>nels are reconstituted into bilayers formed from only<br>pure neutral phospholipid.<br>The bilayer couple model contrasts with models that<br>depend upon cytoskeletal (Guharay an nels are reconstituted into bilayers formed from only<br>pure neutral phospholipid.<br>The bilayer couple model contrasts with models that<br>depend upon cytoskeletal (Guharay and Sachs, 1984) or<br>extracellular protein interactions pure neutral phospholipid.<br>The bilayer couple model contrasts with models that<br>depend upon cytoskeletal (Guharay and Sachs, 1984) or<br>extracellular protein interactions (Howard et al., 1988;<br>Wang et al., 1993). Although dif



PHARMACOLOGICAL REVIEWS

PHARMACOLOGY OF MECHANOGATED<br>
mechanosensitivity need not be mutually exclusive, it is<br>
interesting that chlorpromazine and trinitrophenol also<br>
stimulate SA cation channels in chick skeletal muscle<br>
sme PHARMACOLOGY OF MECHANOGATE<br>mechanosensitivity need not be mutually exclusive, it is<br>interesting that chlorpromazine and trinitrophenol also<br>astimulate SA cation channels in chick skeletal muscle<br>preparation (Sokabe et al. mechanosensitivity need not be mutually exclusive, it is<br>interesting that chlorpromazine and trinitrophenol also<br>stimulate SA cation channels in chick skeletal muscle<br>preparation (Sokabe et al., 1993) where the initial cyinteresting that chlorpromazine and trinitrophenol also<br>stimulate SA cation channels in chick skeletal muscle<br>preparation (Sokabe et al., 1993) where the initial cy-<br>toskeleton model was developed (Guharay and Sachs,<br>1984) stimulate SA cation channels in chick skeletal mus<br>preparation (Sokabe et al., 1993) where the initial<br>toskeleton model was developed (Guharay and Sac<br>1984). On the other hand, lipid molecules have be<br>shown to trigger chan preparation (Sokabe et al., 1993) where the initial cy-<br>toskeleton model was developed (Guharay and Sachs, th<br>1984). On the other hand, lipid molecules have been di<br>shown to trigger changes in the elasticity of the cytoske toskeleton model was developed (Guharay and Sachs, th<br>1984). On the other hand, lipid molecules have been dishown to trigger changes in the elasticity of the cytoskel-<br>etal network in plant cells (Grabski et al., 1994), ra 1984). On the other hand, lipid molecules have bee<br>shown to trigger changes in the elasticity of the cytoske<br>etal network in plant cells (Grabski et al., 1994), raisin<br>the possibility that amphiphiles and amphipaths hav<br>mu shown to trigger changes in the elasticity of the cytoske<br>etal network in plant cells (Grabski et al., 1994), raisin<br>the possibility that amphiphiles and amphipaths hav<br>multiple sites of action capable of influencing MG ch

the possibility that amphiphiles and amphipaths have pro<br>multiple sites of action capable of influencing MG chan-<br>ind<br>nel activity.<br>2. Fatty acids and lipids (amphiphilic molecules). Am-<br>phiphilic molecules have polar head multiple sites of action capable of influencing MG chan-<br>nel activity. fat<br>2. Fatty acids and lipids (amphiphilic molecules). Am-<br>phiphilic molecules have polar heads attached to a long Ar-<br>hydrophobic tail and include suc nel activity.<br>
2. Fatty acids and lipids (amphiphilic molecules). Amphiphilic molecules have polar heads attached to a long<br>
hydrophobic tail and include such compounds as fatty<br>
acids and lipid molecules. Recent studies i 2. Fatty acids and lipids (amphiphilic molecules). Am-<br>phiphilic molecules have polar heads attached to a long<br>hydrophobic tail and include such compounds as fatty in<br>acids and lipid molecules. Recent studies indicate that phiphilic molecules have polar heads attached to a long Ahydrophobic tail and include such compounds as fatty in acids and lipid molecules. Recent studies indicate that or fatty acids activate various MG channels independe hydrophobic tail and include such compounds as fatty<br>acids and lipid molecules. Recent studies indicate that<br>fatty acids activate various MG channels independent of<br>fatty acid metabolic pathways (i.e., cyclo-oxygenase or<br>l acids and lipid molecules. Recent studies indicate that<br>fatty acids activate various MG channels independent of<br>atty acid metabolic pathways (i.e., cyclo-oxygenase of<br>lipoxygenase pathways) (Kiber et al., 1992; Kim, 1992<br>P fatty acids activate various MG channels independent of variety of mechanisms (for review see Meves, 1994).<br>fatty acid metabolic pathways (i.e., cyclo-oxygenase or A number of features distinguish amphipathic from<br>lipoxyg fatty acid metabolic pathways (i.e., cyclo-oxygenase<br>lipoxygenase pathways) (Kiber et al., 1992; Kim, 199<br>Petrou et al., 1994; Kim et al., 1995). In particulation<br>Kirber et al. (1992) demonstrated that arachidonic as<br>incr lipoxygenase pathways) (Kiber et al., 1992; Kim, 1992<br>Petrou et al., 1994; Kim et al., 1995). In particular<br>Kirber et al. (1992) demonstrated that arachidonic aci<br>increases or modulates the activity of a large conduc<br>tanc Petrou et al., 1994; Kim et al., 1995). In particular, time-<br>Kirber et al. (1992) demonstrated that arachidonic acid slincreases or modulates the activity of a large conduc-<br>tance, SA K<sup>+</sup><sub>(Ca)</sub> channel in rabbit arterial Kirber et al. (1992) demonstrated that arachidonic acid<br>increases or modulates the activity of a large conduc-<br>tance, SA  $K^+{}_{(Ca)}$  channel in rabbit arterial smooth mus-<br>cle. This effect does not depend on the generation increases or modulates the activity of a large conductance, SA  $K^+{}_{(Ca)}$  channel in rabbit arterial smooth muscle. This effect does not depend on the generation of arachidonic acid metabolites because saturated fatty aci tance, SA  $K^+(C_{\alpha})$  channel in rabbit arterial smooth mus-<br>cle. This effect does not depend on the generation of the<br>arachidonic acid metabolites because saturated fatty ac-<br>or ids such as myristic and linoelaidic acids, cle. This effect does not depend on the generation of arachidonic acid metabolites because saturated fatty acids such as myristic and linoelaidic acids, which are not substrates for the enzymes that convert arachidonic aci arachidonic acid metabolites because saturated fatty accids such as myristic and linoelaidic acids, which are not resubstrates for the enzymes that convert arachidonic acid I to active metabolites, also activate the channe ids such as myristic and linoelaidic acids, which are not<br>substrates for the enzymes that convert arachidonic acid Ir<br>to active metabolites, also activate the channel. Further ch<br>evidence of a direct effect was indicated b substrates for the enzymes that convert arachidonic acid<br>to active metabolites, also activate the channel. Further<br>evidence of a direct effect was indicated by cell-free<br>patch experiments in which activation by fatty acid to active metabolites, also activate the channel. Further clevidence of a direct effect was indicated by cell-free tipatch experiments in which activation by fatty acids was pretained in the absence of soluble cytoplasmic evidence of a direct effect was indicated by cell-free tine<br>patch experiments in which activation by fatty acids was poli-<br>retained in the absence of soluble cytoplasmic enzymes ind<br>(Kirber et al., 1992). Another SA K<sup>+</sup> patch experiments in which activation by fatty acids was<br>retained in the absence of soluble cytoplasmic enzymes<br>(Kirber et al., 1992). Another SA K<sup>+</sup> channel, in this<br>case in gastric smooth muscle, also displays fatty aci retained in the absence of soluble cytoplasmic enzyme<br>(Kirber et al., 1992). Another SA K<sup>+</sup> channel, in thicase in gastric smooth muscle, also displays fatty aci<br>activation (Petrou et al., 1994). However, although neg<br>ati (Kirber et al., 1992). Another SA  $K^+$  channel, in this et case in gastric smooth muscle, also displays fatty acid stractivation (Petrou et al., 1994). However, although negatively charged fatty acids stimulate MG channe case in gastric smooth muscle, also displays fatty acid stractivation (Petrou et al., 1994). However, although negatively charged fatty acids stimulate MG channel activersity, positively charged fatty acids inhibit activi activation (Petrou et al., 1994). However, although negatively charged fatty acids stimulate MG channel activity, positively charged fatty acids inhibit activity (see the above in Section III, A.4.j), and neutral analogs atively charged fatty acids stimulate MG channel activity, positively charged fatty acids inhibit activity (see above in Section III, A.4.j), and neutral analogs are without effect (table 5). This SA K<sup>+</sup> channel seems lik ity, positively charged fatty acids inhibit activity (see<br>above in Section III, A.4.j), and neutral analogs are<br>without effect (table 5). This SA  $K^+$  channel seems likely<br>to be indirectly mechanosensitive (see mechanism above in Section III, A.4.j), and neutral analogs are<br>without effect (table 5). This SA  $K^+$  channel seems likely<br>to be indirectly mechanosensitive (see mechanisms<br>above) because stretch activation occurs with latencies<br> without effect (table 5). This SA  $K^+$  channel seems likely al.,<br>to be indirectly mechanosensitive (see mechanisms cha<br>above) because stretch activation occurs with latencies me<br>of seconds rather than milliseconds (Ordwa to be indirectly mechanosensitive (see mechanisms<br>above) because stretch activation occurs with latencies<br>of seconds rather than milliseconds (Ordway et al.,<br>1991), persists for seconds after removal of stretch, and<br>activa above) because stretch activation occurs with latencies<br>of seconds rather than milliseconds (Ordway et al.,<br>1991), persists for seconds after removal of stretch, and<br>activation can be suppressed by perfusion with albumin,<br> of seconds rather than milliseconds (Ordway et al., an 1991), persists for seconds after removal of stretch, and the activation can be suppressed by perfusion with albumin, (Stephich is known to remove fatty acids from mem 1991), persists for seconds after removal of stretch, and that that membressed by perfusion with albumin, (S<br>which is known to remove fatty acids from membranes<br>(Ordway et al., 1995). These observations have led to the an activation can be suppressed by perfusion with albumin,<br>which is known to remove fatty acids from membranes<br>(Ordway et al., 1995). These observations have led to the<br>proposal that membrane stretch alters channel activity<br>b which is known to remove fatty acids from membrane<br>(Ordway et al., 1995). These observations have led to the<br>proposal that membrane stretch alters channel activit<br>by generation of fatty acids, possibly via a stretch ser<br>si proposal that membrane stretch alters channel activity<br>by generation of fatty acids, possibly via a stretch sen-<br>sitive membrane phospholipase (Jukka et al., 1995).<br>In a third cell type, involving neurons from the mes-

there are a number of fatty acid-activated SA  $K^+$  chanencephalic and hypothalamic regions of the rat brain,<br>there are a number of fatty acid-activated SA  $K^+$  chan-<br>nels that can be distinguished by their open channel sitive membrane phospholipase (Jukka et al., 1995).<br>In a third cell type, involving neurons from the mes-<br>encephalic and hypothalamic regions of the rat brain,<br>there are a number of fatty acid-activated SA  $K^+$  chan-<br>nel In a third cell type, involving neurons from the mes-<br>encephalic and hypothalamic regions of the rat brain, cathere are a number of fatty acid-activated SA  $K^+$  chan-<br>nels that can be distinguished by their open channel encephalic and hypothalamic regions of the rat brain, cat<br>there are a number of fatty acid-activated SA K<sup>+</sup> chan-<br>nels that can be distinguished by their open channel cha<br>properties. In all cases, albumin fails to reduce there are a number of fatty acid-activated SA  $K^+$  channels that can be distinguished by their open channel corpoperties. In all cases, albumin fails to reduce stretch the sensitivity, indicating that stretch and fatty a nels that can be distinguished by their open change<br>properties. In all cases, albumin fails to reduce stret<br>sensitivity, indicating that stretch and fatty acids m<br>activate this channel by different mechanisms (Kim<br>al., 199 properties. In all cases, albumin fails to reduce stretch<br>sensitivity, indicating that stretch and fatty acids may<br>activate this channel by different mechanisms (Kim et<br>al., 1995). A similar conclusion was made for the ar sensitivity, indicating that stretch and fatty acids may Interactivate this channel by different mechanisms (Kim et Al<sup>3-1</sup> al., 1995). A similar conclusion was made for the arachiantle al., donic sensitive SA K<sup>+</sup> channe

interesting that chlorpromazine and trinitrophenol also acids myristic acid and oleic acid, which activate the<br>stimulate SA cation channels in chick skeletal muscle smooth muscle  $K^+$  channels, have no effect on the neu-ED MEMBRANE ION CHANNELS 247<br>
neurons and smooth muscle is that the saturated fatty<br>
acids myristic acid and oleic acid, which activate the<br>
smooth muscle  $K^+$  channels, have no effect on the neu-ED MEMBRANE ION CHANNELS 247<br>neurons and smooth muscle is that the saturated fatty<br>acids myristic acid and oleic acid, which activate the<br>smooth muscle  $K^+$  channels, have no effect on the neu-<br>ronal channels. Taken toge neurons and smooth muscle is that the saturated fatty<br>acids myristic acid and oleic acid, which activate the<br>smooth muscle  $K^+$  channels, have no effect on the neu-<br>ronal channels. Taken together, the evidence indicates<br> neurons and smooth muscle is that the saturated fatty<br>acids myristic acid and oleic acid, which activate the<br>smooth muscle  $K^+$  channels, have no effect on the neu-<br>ronal channels. Taken together, the evidence indicates<br> acids myristic acid and oleic acid, which activate the smooth muscle  $K^+$  channels, have no effect on the neuronal channels. Taken together, the evidence indicates that the SA  $K^+$  channels in muscle and neurons involve smooth muscle  $K^+$  channels, have no effect on the neu-<br>ronal channels. Taken together, the evidence indicates<br>that the SA  $K^+$  channels in muscle and neurons involve<br>direct fatty acid activation of the channel protein ronal channels. Taken together, the evidence indicates<br>that the SA K<sup>+</sup> channels in muscle and neurons involve<br>direct fatty acid activation of the channel protein itself<br>or an associated regulatory protein on smooth muscl that the SA  $K^+$  channels in muscle and neurons involve<br>direct fatty acid activation of the channel protein itself<br>or an associated regulatory protein on smooth muscle<br>and neurons. The fact that the fatty acid activation direct fatty acid activation of the channel protein itself<br>or an associated regulatory protein on smooth muscle<br>and neurons. The fact that the fatty acid activation<br>profile of K<sup>+</sup> channels in muscle and neurons differs<br>in or an associated regulatory protein on smooth muscle<br>and neurons. The fact that the fatty acid activation<br>profile of  $K^+$  channels in muscle and neurons differs<br>indicates there may be a number of cell type-specific<br>fatty and neurons. The fact that the fatty acid activation<br>profile of K<sup>+</sup> channels in muscle and neurons differs<br>indicates there may be a number of cell type-specific<br>fatty acid binding sites, which may or may not be in-<br>volved profile of  $K^+$  channels in muscle and neurons differentiates there may be a number of cell type-specificity acid binding sites, which may or may not be if volved in conferring mechanosensitivity on the channel Arachidon indicates there may be a number of cell type-specific<br>fatty acid binding sites, which may or may not be in-<br>volved in conferring mechanosensitivity on the channel.<br>Arachidonic acid and other fatty acids, apart from effectfatty acid binding sites, which may or may not be in-<br>volved in conferring mechanosensitivity on the channel.<br>Arachidonic acid and other fatty acids, apart from effect-<br>ing the SA channels described above, also have action voived in coinering mechanisses stavity on the channel.<br>
Arachidonic acid and other fatty acids, apart from effect-<br>
ing the SA channels described above, also have actions<br>
on a wide range of other non-MG channels involvin

ing the SA channels described above, also have action a wide range of other non-MG channels involving variety of mechanisms (for review see Meves, 1994). A number of features distinguish amphipathic from amphiphilic activa on a wide range of other non-MG channels involving a variety of mechanisms (for review see Meves, 1994).<br>A number of features distinguish amphipathic from amphiphilic activation. First, the time course of activation diffe variety of mechanisms (for review see Meves, 1994).<br>A number of features distinguish amphipathic from<br>amphiphilic activation. First, the time course of activa-<br>tion differs. Whereas amphipaths activate the channel<br>slowly A number of features distinguish amphipathic from<br>amphiphilic activation. First, the time course of activa-<br>tion differs. Whereas amphipaths activate the channel<br>slowly (~1 hour), fatty acid activation is relatively fast<br> amphiphilic activation. First, the time course of activation differs. Whereas amphipaths activate the channel slowly (~1 hour), fatty acid activation is relatively fast and occurs in seconds. Second, at least for the  $K^+$ tion differs. Whereas amphipaths activate the channel slowly ( $\sim$ 1 hour), fatty acid activation is relatively fast and occurs in seconds. Second, at least for the  $K^+(C_a)$ , fatty acids are not capable of activating the c slowly ( $\sim$ 1 hour), fatty acid activation is relatively fast<br>and occurs in seconds. Second, at least for the  $K^+_{(Ca)}$ ,<br>fatty acids are not capable of activating the channel in<br>the absence of basal activity (i.e., in zer and occurs in seconds. Second, at least for the  $K^+(Ca)$ , fatty acids are not capable of activating the channel in the absence of basal activity (i.e., in zero external Ca<sup>2+</sup> or at very negative potentials), indicating a Fatty acids are not capable of activating the channel in<br>the absence of basal activity (i.e., in zero external  $Ca^{2+}$  or at very negative potentials), indicating a modulatory<br>role rather than primary activation (Kirber e the absence of basal activity (i.e., in zero external Ca<sup>2</sup> or at very negative potentials), indicating a modulator role rather than primary activation (Kirber et al., 1988 In contrast, amphipaths can activate the *E*. *c* or at very negative potentials), indicating a modulatory<br>role rather than primary activation (Kirber et al., 1988).<br>In contrast, amphipaths can activate the  $E$ . coli MG<br>channel in the absence of mechanical stimulation (M role rather than primary activation (Kirber et al., 198<br>In contrast, amphipaths can activate the  $E$ . coli 1<br>channel in the absence of mechanical stimulation (M<br>tinac et al., 1990). Third, the dependence of cha<br>polarity o In contrast, amphipaths can activate the *E*. coli MG<br>channel in the absence of mechanical stimulation (Mar-<br>tinac et al., 1990). Third, the dependence of charge<br>polarity of fatty acid effects differs from the polarity-<br>i channel in the absence of mechanical stimulation (Martinac et al., 1990). Third, the dependence of charge polarity of fatty acid effects differs from the polarity-independent stimulatory effect of amphipaths (Martinac et tinac et al., 1990). Third, the dependence of charge<br>polarity of fatty acid effects differs from the polarity-<br>independent stimulatory effect of amphipaths (Martinac<br>et al., 1990). Finally, although the  $K^{\dagger}_{(Ca)}$  channe polarity of fatty acid effects differs from the polarity-<br>independent stimulatory effect of amphipaths (Martinac<br>et al., 1990). Finally, although the  $K^+{}_{(Ca)}$  channel is<br>stretch-sensitive, it is not clear to what extent independent stimulatory effect of amphipaths (Martinac et al., 1990). Finally, although the  $K^+(C_{\text{ca}})$  channel is stretch-sensitive, it is not clear to what extent stretch and fatty acids can act independently of one a et al., 1990). Finally, although the  $K^+{}_{(Ca)}$  channel stretch-sensitive, it is not clear to what extent st and fatty acids can act independently of one anothe example, it may be stretch sensitivity does not reside the c stretch-sensitive, it is not clear to what extent stretch<br>and fatty acids can act independently of one another. For<br>example, it may be stretch sensitivity does not reside in<br>the channel itself but instead resides in a stre and fatty acids can act independently of one another. For example, it may be stretch sensitivity does not reside in the channel itself but instead resides in a stretch-sensitive phospholipase that generates fatty acids (Br example, it may be stretch sensitivity does not reside<br>the channel itself but instead resides in a stretch-sen<br>tive phospholipase that generates fatty acids (Brophy<br>al., 1993; Jukka et al., 1995). In contrast, with the  $E$ the channel itself but instead resides in a stretch-sense tive phospholipase that generates fatty acids (Brophy al., 1993; Jukka et al., 1995). In contrast, with the  $E$ .  $cc$  channel, it is quite clear from reconstitution tive phospholipase that generates fatty acids (Brophy et al., 1993; Jukka et al., 1995). In contrast, with the *E. coli* channel, it is quite clear from reconstitution experiments, using the purified channel protein, that channel, it is quite clear from reconstitution experiments, using the purified channel protein, that mechanosensitivity arises purely from interactions between the protein and its surrounding bilayer environment (Sukharev channel, it is quite clear from reconstitution experiments, using the purified channel protein, that mechanosensitivity arises purely from interactions between the protein and its surrounding bilayer environment (Sukharev anosensitivity arises purely from interactions between<br>the protein and its surrounding bilayer environment<br>(Sukharev et al., 1994).<br>3. Other activators. As in the case with blockers, there<br>are a number of chemicals that ha

the protein and its surrounding bilayer environment<br>(Sukharev et al., 1994).<br>3. Other activators. As in the case with blockers, there<br>are a number of chemicals that have been reported to<br>have activating effects on specific

3. Other activators. As in the case with blockers, the<br>are a number of chemicals that have been reported<br>have activating effects on specific MG channels.<br>a. ALUMINOFLUORIDE. In contrast to blocking effects<br>Al<sup>3+</sup> describe are a number of chemicals that have been reported to<br>have activating effects on specific MG channels.<br>a. ALUMINOFLUORIDE. In contrast to blocking effects of<br> $Al^{3+}$  described above, it has been reported that alumi-<br>nofluo have activating effects on specific MG channels.<br>
a. ALUMINOFLUORIDE. In contrast to blocking effects of<br>
Al<sup>3+</sup> described above, it has been reported that alumi-<br>
nofluoride (20  $\mu$ M AlCl<sub>3</sub> plus 20 mM KF) activates a S a. ALUMINOFLUORIDE. In contrast to blocking effects of  $Al^{3+}$  described above, it has been reported that aluminofluoride (20  $\mu$ M AlCl<sub>3</sub> plus 20 mM KF) activates a SA cation channel in gastric smooth muscle cells (Hisa  $Al^{3+}$  described above, it has been reported that a nofluoride (20  $\mu$ M AlCl<sub>3</sub> plus 20 mM KF) activates cation channel in gastric smooth muscle cells (Hiss al., 1993). However, AlF<sub>3</sub> effects were studied channel activ nofluoride (20  $\mu$ M AlCl<sub>3</sub> plus 20 mM KF) activates a SA cation channel in gastric smooth muscle cells (Hisada et al., 1993). However, AlF<sub>3</sub> effects were studied on SA channel activity activated by membrane hyperpolari al., 1993). However,  $\text{AlF}_3$  effects were studied on SA channel activity activated by membrane hyperpolarization rather than by stretch (see Hisada et al., 1991). Interestingly, in contrast to the plant study in which al., 1993). However, AlF<sub>3</sub> effects were studied on SA<br>channel activity activated by membrane hyperpolariza-<br>tion rather than by stretch (see Hisada et al., 1991).<br>Interestingly, in contrast to the plant study in which<br>Al channel activity activated by membrane hyperpolariza-<br>tion rather than by stretch (see Hisada et al., 1991).<br>Interestingly, in contrast to the plant study in which<br> $Al^{3+}$  was reported to have an inhibitory effect (Ding e tion rather than by stretch (see Hisada et al., 1991).<br>Interestingly, in contrast to the plant study in which<br> $Al^{3+}$  was reported to have an inhibitory effect (Ding et<br>al., 1993), application of 20  $\mu$ M AlCl<sub>3</sub> had no e Interestingly, in contrast to the plant study in which  $Al^{3+}$  was reported to have an inhibitory effect (Ding et al., 1993), application of 20  $\mu$ M AlCl<sub>3</sub> had no effect on SA channel activity when applied in the absenc

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remains unknown but it has been proposed that this lend that the sactivation may play a role in smooth muscle contraction activation may play a role in smooth muscle contraction may play a role in smooth muscle contraction<br>(Hisada et al., 1993). 248<br>remains unknown but<br>activation may play a r<br>(Hisada et al., 1993).<br>b. ETHYL-N-PHENYLCA mains unknown but it has been proposed that t<br>tivation may play a role in smooth muscle contract<br>lisada et al., 1993).<br>b. ETHYL-N-PHENYLCARBAMATE. The herbicide, ethyl<br>lenylcarbamate, which is known to interfere w

activation may play a role in smooth muscle contraction<br>(Hisada et al., 1993).<br>b. ETHYL-N-PHENYLCARBAMATE. The herbicide, ethyl-N-<br>phenylcarbamate, which is known to interfere with<br>gravitropism in plants, has been shown to (Hisada et al., 1993). <br>b. ETHYL-N-PHENYLCARBAMATE. The herbicide, ethyl-N-<br>phenylcarbamate, which is known to interfere with<br>gravitropism in plants, has been shown to gradually s<br>stimulate MG channel activity in onion pr b. ETHYL-N-PHENYLCARBAMATE. The herbicide, ethyl-N-<br>phenylcarbamate, which is known to interfere with chaparavitropism in plants, has been shown to gradually sor<br>stimulate MG channel activity in onion protoplasts over pou phenylcarbamate, which is known to interfere with characterization in plants, has been shown to gradually setimulate MG channel activity in onion protoplasts over phechanism of action has the mechanism of action has dinot gravitropism in plants, has been shown to gradually<br>stimulate MG channel activity in onion protoplasts over<br>the concentration range of 10 to 1000  $\mu$ M (Ding and<br>Fickard, 1993a). Although the mechanism of action has<br>not b stimulate MG channel activity in onion protoplasts over<br>the concentration range of 10 to 1000  $\mu$ M (Ding and<br>Pickard, 1993a). Although the mechanism of action has<br>not been determined, this compound is known to alter<br>the

Pickard, 1993a). Although the mechanism of action has<br>not been determined, this compound is known to alter<br>the plant cytoskeleton (Nick et al., 1991).<br>c. CYTOCHALASINS. A specific theory of SA channel<br>activation is based o not been determined, this compound is known to alter<br>the plant cytoskeleton (Nick et al., 1991).<br>c. CYTOCHALASINS. A specific theory of SA channel<br>activation is based on cytoskeletal involvement in fo-<br>cusing mechanical en the plant cytoskeleton (Nick et al., 1991).<br>
c. CYTOCHALASINS. A specific theory of SA channel<br>
activation is based on cytoskeletal involvement in fo-<br>
cusing mechanical energy onto the SA channel. Be-<br>
cause several class c. CYTOCHALASINS. A specific theory of SA channel accivation is based on cytoskeletal involvement in fo-<br>ecusing mechanical energy onto the SA channel. Be-<br>cause several classes of compounds interact with spe-<br>cific cytosk activation is based on cytoskeletal involvement in fo-<br>cusing mechanical energy onto the SA channel. Be-<br>cause several classes of compounds interact with spe-<br>cific cytoskeletal proteins, a reasonable assumption is<br>that at cusing mechanical energy onto the SA channel. Be-<br>cause several classes of compounds interact with spe-<br>cific cytoskeletal proteins, a reasonable assumption is<br>that at least one or more of these drugs may have<br>affects on c cause several classes of compounds interact with specific cytoskeletal proteins, a reasonable assumption is methat at least one or more of these drugs may have plaffects on channel activities (see Mills and Mandel, di 1994 affects on channel activities (see Mills and Mandel, 1994). However, as it turns out, the results so far have been either negative or ambiguous. For example, the microtubule disrupting drugs, colchicine and vinblastine, wh affects on channel activities (see Mills and Mandel, 1994). However, as it turns out, the results so far have<br>been either negative or ambiguous. For example, the<br>microtubule disrupting drugs, colchicine and vinblas-<br>tine, 1994). However, as it turns out, the results so far have evoked<br>been either negative or ambiguous. For example, the of MG<br>microtubule disrupting drugs, colchicine and vinblas-<br>plays itine, while blocking mechanotransductio been either negative or ambiguous. For example, the<br>microtubule disrupting drugs, colchicine and vinblas-<br>tine, while blocking mechanotransduction in lower in-<br>vertebrates, have been shown to have no effect on SA<br>channels microtubule disrupting drugs, colchicine and vinblas-<br>tine, while blocking mechanotransduction in lower in-<br>vertebrates, have been shown to have no effect on SA to<br>channels activity in at least two different vertebrate re<br> tine, while blocking mechanotransduction in lower invertebrates, have been shown to have no effect on SA channels activity in at least two different vertebrate preparations (see Section III, A.4.n). In the case of cytochal vertebrates, have been shown to have no effect on SA to<br>channels activity in at least two different vertebrate rol<br>preparations (see Section III, A.4.n). In the case of con<br>cytochalasins, which are known to selectively dis channels activity in at least two different vertebrate<br>preparations (see Section III, A.4.n). In the case of<br>cytochalasins, which are known to selectively disrupt<br>actin filaments, the reports on SA channels have been<br>contr preparations (see Section III, A.4.n). In the case of cytochalasins, which are known to selectively disrupt actin filaments, the reports on SA channels have been contradictory between laboratories; even conflicting reports cytochalasins, which are known to selectively disrupt<br>actin filaments, the reports on SA channels have been<br>contradictory between laboratories; even conflicting<br>reports have arisen from a single laboratory. The ba-<br>sis of actin filaments, the reports on SA channels have b<br>contradictory between laboratories; even conflict<br>reports have arisen from a single laboratory. The<br>sis of the discrepancies is that some studies rep<br>that cytochalasins in contradictory between laboratories; even conflicting threports have arisen from a single laboratory. The baresis of the discrepancies is that some studies report age that cytochalasins increase the SA channel's sensitiv-<br>i reports nave arisen from a single laboratory. The ba-<br>sis of the discrepancies is that some studies report age<br>that cytochalasins increase the SA channel's sensitiv-<br>the ty to stretch (Guharay and Sachs, 1984; Small and MC sis of the discrepancies is that some studies report age that cytochalasins increase the SA channel's sensitivity to stretch (Guharay and Sachs, 1984; Small and MC Morris, 1994), whereas others report no effect on by stret that cytochalasins increase the SA channel's sensitivity to stretch (Guharay and Sachs, 1984; Small and Morris, 1994), whereas others report no effect on stretch sensitivity (Sokabe et al., 1991; O.P.H. and D.W.M., unpubli ity to stretch (Guharay and Sachs, 1984; Small and M<br>Morris, 1994), whereas others report no effect on by<br>stretch sensitivity (Sokabe et al., 1991; O.P.H. and lo<br>D.W.M., unpublished observations). Despite the ap-<br>parent fa Morris, 1994), whereas others report no effect on stretch sensitivity (Sokabe et al., 1991; O.P.H. and D.W.M., unpublished observations). Despite the apparent failure of pharmacological means to clearly implicate specific stretch sensitivity (Sokabe et al., 1991; O.P.H.<br>D.W.M., unpublished observations). Despite the<br>parent failure of pharmacological means to cle<br>implicate specific cytoskeletal proteins in SA chai<br>function, other studies, us D.W.M., unpublished observations). Despite the<br>parent failure of pharmacological means to clear<br>implicate specific cytoskeletal proteins in SA chan<br>function, other studies, using nonpharmacolog<br>means, have clearly implicat parent failure of pharmacological means to clearly climplicate specific cytoskeletal proteins in SA channel function, other studies, using nonpharmacological means, have clearly implicated some form of cytoskel-<br>etal invol miplicate specific cytosketetal proteins in SA chained<br>function, other studies, using nonpharmacological *A*<br>means, have clearly implicated some form of cytoskel-<br>etal involvement (Hamill and McBride, 1995a). These<br>studie function, other studies, using nonpharmacological<br>means, have clearly implicated some form of cytoskel-<br>etal involvement (Hamill and McBride, 1995a). These<br>studies involve conditions in which the membrane in<br>the patch is p means, have clearly implicated some form of cytoskel-<br>etal involvement (Hamill and McBride, 1995a). These<br>studies involve conditions in which the membrane in<br>the patch is physically decoupled from the underlying<br>cytoskele etal involvement (Hamill and McBride, 1995a). These<br>studies involve conditions in which the membrane in<br>the patch is physically decoupled from the underlying<br>cytoskeleton (Hamill and McBride, 1992) or in which<br>cytoskeleton studies involve conditions in which the membrane in<br>the patch is physically decoupled from the underlying<br>cytoskeleton (Hamill and McBride, 1992) or in which<br>cytoskeleton free vesicles of plasma membrane have<br>been studied the patch is physically decoupled from the underlying<br>cytoskeleton (Hamill and McBride, 1992) or in which<br>cytoskeleton free vesicles of plasma membrane have<br>been studied (Hamill et al., 1995; Zhang et al., 1996).<br>Under bot cytoskeleton (Hamill and McBride, 19<br>cytoskeleton free vesicles of plasma<br>been studied (Hamill et al., 1995; Zha<br>Under both conditions, mechanosens<br>lost entirely or significantly reduced. ed (Hamill et al., 1995; Zhang et<br>h conditions, mechanosensitivity<br>ly or significantly reduced.<br>**IV. Summary and Conclusions**<br>rticle, the actions, mechanisms and Under both conditions, mechanosensitivity is either<br>lost entirely or significantly reduced.<br>IV. Summary and Conclusions<br>In this article, the actions, mechanisms and applica-<br>tions of various ions and drugs that interact wi

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has been found that display In this article, the actions, mechanisms and applica-<br>tions of various ions and drugs that interact with MG<br>channels have been discussed. At present, no compound<br>has been found that displays the high specificity and<br>affin tions of various ions and drugs that interact with Mechannels have been discussed. At present, no compoun<br>has been found that displays the high specificity an<br>affinity exhibited by tetrodotoxin or  $\alpha$ -bungarotoxin tha<br>pr channels have been discussed. At present, no compound<br>has been found that displays the high specificity and<br>affinity exhibited by tetrodotoxin or  $\alpha$ -bungarotoxin that<br>proved so useful in the functional and structural ch has been found that displays the high specificity and affinity exhibited by tetrodotoxin or  $\alpha$ -bungarotoxin that proved so useful in the functional and structural characterization of the voltage-gated Na<sup>+</sup> channel and

activation may play a role in smooth muscle contraction discovered since Paintal's review that clearly block MG<br>
(Hisada et al., 1993).<br>
b. ETHYL-N-PHENYLCARBAMATE. The herbicide, ethyl-N-<br>
b. ETHYL-N-PHENYLCARBAMATE. The HAMILL AND MCBRIDE<br>that this less, three different classes of compounds have been MCBRIDE<br>less, three different classes of compounds have been<br>discovered since Paintal's review that clearly block MG<br>channels. These compounds, represented by amiloride, MCBRIDE<br>less, three different classes of compounds have been<br>discovered since Paintal's review that clearly block MG<br>channels. These compounds, represented by amiloride,<br>gentamicin and gadolinium, act mainly on the SA cati less, three different classes of compounds have been<br>discovered since Paintal's review that clearly block MG<br>channels. These compounds, represented by amiloride,<br>gentamicin and gadolinium, act mainly on the SA cation<br>chann less, three different classes of compounds have be discovered since Paintal's review that clearly block l channels. These compounds, represented by amilorizentamicin and gadolinium, act mainly on the SA cat channel, which discovered since Paintal's review that clearly block MC<br>channels. These compounds, represented by amiloride<br>gentamicin and gadolinium, act mainly on the SA cation<br>channel, which appears to be shared by many nonsen<br>sory and gentamicin and gadolinium, act mainly on the SA cation<br>channel, which appears to be shared by many nonsen-<br>sory and some mechanosensory cells. Each class of com-<br>pound can be distinguished by the voltage and concen-<br>tratio gentamicin and gadolinium, act mainly on the SA cation<br>channel, which appears to be shared by many nonsen-<br>sory and some mechanosensory cells. Each class of com-<br>pound can be distinguished by the voltage and concen-<br>tratio channel, which appears to be shared by many nonsensory and some mechanosensory cells. Each class of compound can be distinguished by the voltage and concentration dependence of the block and most likely involves different pound can be distinguished by the voltage and concentration dependence of the block and most likely involves different mechanisms of blocking action. In general, the MG channel blocker pharmacology indicates a variety of " "receptor sites" on MG channels. The recognition and tration dependence of the block and most likely involves<br>different mechanisms of blocking action. In general, the<br>MG channel blocker pharmacology indicates a variety of<br>"receptor sites" on MG channels. The recognition and<br> different mechanisms of blocking action. In general, the MG channel blocker pharmacology indicates a variety of "receptor sites" on MG channels. The recognition and acceptance of such receptors should provide added impetus MG channel blocker<br>
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venoms and toxins.<br>
In the case of act eceptor sites" on MG channels. The recognition and<br>ceptance of such receptors should provide added im-<br>tus for continued screening for more potent drugs,<br>noms and toxins.<br>In the case of activators, little is understood of

that at least one or more of these drugs may have phiphilic compounds stimulate MG channels, although affects on channel activities (see Mills and Mandel, different bilayer and protein mechanisms have been 1994). However, acceptance of such receptors should provide added impetus for continued screening for more potent drugs, venoms and toxins.<br>In the case of activators, little is understood of the mechanisms by which the various amphipathic pecus for continued screening for more potent drugs,<br>venoms and toxins.<br>In the case of activators, little is understood of the<br>mechanisms by which the various amphipathic and am-<br>phiphilic compounds stimulate MG channels, In the case of activators, little is understood of the mechanisms by which the various amphipathic and amphiphilic compounds stimulate MG channels, although different bilayer and protein mechanisms have been evoked. Even phiphilic compounds stimulate MG channels, although phiphilic compounds stimulate MG channels, although<br>different bilayer and protein mechanisms have been<br>evoked. Even less is understood of the role the new class<br>of MG K<sup>+</sup> channel and their modulation by fatty acids<br>plays different bilayer and protein mechanisms have been<br>evoked. Even less is understood of the role the new class<br>of MG K<sup>+</sup> channel and their modulation by fatty acids<br>plays in physiological and perhaps pathological pro-<br>cess evoked. Even less is understood of the role the new class<br>of MG K<sup>+</sup> channel and their modulation by fatty acids<br>plays in physiological and perhaps pathological pro-<br>cesses. However, given that K<sup>+</sup> channels in general te of MG  $K^+$  channel and their modulation by fatty acids<br>plays in physiological and perhaps pathological pro-<br>cesses. However, given that  $K^+$  channels in general tend<br>to reduce the excitability of nerve and muscle, plaus plays in physiological and perhaps pathological processes. However, given that  $K^+$  channels in general tend to reduce the excitability of nerve and muscle, plausible roles include fatty acid regulation of vascular tone cesses. However, given that  $K^+$  channels in general tend<br>to reduce the excitability of nerve and muscle, plausible<br>roles include fatty acid regulation of vascular tone and<br>control of neuronal network excitability. In bo to reduce the excitability of nerve and muscle, plausible<br>roles include fatty acid regulation of vascular tone and<br>control of neuronal network excitability. In both cases,<br>more detailed understanding is required regarding roles include fatty acid regulation of vascular tone and<br>control of neuronal network excitability. In both cases,<br>more detailed understanding is required regarding the<br>physiological stimuli that modulate these channels<br>thr control of neuronal network excitability. In both cases,<br>more detailed understanding is required regarding the<br>physiological stimuli that modulate these channels<br>through their fatty acid receptors. It may turn out that<br>rec more detailed understanding is required regarding the<br>physiological stimuli that modulate these channels<br>through their fatty acid receptors. It may turn out that<br>recognition and/or development of cell-type specific<br>agents through their fatty acid receptors. It may turn out that<br>recognition and/or development of cell-type specific<br>agents that activate such MG channels will possess high<br>therapeutic potential. In any case, the observation that through their fatty acid receptors. It may turn out that<br>recognition and/or development of cell-type specific<br>agents that activate such MG channels will possess high<br>therapeutic potential. In any case, the observation that recognition and/or development of cell-type specific<br>agents that activate such MG channels will possess high<br>therapeutic potential. In any case, the observation that<br>MG channels can be chemically blocked and/or activated<br>b agents that activate such MG channels will posses<br>therapeutic potential. In any case, the observation<br>MG channels can be chemically blocked and/or acti<br>by a wide range of compounds requires revision<br>long-standing conclusio therapeutic potential. In any case, the observation that MG channels can be chemically blocked and/or activated<br>by a wide range of compounds requires revision of the long-standing conclusion of Paintal that mechanotrans-<br>d MG channels can boy a wide range of<br>long-standing concl<br>duction is a proce<br>chemical influence. *Acknowledgements.* Our research is supported by the National stitutes of Health, the National Science Foundation and the Mus-

chemical influence.<br>
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