Voltage-Dependent Antagonist/Agonist Actions of Taurine on Ca\textsuperscript{2+}-Activated Potassium Channels of Rat Skeletal Muscle Fibers

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ABSTRACT
Emerging evidence supports the idea that taurine exerts some of its actions through inhibition of inward rectifier K\textsuperscript{+} channels, ATP-sensitive K\textsuperscript{+} channels, and voltage-dependent K\textsuperscript{+} channels. However, to date not much is known about the effects of this sulfonic amino acid on Ca\textsuperscript{2+}-activated K\textsuperscript{+} (K\textsubscript{Ca2+}) channels, which are widely expressed in various tissues, including skeletal muscle. In the present work, the effects of taurine on K\textsubscript{Ca2+} channels of rat skeletal muscle fibers were investigated using the patch-clamp technique. The application of the amino acid to the internal side of the excised macropatches induced a dose-dependent decrease in the outward K\textsubscript{Ca2+} currents recorded at positive membrane potentials in the presence of 8 to 16 \textmu{}M concentrations of free Ca\textsuperscript{2+} ions in the bath with an IC\textsubscript{50} of 31.9 \times 10^{-3} \pm 1 M (slope factor = 1.2) (n = 11 patches). In contrast, at negative membrane potentials taurine caused an enhancement of the muscular inward K\textsubscript{Ca2+} currents with a DE\textsubscript{50} drug concentration needed to enhance the current by 50%) of 46.7 \times 10^{-3} \pm 2 M (slope factor = 1.3) (n = 9 patches). Single channel analysis revealed that this effect was mediated by changes in the reversal potential of the K\textsubscript{Ca2+} channel for K\textsuperscript{+} ions with no changes in the gating properties or in the sensitivity of the channel to Ca\textsuperscript{2+} ions. Taurine also did not affect the single channel conductance. In conclusion, taurine shows a voltage-dependent dualistic action on K\textsubscript{Ca2+} channels, being an inhibitor of the channel at positive membrane potentials and an activator at negative membrane potentials.

In the last few years, the attention of several laboratories has been focused on the investigation of the cellular mechanisms by which taurine, a well known sulfonic amino acid abundantly distributed in different tissues including skeletal muscle, exerts its effects. This comes from the fact that taurine shows several interesting properties, such as antioxidant, osmo-regulator control of the Ca\textsuperscript{2+} homeostasis and antischemic properties (Huxtable and Sebring, 1986; Conte Camerino et al., 1989; Pasantes-Morales et al., 1998). “In vivo” studies have also shown that taurine antagonizes the age-dependent impairment of the contractility function of skeletal muscle fibers in aged rats (Pierno et al., 1998).

Emerging evidence indicates that taurine exerts its actions by interacting with different ion channels, including K\textsuperscript{+} channels (Conte Camerino et al., 1989; Satoh, 1998a). For example, taurine inhibits the inward rectifier K\textsuperscript{+} channel of isolated cardiomyocytes by reducing the channel open probability without affecting the single channel conductance (Satoh, 1998b). ATP-sensitive K\textsuperscript{+} (K\textsubscript{ATP}) channels of cardiac and skeletal muscle fibers are also inhibited by the sulfonic amino acid. In fact, we have shown that taurine induces a reversible inhibition of the muscular K\textsubscript{ATP} channel interacting with the sulfonylurea receptor (SUR) subunit without affecting the Ca\textsuperscript{2+} binding site (Tricarico et al., 2000a). In the case of voltage-dependent K\textsuperscript{+} channels, the action of taurine has been described to be Ca\textsuperscript{2+}-dependent; in fact, the amino acid behaves as an agonist of the cardiac delayed rectifier K\textsuperscript{+} channel at low internal Ca\textsuperscript{2+} concentrations (10^{-8} M) and as an antagonist in the presence of a high internal Ca\textsuperscript{2+} concentration (10^{-6} M) (Satoh, 1998a).

The physiological significance of the observed inhibitory effects shown by taurine on different classes of K\textsuperscript{+} channels remains to be elucidated. One possibility is that taurine can serve to protect the fibers against ischemic insults. In fact, a release of the amino acid occurs during periods of ischemia reperfusion in cardiac fibers, and this would allow the opening of K\textsubscript{ATP} channels and other K\textsuperscript{+} channels with rapid repolarization of the fibers and cytoprotective effects (Allo et al., 1997; Suleiman et al., 1997; Saransari and Oja, 1998; Tricarico et al., 2000a).

Although some of the therapeutic effects of this amino acid appear to involve the interaction of taurine with different classes of K\textsuperscript{+} channels, currently no data is available on the
action of taurine on another type of K\(^+\) channel widely expressed in the tissues, including skeletal muscle, the Ca\(^{2+}\)- activated K\(^+\) (K\(_{Ca2}\)) channels. The opening of this type of channel, triggered by cellular depolarization and elevated intracellular Ca\(^{2+}\) ions in the excitable tissues, increases the duration of the hyperpolarization phase between bursts of action potentials, reducing the firing capability of the fibers (Hille, 1984; Tricarico et al., 1997). This helps to reduce the intracellular accumulation of Ca\(^{2+}\) ions occurring during bursts of action potentials in the fibers. However, persistent abnormal opening of muscle K\(_{Ca2}\) channels may also lead to the accumulation of K\(^+\) ions inside the t-tubule during muscle contraction, thus contributing to the phenomenon known as muscle fatigue.

In the present work, the effects of different concentrations of taurine applied "in vitro" on the intracellular face of patches excised from native skeletal muscle fibers were investigated using the patch-clamp technique on K\(_{Ca2}\) channels.

Materials and Methods

Muscle Preparations and Single Fiber Isolation. The flexor digitorum brevis (FDB) muscles were dissected from the rats under urethane anesthesia (1.2 g/kg). After dissection, the animals were rapidly killed with an overdose of urethane according to the Guide for Care and Use of Laboratory Animals prepared by the National Academy of Sciences (Washington, DC). Single muscle fibers were prepared from FDB muscles by enzymatic dissociation, as previously described (Tricarico and Conte Camerino, 1994).

Drugs and Solutions. The normal Ringer's solution contained 145 mM NaCl, 5 mM KCl, 1 mM MgCl\(_2\), 0.5 mM CaCl\(_2\), 5 mM glucose, and 10 mM MOPS, pH = 7.2. The patch-pipette solution contained 150 mM KCl, 2 mM CaCl\(_2\), and 10 mM MOPS, pH = 7.2. The bath solution contained 150 or 30 mM KCl, 5 mM EGTA, and 10 mM MOPS, pH = 7.2. CaCl\(_2\) was added to the bath solution to give a free Ca\(^{2+}\) ion concentration of 8 \(\mu\)M or 16 \(\mu\)M. The calculation of the free Ca\(^{2+}\) ion concentration in the bath was performed as previously described (Tricarico et al., 1997, 2000b). Taurine was dissolved in the bath solution and tested in a range of concentrations from 10 to 100 mM, and free Ca\(^{2+}\) ions (Tricarico et al., 1997, 2000a). The single channel current of K\(_{Ca2}\) channels was measured using the cursor method provided by the Fetchan program (Axon Instruments). The single channel conductance was calculated as the slope of the voltage-current relationship of the channel in the range of potentials from −70 to +70 mV. No correction for liquid-junction potential was made, and it was estimated to be <1 mV in our experimental conditions.

The effects of taurine on the gating properties of single K\(_{Ca2}\) channels were expressed as the open probability \((N \cdot P_{\text{open}})\) of the number of functional channels \((N) \cdot P_{\text{open}}\). The long-term gating properties and the Ca\(^{2+}\) sensitivity of the channels in the presence or absence of taurine were investigated by plotting the \(N \cdot P_{\text{open}}\) measured every 500 ms against time at different voltages in the presence of different concentrations of internal Ca\(^{2+}\) ions (Tricarico et al., 1997).

Statistics. The data are expressed as mean ± S.E. unless otherwise specified. The concentration-response relationship of K\(_{Ca2}\) current versus drug concentrations constructed at a positive membrane potential of +30 mV and describing the agonist action of taurine on K\(_{Ca2}\) channels fit the following equation: \((I_{\text{drug}} - I_{\text{control}})/I_{\text{control}} = E/(1 + ([\text{Drug}]/IC_{50})^{n})\), whereas the concentration-response relationship of K\(_{Ca2}\) currents versus drug concentrations constructed at a negative membrane potential of −60 mV and describing the agonist action of taurine on K\(_{Ca2}\) channels fit the following equation: \((I_{\text{drug}} - I_{\text{control}})/I_{\text{control}} = E/[1 + (DE_{50}/[\text{Drug}])^{n}]\), where \(E\) is the observed effect (inhibition or activation) of the drug on K\(_{Ca2}\) channels; \(DE_{50}\) is the concentration of the drug needed to enhance the current by 50%; \([\text{Drug}]\) is the concentration of the drug tested; \(n\) is the slope of the curves; and IC\(_{50}\) is the concentration of the drug needed to reduce the currents by 50%. The algorithms of the fitting procedures used were based on the Marquardt least-squares fitting routine.
Results

The application of increasing concentrations of taurine to the macropatches excised from rat skeletal muscle fibers provoked a dose-dependent decrease in the muscle $K_{Ca^{2+}}$ outward currents recorded at a positive membrane potential of $+30 \text{ mV} (V_m)$ in the presence of an $8 \mu M$ concentration of free $Ca^{2+}$ ions in the bath. For example, the outward currents were decreased by 39 and 62% with $20 \cdot 10^{-3}$ and $60 \cdot 10^{-3} \text{ M}$ concentrations of taurine, respectively (Fig. 1A). The IC$_{50}$ of taurine calculated using the fitting routine was $31.9 \pm 1 \text{ M}$ (slope factor = 1.2) ($n = 11$ patches) (Fig. 1B).

In contrast, at negative membrane potentials in the presence of an $8 \mu M$ concentration of free $Ca^{2+}$ ions in the bath, taurine exerted an opposite effect on muscle $K_{Ca^{2+}}$ currents. In fact, $20 \cdot 10^{-3}$ and $60 \cdot 10^{-3} \text{ M}$ concentrations of the sulfonic amino acid enhanced the inward $K_{Ca^{2+}}$ current, increasing it by 56 and 67% at $-40 \text{ mV} (V_m)$, and 31 and 43% at $-60 \text{ mV} (V_m)$, respectively. The DE$_{50}$ of taurine calculated using the fitting routine was $46.7 \pm 1 \text{ M}$ (slope factor = 1.3) ($n = 9$ patches) (Fig. 1B). In the absence of internal $Ca^{2+}$ ions, taurine did not affect activation of $K_{Ca^{2+}}$ currents at negative membrane potentials.

Single channel recordings revealed that the dualistic effects of taurine on $K_{Ca^{2+}}$ currents observed at negative and positive membrane potentials were mainly due to changes in the reversal potential of $K_{Ca^{2+}}$ channel to $K^+$ ions (Fig. 2). This was demonstrated by taurine causing a dose-dependent rightward shift of the current-voltage relationship of the $K_{Ca^{2+}}$ channel from $-0.3 \text{ mV}$ in the absence of taurine to $+9.3 \pm 2$ and $+16 \pm 3 \text{ mV}$ in the presence of $20 \cdot 10^{-3}$ and $60 \cdot 10^{-3} \text{ M}$ concentrations of the sulfonic amino acid, respectively. Accordingly, $20 \cdot 10^{-3}$ and $60 \cdot 10^{-3} \text{ M}$ concentrations of taurine reduced the single channel current at $+30 \text{ mV} (V_m)$ by 42 and 65%, while increasing it by 32 and 44% at $-60 \text{ mV} (V_m)$, respectively. The changes in the single channel currents observed following taurine application to the excised patches matched those observed in the macropatches.

No changes were observed in the single channel conductance following the in vitro application of $20 \cdot 10^{-3}$ and $60 \cdot 10^{-3} \text{ M}$ concentrations of taurine to the patches containing $K_{Ca^{2+}}$ channels. Indeed, the slope conductance calculated from the current-voltage relationships for the $K_{Ca^{2+}}$ channel was $221 \pm 12 \text{ pS} (n = 8)$ in the controls and $228 \pm 9 \text{ pS} (n = 9$ patches) and $222 \pm 10 \text{ pS} (n = 9$ patches) in the presence of $20 \cdot 10^{-3}$ and $60 \cdot 10^{-3} \text{ M}$ concentrations of taurine, respectively (Fig. 2).

Taurine did not affect the long-term gating properties of the $K_{Ca^{2+}}$ channel. In fact, the application of a $30 \cdot 10^{-3} \text{ M}$ concentration of the sulfonic amino acid to excised patches containing multiple $K_{Ca^{2+}}$ channels did not alter the gating or the number of functional channels per patch area at positive or negative membrane potentials (Fig. 3, A–D). Furthermore, taurine did not alter the sensitivity of the $K_{Ca^{2+}}$ channel to $Ca^{2+}$ ions, which is demonstrated by the fact that the gating

Fig. 1. Effects of intracellular application of taurine on $K_{Ca^{2+}}$ currents of rat skeletal muscle fibers. A, digital average of $K_{Ca^{2+}}$ currents of 10 macropatches continuously recorded in inside-out configuration at different voltages in the presence of 150 mM KCl on both sides of the membrane and $8 \mu M$ free $Ca^{2+}$ ions in the bath. At negative membrane potentials, the downward deflection of the current indicates channel opening, whereas at positive membrane potentials, the channel opening is indicated by the upward deflection of the current. The internal application of taurine enhanced the inward $K_{Ca^{2+}}$ currents recorded at negative membrane potentials, while reducing the outward $K_{Ca^{2+}}$ currents at positive membrane potentials. B, dose-response curve of normalized $K_{Ca^{2+}}$ currents against taurine concentrations constructed at membrane potentials of $+30 \text{ mV} (\bullet)$ and at $-60 \text{ mV} (\circ)$ in the presence of 150 mM KCl on both sides of the membrane and $8 \mu M$ free $Ca^{2+}$ ions in the bath. At a membrane potential of $+30 \text{ mV}$, a dose-dependent inhibition of the currents was observed following taurine application to the macropatches. In contrast, a membrane potential of $-60 \text{ mV}$ of taurine caused a dose-dependent activation of the currents.

Fig. 2. Effects of taurine on the current-voltage relationship of the $K_{Ca^{2+}}$ channel of rat skeletal muscle fibers. The single channel currents were recorded in the presence of 150 mM KCl on both sides of the membrane and $8 \mu M$ free $Ca^{2+}$ ions in the bath. The internal application of $20 \cdot 10^{-3} \text{ M} (\bullet)$ or $60 \cdot 10^{-3} \text{ M} (\triangle)$ concentrations of taurine caused a dose-dependent rightward shift of the current-voltage relationship of the $K_{Ca^{2+}}$ channel to more positive potentials than the control (●) without affecting the single channel conductance.
and the number of functional channels per patch area were unchanged after application of a 30·10^{-3} M concentration of taurine to the patches at positive or negative membrane potentials.

In our experimental condition, taurine did not affect leak currents (Fig. 3, B and C). Concentrations of taurine lower than 5·10^{-5} M did not alter the macroscopic or microscopic properties of the K_{Ca^{2+}} channel.

### Discussion

We found that taurine applied on the intracellular face of the membrane patches excised from skeletal muscle fibers induced two opposite effects on sarcolemma K_{Ca^{2+}} currents. At positive membrane potentials, the outward K_{Ca^{2+}} currents decreased, whereas at negative membrane potentials, the sulfonic amino acid induced stimulation of inward K_{Ca^{2+}} currents. This is the result of the rightward shift of the reversal potential of the K_{Ca^{2+}} channel for K^+ ions caused by taurine. Changes in the reversal potentials of ion channels may be related to modifications of the selectivity of the pore to K^+ ions, to alteration of the surface charge potentials, and/or to changes in the local charge density (Hille, 1984). In our study, the observation that taurine altered the reversal potential of the K_{Ca^{2+}} channel for K^+ ions without affecting the single channel conductance supports the hypothesis that the effects of the amino acid are related to changes in the surface charge potentials and/or change in the local charge density rather than to changes in the selectivity of the pore for K^+ ions. It is possible that taurine affected the local charge density by binding to charge residues located at the mouth of the pore of the K_{Ca^{2+}} channel reducing the accessibility of K^+ ions from the intracellular side of the membrane to the conduction pathway. In our experiments, the finding that the slope factor calculated by the fitting routine was about 1 for both the inhibition and activation of the K_{Ca^{2+}} channel by the sulfonic amino acid suggests that the stoichiometry of the interaction of taurine with the binding site is 1:1.

Similarly, a shift of the reversal potentials of the cardiac inward rectifier K^+ channel and the embryonic Na^+ channel toward more negative potentials following extracellular taurine application has also been described (Sutoh, 1995, 1998b). This is not surprising considering that taurine is a charged amino acid capable of altering surface charge potentials by interacting with the polar phase of phospholipids. If the site(s) of interaction are located in the ion channel pore on residues critical for the conduction pathway, modification of the reversal potentials for the carried ion can be expected. Alternately, if the site of interaction of taurine is located in proximity to subunits critical for controlling channel activity and the pharmacological properties of the channel, changes in gating and in the response of the channel to drugs can be expected. This phenomenon occurs in the case of the action of taurine on muscle K\textsubscript{ATP} channels in which the sulfonic amino acid induces a reversible inhibition of the muscular channel rather than to changes in the selectivity of the pore for K^+ ions. It is possible that taurine affected the local charge density by binding to charge residues located at the mouth of the pore of the K_{Ca^{2+}} channel reducing the accessibility of K^+ ions from the intracellular side of the membrane to the conduction pathway. In our experiments, the finding that the slope factor calculated by the fitting routine was about 1 for both the inhibition and activation of the K_{Ca^{2+}} channel by the sulfonic amino acid suggests that the stoichiometry of the interaction of taurine with the binding site is 1:1.

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interacting with a site allosterically coupled to the SUR of the 
K\textsubscript{ATP} channel complex at the interface between the mem-
brane phospholipids and the SUR protein without altering
the reversal potential for K\textsuperscript{+} ions (Tricarico et al., 2000a).

From a pharmacological point of view, taurine can therefore
be considered an inhibitor of several classes of K\textsuperscript{+}
channels, including Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels. In skeletal muscle,
the capability of the sulfonic amino acid to reduce the
outward KCa\textsubscript{2+} current, even in the presence of the natural
stimulatory ligand of the Ca\textsuperscript{2+} ions, may have important
implications in those conditions associated with hyperkale-
mic states, such as ischemia-reperfusion and muscle fatigue,
or in cases of an impairment of muscle contraction, such as
the aging process (Pierno et al., 1998). The action of taurine,
through inhibition of the outward currents carried by KCa\textsubscript{2+}
channels, would reduce the hyperpolarization phase follow-
ing the firing of action potentials, thus controlling the Ca\textsuperscript{2+}
homeostasis of the fibers and contributing to Ca\textsuperscript{2+}-
dependent physiological functions, such as muscle contraction. This cor-
responds with the fact that taurine supplementation shows
therapeutic effects, improving the contractility functions of
aged rat skeletal muscle (Pierno et al., 1998).

We believe that the agonist action shown by taurine at
negative membrane potentials on inward currents of KCa\textsubscript{2+}
channels may have implications in those pathophysiological
conditions associated with taurine depletion, such as ischemia-reperfusion in which a loss of taurine can favor the
opening of KCa\textsubscript{2+} channels and other K\textsuperscript{+} channels with fiber
repolarization and cytoprotective effects (McPherson et al.,
1993; Hearse, 1995; Han et al., 1996; Tricarico et al., 2000a).
This corresponds with the observation that the loss of taurine
from the tissues is considered as a protective mechanism
against ischemia (Allo et al., 1997; Suleiman et al., 1997).

References
Allo SN, Bagby L and Schaffer SW (1997) Taurine depletion, a novel mechanism for
Conte Camerino D, De Luca A, Mambrini M, Ferrarini E, Francioni F, Gotti A and
Han J, Euiyong K, Won-Kyung H and Yung EE (1996) Blockade of the ATP-sensitive
potassium channel by taurine in rabbit ventricular myocytes. J Mol Cell Cardiol
28:2043–2050.
Hearse DJ (1995) Activation of ATP-sensitive potassium channels: a novel pharma-
Hille B (1984) Potassium channels and chloride channels, in Ion Channels of Excit-
Huxtable RJ and Sebring LJ (1986) Towards a unifying theory for the actions of
McPherson CD, Pierce GN and Cole WC (1993) Ischemic cardioprotection by ATP-
sensitive K\textsuperscript{+} channel involves high-energy phosphate preservation. Am J Physiol
265:H1809–H1818.
Pasantes-Morales H, Quesada O and Moran J (1998) Taurine: an osmolyte in mamma-
lian tissues, in Taurine 3: Cellular and Regulatory Mechanisms (Schaffer
administration of taurine to aged rats improves the electrical and con-
Saranasi P and Oja SS (1998) Mechanism of ischemia-induced taurine release in
Satoh H (1995) Taurine-induced hyperpolarizing shift of the reversal potentials of
the fast Na\textsuperscript{+} current in embryonic chick cardiomyocytes. Gen Pharmacol
Satoh H (1998a) Cardiac actions of taurine as a modulator of the ion channels, in
Taurine 3: Cellular and Regulatory Mechanisms (Schaffer S, Lombardini JB
Satoh H (1998b) Inhibition by taurine of the inwardly rectifying K\textsuperscript{+} channel in
Suleiman MS, Moffatt AC, Dihmis WC, Caputo M, Hutter JA, Angelini GD and
Bryan AJ (1997) Effect of ischemia and reperfusion on the intracellular concen-
tration of taurine and glutamine in the hearts of patients undergoing coronary
Tricarico D, Barbieri M and Conte Camerino D (2000a) Taurine blocks ATP-sensitive
potassium channels of rat skeletal muscle fibres interfering with the sulphonyla-
Tricarico D, Barbieri M and Conte Camerino D (2000b) Aetazolamide opens the
muscular KCa\textsubscript{2+}-channel: a novel mechanism of action that may explain the
therapeutic effect of the drug in the hypokalemic periodic paralysis. Ann Neurol
Tricarico D and Conte Camerino D (1994) ATP-sensitive K\textsuperscript{+} channels of skeletal
muscle fibers from young adult and aged rats: possible involvement of thiol-
dependent redox mechanisms in the age-related modifications of their biophysical
Tricarico D, Petruzzi R and Conte Camerino D (1997) Changes of the biophysical
properties of calcium-activated potassium channels of rat skeletal muscle fibers

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