ELSEVIER

European Journal of Pharmacology 316 (1996) 97–103

ejp

Na^+/Ca^{2+} exchange current: lack of effect of taurine

Yasuhiro Katsube *, Nicholas Sperelakis

Department of Molecular and Cellular Physiology, College of Medicine, University of Cincinnati, P.O. Box 670576, Cincinnati, OH 45267, USA

Received 23 May 1996; revised 8 August 1996; accepted 13 August 1996

Abstract

The intracellular taurine content is very high in some types of cells, including myocardial cells, and taurine becomes depleted in failing hearts. The effect of taurine on inward (forward) and outward (reversal) Na^+/Ca^{2+} exchange current ($I_{Na/Ca}$) was examined in freshly isolated rat (11–20-day-old) ventricular cells using whole-cell voltage clamp. $I_{Na/Ca}$ was evoked by a 300 ms ramp hyperpolarizing pulse at a rate of 0.67 V/s (from +60 to −140 mV) from a holding potential of −40 mV. Under the condition of 500 nM Ca^{2+} in the pipette, when the bath solution was changed from 150 mM Li^+ to 150 mM Na^+, an inward $I_{Na/Ca}$ was initiated. On the other hand, under the condition of 50 mM Na^+ and 56 nM Ca^{2+} in the pipette, when the bath solution was changed from Na^+-free, Ca^{2+}-free solution to Na^+-free, 2 mM Ca^{2+}, an outward $I_{Na/Ca}$ was initiated. Both inward and outward $I_{Na/Ca}$ were completely blocked by 5 mM Ni^{2+}, helping to identify the current as $I_{Na/Ca}$. Forward and reversal $I_{Na/Ca}$ was measured in the absence (control) and presence of 30 mM taurine added to the bath. The current densities (pA/pF) of inward $I_{Na/Ca}$ at −50 mV were 0.75 ± 0.12 in control and 0.73 ± 0.11 in presence of 30 mM taurine. Outward $I_{Na/Ca}$ at +50 mV were 0.73 ± 0.08 in control and 0.65 ± 0.02 in 30 mM taurine. There were no significant differences between control and taurine for both inward and outward $I_{Na/Ca}$. Therefore, the various effects of taurine reported on the heart are not caused by a direct effect of taurine on Na/Ca exchange.

Keywords: Taurine; Na^+-Ca^{2+} exchange; Ventricular myocyte, rat; Patch-clamp

1. Introduction

Although plasma taurine (sulfur-containing amino acid) concentrations are usually 50–600 μmol/l, myocardial tissue concentrations have been reported to be 6–30 mmol/kg wet weight (i.e., 50–200 times higher in the cardiomyocyte) (Chapman et al., 1993a). Higher than normal taurine levels have been found in heart tissue from patients with congestive heart failure (Huxtable and Bressler, 1974), while the taurine content of the heart decreases during ischemia (Crass and Lombalsini, 1977). Cats fed a taurine-deficient diet develop a cardiomyopathy, which is reversible on dietary supplementation with taurine (Pion et al., 1987). These data suggest that taurine plays an important role in cardiomyocytes.

Taurine has achieved some success in treating patients with chronic congestive heart failure (Azuma et al., 1982, 1985, 1992). Preoperative rapid intravenous infusion of taurine reduced cell damage during coronary bypass graft surgery (Milei et al., 1992). Taurine has been used as a convenient marker of myocardial injury because of its high concentration in cardiomyocytes (Waldenström et al., 1995). In basic research on the heart, many findings have been reported on the effects of taurine (see review-type articles: Azuma and Schaffer (1993), Sperelakis and Satoh (1993)). The main effects of taurine on the heart are its cardioprotective actions, such as on the Ca^{2+} paradox (Kramer et al., 1981; Yamauchi-Takihara et al., 1988; Suleiman and Chapman, 1993), hypoxic injury (Sawamura et al., 1986a), and Na^+ overloading (Suleiman et al., 1992; Chapman et al., 1993b). The positive inotropic and cardioprotective actions of taurine may be related to its ability to alter Ca^{2+} movements and to alter Na^+ movements via the Na^+/taurine cotransport.

Taurine exerts actions on several types of ion channels of cardiac muscle. However, these actions are complex. For example, Sawamura et al. (1990) showed that taurine *inhibited* $I_{Ca(L)}$ in 3.6 mM $[Ca]_o$ and *stimulated* it in 0.8 mM $[Ca]_o$. They concluded that one action of taurine is to normalize Ca^{2+} movement through the sarcolemma and to

* Corresponding author. Tel.: (1-513) 558-3126; Fax: (1-513) 558-2668.

PII S0014-2999(96)00652-8

keep $[Ca]_i$ relatively constant. Consistent with this, Satoh and Sperelakis (1993) showed that taurine *inhibited* $I_{Ca(L)}$ at high $[Ca]_i$ (pCa 7), whereas it *stimulated* $I_{Ca(L)}$ at low $[Ca]_i$ (pCa 10). Thus, taurine has a normalizing action on I_{Ca} currents, depending on $[Ca]_i$ as well as on $[Ca]_o$. Taurine also protected against the decline of the Ca^{2+} current-dependent slow action potentials produced by hypoxia (Sawamura et al., 1986a,b). In addition, taurine appeared to stimulate the fast (T-type) Ca^{2+} current ($I_{Ca(T)}$) and a fast transient component of the tetrodotoxin-insensitive Na^+ current ($I_{Na(s)}$).

Taurine also modulates the Na^+ channels. For example, Satoh and Sperelakis (1992) showed that the tetrodotoxin-sensitive fast Na^+ current ($I_{Na(f)}$) was stimulated in some cells by the lower concentrations of taurine (1 and 5 mM), but depressed in the other cells and depressed $I_{Na(f)}$ in all cells at higher concentrations (10, 20 mM). In agreement, Schanne and Dumaine (1992) showed that taurine (20 mM) caused an inhibition of I_{Na} channels at test potentials positive to −45 mV.

Earm et al. (1993) reported that taurine increased the Ca release-dependent Na^+/Ca^{2+} exchange current, which was caused by enhancement of intracellular Ca^{2+} transient from sarcoplasmic reticulum. This report showed that taurine played an *indirect* but important role on Na/Ca exchanger. The present experiments were designed to examine whether taurine would have any *direct* effect on the Na/Ca exchange current in single isolated rat ventricular myocytes using the whole-cell voltage-clamp technique.

2. Materials and methods

2.1. Cell preparation

Freshly isolated single cells were prepared from ventricles of young (11–20-day-old) Sprague-Dawley rats. The rats were decapitated under the CO_2 anesthesia, and the hearts were removed and rinsed in oxygenated Tyrode solution, then immersed in Ca^{2+}-free Tyrode solution for 30 min at room temperature. The ventricles were dissected after the spontaneous beatings had ceased and small pieces of the ventricles were enzymatically digested for 50 min in Ca^{2+}-free Tyrode solution (37°C) containing collagenase (1.0 mg/ml, Wako, Osaka, Japan). After incubation, the cells were mechanically dispersed in the modified KB (Kraftbruhe = power soup) solution using a Pasteur pipette. The cell suspension was stored in a refrigerator (4°C) until used.

2.2. Solution and drugs

The solutions and protocol used were similar to those first described by Kimura et al. (1987). The normal Tyrode solution contained (in mM): NaCl 143, KCl 5.4, NaH_2PO_4 0.33, $MgCl_2$ 0.5, $CaCl_2$ 1.8, glucose 5.5, Hepes 5, and pH adjusted to 7.4 with NaOH. The modified KB solution contained (in mM): K-glutamate 50, KOH 20, KCl 40, KH_2PO_4 20, $MgCl_2$ 3, glucose 10, EGTA 0.5, Hepes 10 and pH adjusted to 7.4 with KOH. The 150 mM Na^+ external solution contained (in mM): NaCl 150, $MgCl_2$ 1, CsCl 2, $BaCl_2$ 1, Hepes 5, ouabain 0.02, nifedipine 0.002, and pH adjusted to 7.4 with Trizma base, and the 150 mM Li^+ external solution was made by replacing NaCl with equimolar LiCl. The 2 mM Ca^{2+} external solution was made by adding 2 mM $CaCl_2$ into the 150 mM Li^+ external solution. The Cs^+-rich internal solution contained (in mM): CsOH 120, aspartic acid 80, CsCl 20, $MgCl_2$ 2, MgATP 5, K_2-creatinephosphate 5, EGTA 10, Hepes 5, and pH adjusted to 7.4 with CsOH. The Na^+-rich internal solution was made by substituting 50 mM NaOH for an equimolar amount of CsOH. The internal solution was about 40% hyperosmotic, but did not appreciably affect the exchange current (forward mode) reported by Kimura et al. (1987).

To prevent the cell from contracture caused by Ca^{2+} entering in exchange for Na^+, 30 mM EGTA was put in the pipette solution so that the buffering capacity for Ca^{2+} was increased. The concentration of free Ca^{2+}, which was calculated by using Fabiato and Fabiato's equation, was adjusted by adding $CaCl_2$ to the internal solution. As a result, the following combinations were used: pCa 7.25 (free Ca^{2+} 56 nM = 30 mM EGTA + 15 mM $CaCl_2$), and pCa 6.3 (free Ca^{2+} 500 nM = 10 mM EGTA + 8.94 mM $CaCl_2$). As blockers in the external solution, ouabain was used to block the Na^+-K^+ pump, $BaCl_2$ and CsCl to block K^+ channels, and nifedipine to block Ca^{2+} channels.

2.3. Whole-cell voltage clamp recordings

Voltage-clamp recordings were performed in the whole-cell configuration of the patch-clamp method by using patch clamp amplifier (Axopatch-1D, Axon Instruments, USA) and heat-polished borosilicate glass pipettes (World Precision Instruments, USA) with resistances of 2–6 MΩ when filled with the pipette solution. The cell suspension was placed into a small chamber (1.4 ml) on the stage of an inverted microscope (Diaphoto, Nikon, Japan). Then they were constantly perfused with the external solution at a rate of 1.8 ml/min. Current and voltage signals were filtered with a cut-off frequency of 1 kHz, and digitized by an A/D converter (TL-1, Axon Instruments) and sampled at 2.7 kHz. Current and voltage signals were stored in IBM-AT personal computer using the pCLAMP software (ver. 5.0.5, Axon Instruments).

The external solutions were heated by a water jacket before entering the recording chamber. The temperature of the bath solution was measured using a small thermistor. All experiments were performed at 35–37°C unless otherwise stated.

2.4. Measurement of Na^+/Ca^{2+} exchange current

The current/voltage (I/V) curves were obtained using ramp pulses (Fig. 1B). The shape of the ramp pulse was of three phases: an initial 100 mV depolarizing phase from a holding potential of −40 mV, a second hyperpolarization of 200 mV, and a third phase returning to a holding potential at a rate of 0.67 V/s. The I/V curves were measured during the second hyperpolarizing portion. *Forward mode*: The pipette solution contained Na^+-free and 500 nM Ca^{2+} (pCa 6.3) (Fig. 1A). Changing the bathing solution from 150 mM Li^+ (Na^+-free) to 150 mM Na^+, the inward $I_{Na/Ca}$ (carried by Na^+ influx) was initiated. Since the external solution did not contain Ca^{2+}, the theoretical reversal potential should be at plus infinity. Therefore, the $I_{Na/Ca}$ was inward at all membrane potentials tested. *Reverse mode*: The pipette solution contained 50 mM Na^+ and 56 nM Ca^{2+} (pCa 7.25) (Fig. 1A). Changing the bathing solution from 150 mM Li^+ to 150 Li^+ containing 2 mM Ca^{2+}, the outward $I_{Na/Ca}$ (carried by Na^+ efflux) was initiated. Since the external solution contained 150 mM Li^+ (Na^+-free), the $I_{Na/Ca}$ was outward at all membrane potentials tested.

2.5. Statistical analysis

All data are presented as mean ± S.E. Statistical analyses were performed using Student's paired or unpaired

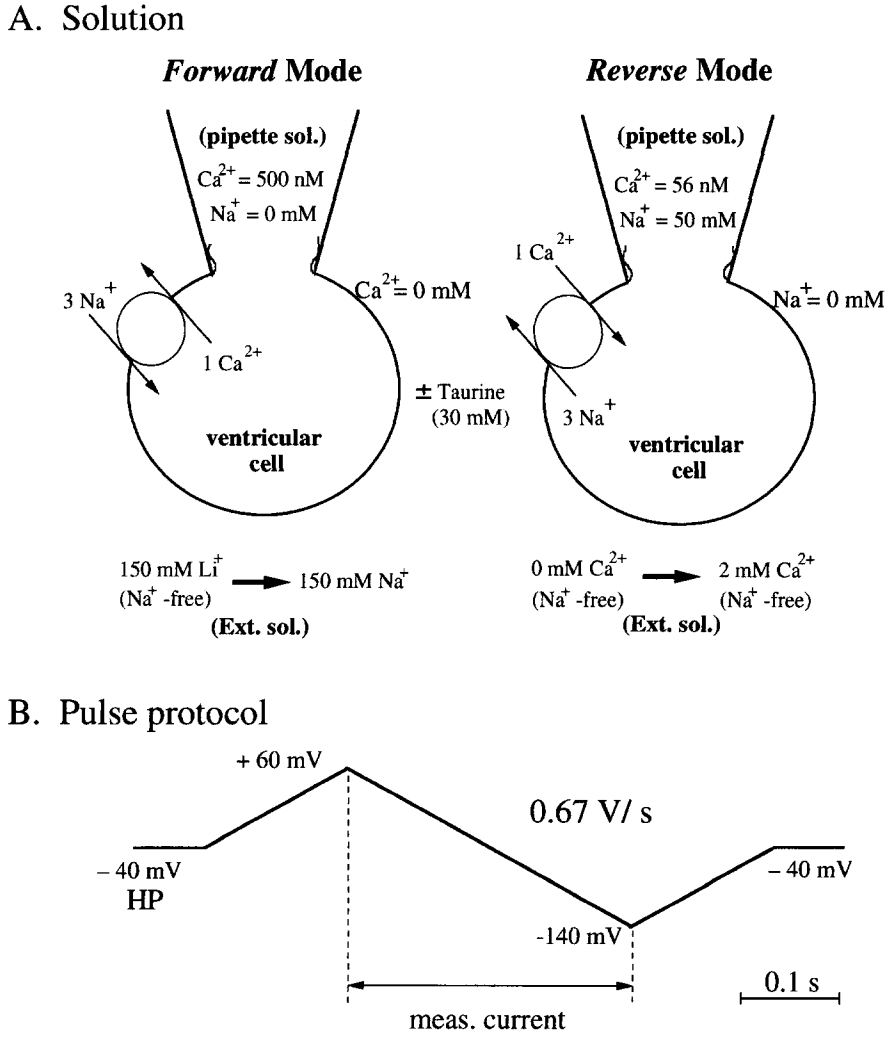

Fig. 1. Diagram of method used to measure the Na^+/Ca^{2+} exchange current in the rat ventricular myocytes. The ramp pulse had three phases: an initial 100 mV depolarizing phase from a holding potential of −40 mV, a second hyperpolarizing phase of 200 mV, and a third phase returning to the holding potential. The slope of the ramp was 200 mV/0.3 s. The I/V curve was measured during the second hyperpolarizing portion. *Forward mode*: the pipette solution contained 500 nM Ca^{2+} (pCa 6.3). Changing the bathing solution from 150 mM Li^+ (Na^+-free) to 150 mM Na^+, the inward Na^+/Ca^{2+} exchange current (carried by Na^+ influx) was initiated. *Reverse mode*: the pipette solution contained 50 mM Na^+. Changing the bathing solution from Ca^{2+}-free to 2 mM Ca^{2+}, the outward Na^+/Ca^{2+} exchange current (carried by Na^+ efflux) was initiated. Taurine (30 mM) was added in the external solution. The external solution contained ouabain (20 μM) to block the Na^+-K^+ pump, $BaCl_2$ (1 mM) and CsCl (2 mM) to block K^+ channels, and nifedipine (2 μM) to block slow Ca^{2+} channels. In the presence of these blockers, time-dependent ionic currents and Na^+-K^+ pump current were mostly blocked, and the remaining conductance showed a nearly linear I/V relation.

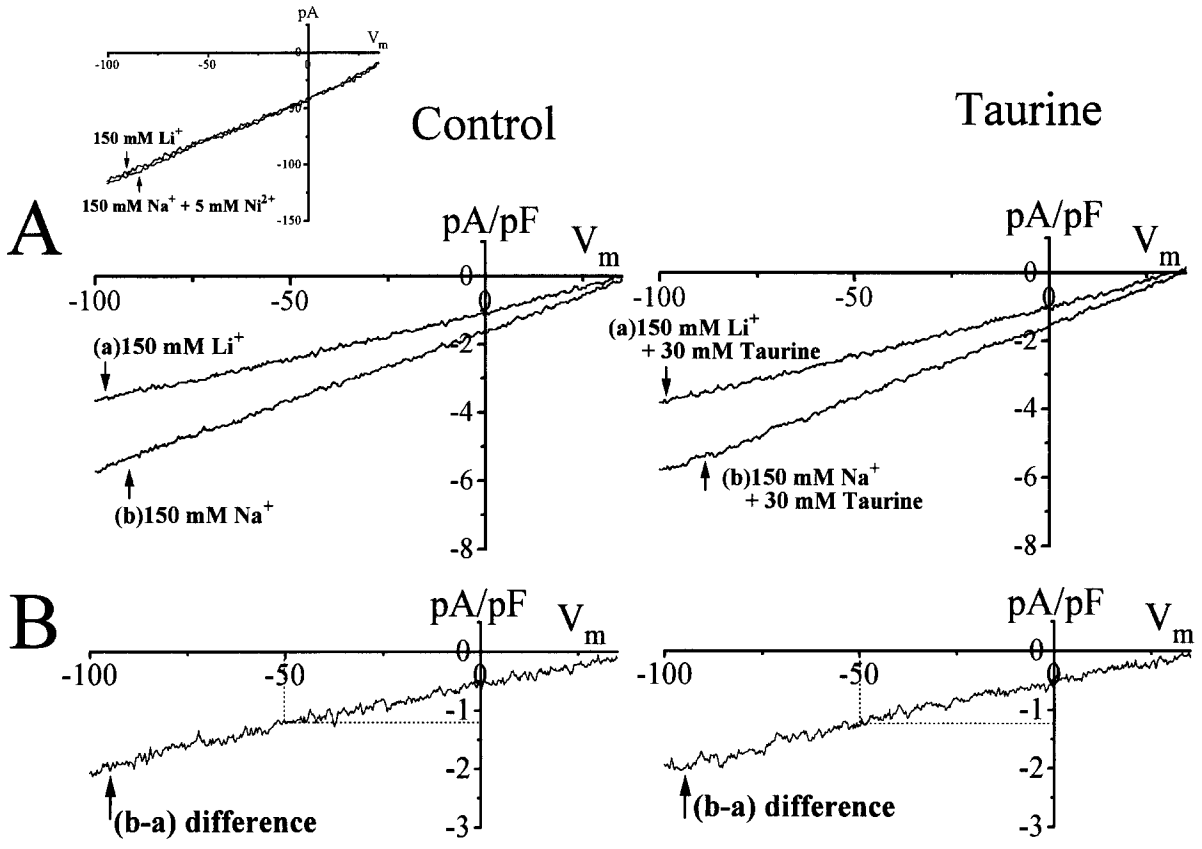

Fig. 2. Effect of taurine (30 mM) on inward Na^+/Ca^{2+} exchange current in the rat ventricular cell. The inward Na^+/Ca^{2+} exchange current was elicited by ramp pulse for 300 mV duration (from +60 mV to −140 mV) from a holding potential of −40 mV. The cell in control and in 30 mM taurine is from the same cell (10-day-old rat ventricular myocyte). Ordinate represents current density obtained by normalizing the current to the membrane capacitance. (A) Under the condition of 500 nM Ca^{2+} and Na^+-free in the pipette, when the bath solution was changed from 150 mM Li^+ (a) to 150 mM Na^+(b), the membrane current shifted inward. 30 mM taurine was added to the bath solution. (B) Difference currents (b–a) (inward $I_{Na/Ca}$) were shown in (B). The inward $I_{Na/Ca}$ (at −50 mV) were 45 pA in control and 47 pA in the presence of 30 mM taurine. Therefore, as C_m was 38 pF the current densities were calculated to be 1.2 pA/pF in both groups.

t-test and $P < 0.05$ was defined as significant. Fig. 2 and Fig. 3 were re-filtered with cut-off frequency of 500 Hz.

3. Results

The internal solutions used for the *forward* mode and *reverse* mode, and the changes mode in the extracellular solutions to initiate the exchange current are depicted in Fig. 1. In our solution, Na^+-K^+ pump was blocked by external ouabain, K^+ current channels were blocked by internal and external Cs^+ and external Ba^{2+}, and Ca^{2+} channels were blocked by external nifedipine. In the presence of these blockers, time-dependent currents were mostly blocked and the remaining conductance showed a nearly linear I/V relationship.

3.1. Effect of taurine on the inward Na^+/Ca^{2+} exchange current

Fig. 2 shows the representative examples. Both control and taurine are from the same cell (10-day-old rat ventricular myocyte). Under the condition of 500 nM Ca^{2+} (pCa = 6.3) and Na^+-free in the pipette, when the bath solution was changed from 150 mM Li^+ (a) to 150 mM Na^+ (b), the membrane current shifted inward. The difference current (b–a) shows the inward $I_{Na/Ca}$ carried by Na^+ influx. In this experiment, the inward $I_{Na/Ca}$ values (at −50 mV) were 45 pA in control and 47 pA in presence of 30 mM taurine in the bath. Therefore, current densities were calculated to be 1.2 pA/pF in both groups (C_m = 38 pF). The inward current was blocked completely by 5 mM Ni^{2+} (Fig. 2, inset). We examined the effect of 30 mM taurine on the inward $I_{Na/Ca}$ of 10 cells from young rat ventricular myocytes. The current densities were 0.75 ± 0.12 pA/pF in control and 0.73 ± 0.11 in the presence of taurine at the membrane potential of −50 mV (Fig. 4).

3.2. Effect of taurine on the outward Na^+/Ca^{2+} exchange current

Under the condition of 50 mM Na^+ and 56 nM Ca^{2+} (pCa = 7.25) in the pipette, when the bath solution was changed from Na^+-, Ca^{2+}-free (a) to Na^+-free, 2.0 mM

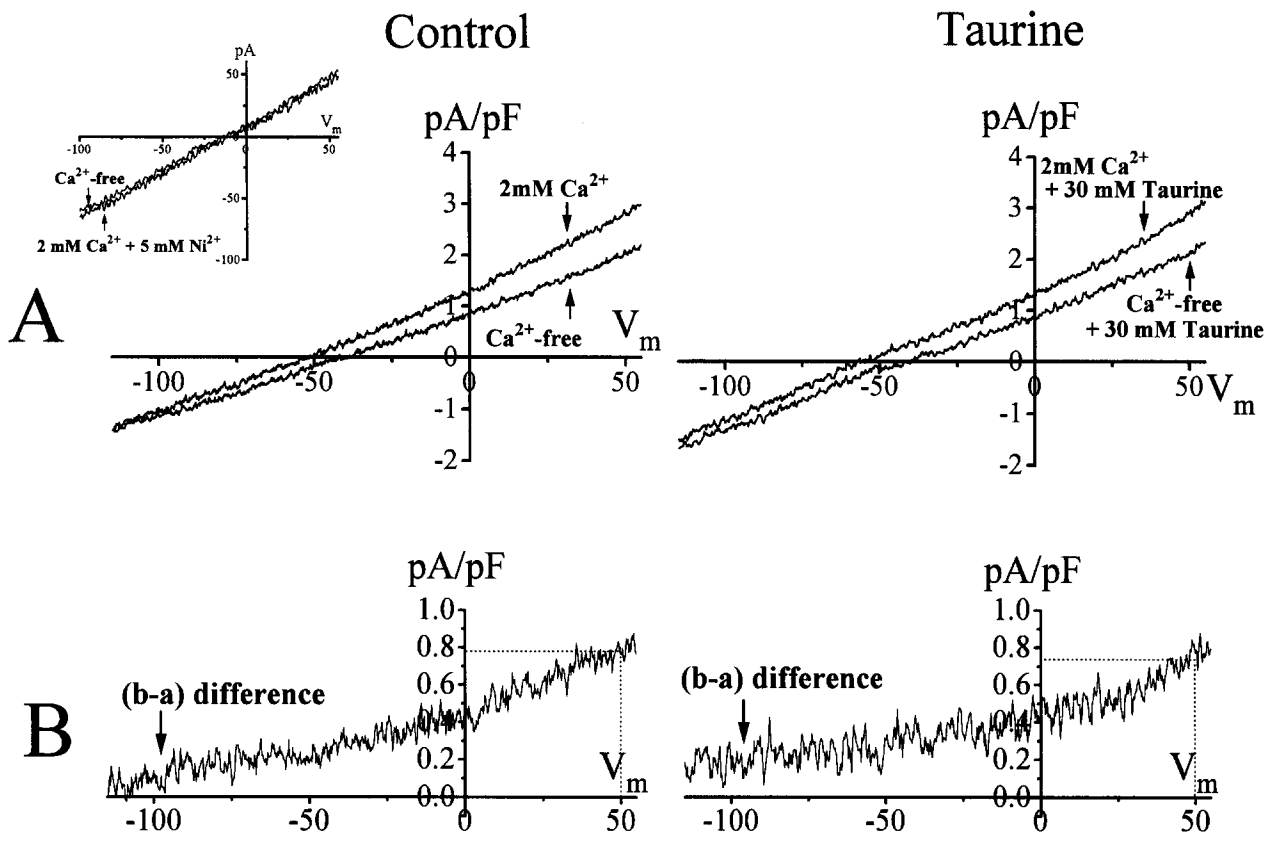

Fig. 3. Effect of taurine (30 mM) on outward Na^+/Ca^{2+} exchange current in the rat ventricular cells. Pulse protocol is the same that of inward Na^+/Ca^{2+} exchange current. The cells in control (15-day-old) and in the presence of 30 mM taurine (9-day-old) are from different cells. (A) Under the condition of 56 nM Ca^{2+} and 50 mM Na^+, when the bath solution was changed from Ca^{2+}-free (a) to 2 mM Ca^{2+} (b), the membrane current shifted outward. 30 mM taurine was added to the bath solution. (B) Difference currents (b–a) (outward $I_{Na/Ca}$) are shown in (B). The outward $I_{Na/Ca}$ (at +50 mV) were 27 pA in control and 23 pA in the presence of 30 mM taurine. Therefore, the current densities were calculated to be 0.77 pA/pF in control (C_m = 35 pF) and 0.77 pA/pF in the presence of taurine (C_m = 30 pF).

Ca^{2+} (b), the membrane current shifted outward (carried by Na^+ efflux). The difference current (b–a) shows the outward $I_{Na/Ca}$. In these cells, the outward $I_{Na/Ca}$ were 27 pA in control and 23 pA in the presence of 30 mM taurine, therefore the current densities (at +50 mV) were calculated to be 0.77 pA/pF in control (C_m = 35 pF) and 0.77 pA/pF in the presence of taurine (C_m = 30 pF). The outward current was completely blocked by 5 mM Ni^{2+} (Fig. 3, inset). The current densities of the outward $I_{Na/Ca}$ were 0.73 ± 0.08 pA/pF in control (n = 7) and 0.65 ± 0.02 pA/pF in presence of 30 mM taurine (n = 4) at the membrane potential of +50 mV (Fig. 4).

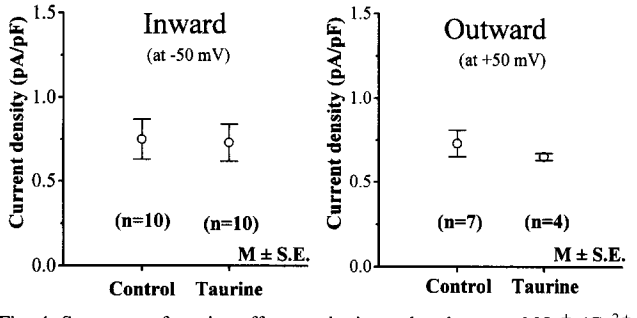

Fig. 4. Summary of taurine effect on the inward and outward Na^+/Ca^{2+} exchange currents. The current densities (pA/pF) were 0.75 ± 0.12 in control and 0.73 ± 0.11 in the presence of 30 mM taurine on the inward $I_{Na/Ca}$. On the other hand, the current densities were 0.73 ± 0.08 pA/pF in control and 0.65 ± 0.02 pA/pF in presence of 30 mM taurine on the outward $I_{Na/Ca}$. There were no significant differences between the two groups on the inward and outward $I_{Na/Ca}$.

The summary of the effect of taurine on inward and outward $I_{Na/Ca}$ are shown in Fig. 4. There were no significant differences between the two groups in both inward and outward $I_{Na/Ca}$.

4. Discussion

The present study was performed to determine the *direct* effect of taurine on the Na^+/Ca^{2+} exchange current in rat ventricular myocytes using the whole-cell voltage-clamp technique. Our results showed that taurine (30 mM) applied externally did not directly affect $I_{Na/Ca}$, both in the inward (forward mode) and outward (reversal mode) directions. To allow measurement of any direct effect of taurine on the exchange, the following protocol was used: (1) blocking drugs were present to block all types of ion

channel currents; (2) to prevent indirect effects mediated by Ca^{2+} release from the sarcoplasmic reticulum, a high EGTA concentration was used in the pipette solution; (3) to control for any possible effect of taurine on the background current, taurine was added in both external solutions: the 150 mM Li^+ solution and 150 mM Na^+ solution for measuring inward $I_{Na/Ca}$, and the Ca^{2+}-free solution and 2 mM Ca^{2+} solution for measuring outward $I_{Na/Ca}$. This protocol allows any direct effect of taurine on the exchanger to be observed.

These results are in agreement with the biochemical study by Hamaguchi et al. (1991), who reported that 10 mM taurine had no effect on the activity of the Na^+/Ca^{2+} exchanger. In contrast, 300 μM methionine produced about a four-fold decrease in sarcolemmal Na^+/Ca^{2+} exchange activity.

Earm et al. (1993) showed an enhancement of the Na^+/Ca^{2+} exchange current tail produced by 20 mM taurine that was caused by taurine-induced release of Ca^{2+} from the sarcoplasmic reticulum. In their experiments, the pipette solution contained only 0.1 mM EGTA, thus allowing an increase in $[Ca]_i$ to be produced (i.e., low internal Ca^{2+} buffering). Therefore, the observed increase in Na^+/Ca^{2+} exchange current was due to Ca^{2+} release from the sarcoplasmic reticulum and not to a direct effect of taurine on the exchanger. In contrast, in our experiments, the pipette solution contained 10 mM EGTA to prevent a rise in $[Ca]_i$. However, Steele et al. (1990), using chemically skinned rat heart, showed that taurine caused a marked increase in the ability of the sarcoplasmic reticulum to accumulate Ca^{2+} (and a small increase in myofilament Ca^{2+} sensitivity).

Earm et al. (1993) also showed that application of 10–30 mM taurine into the sarcoplasm, in the presence of 30 mM $[Na]_i$, increased the outward background current. They suggested that an electrogenic cotransport of taurine and Na^+ can occur, and therefore taurine may help prevent Na^+ overload and thereby protect against damage from hypoxia and ischemia.

In addition, Earm et al. (1993) reported inhibition of the ATP-sensitive K^+ current by taurine (10–20 mM) in the pipette. They suggested that taurine might act like an antiarrhythmic by blocking ATP-sensitive K^+ current and exerting protective effects against arrhythmias induced by hypoxia. Sperelakis et al. (1992) showed that bath application of taurine (20 mM) increased outward K^+ currents (I_K) in embryonic chick ventricular cells at pCa 10, whereas it decreased I_K at pCa 7.

In summary, we demonstrated that taurine did not *directly* affect the Na^+/Ca^{2+} exchanger in rat ventricular myocytes. However, the Na/Ca exchanger is *indirectly* affected by taurine, i.e., whenever $[Ca]_i$ rises. Thus, the cardioprotective effects and the $[Ca]_i$-stabilizing effects of taurine are not mediated by regulation of the Na/Ca exchanger. Instead, taurine exerts potent effects on $I_{Ca(L)}$ and $I_{Na(f)}$ (and I_K), which act to modify $[Ca]_i$ and $[Na]_i$.

Acknowledgements

We thank Ms. Sheila Blank for preparation of the cells. This work was supported by National Institutes of Health grant HL-31942.

References

Azuma, J. and S.W. Schaffer, 1993, Protective effect of taurine on the failing heart and its clinical application, in: Ionic Channels and Effect of Taurine on the Heart, eds. D. Noble and Y.E. Earm (Kluwer Academic Publishers, Boston, MA) p. 139.

Azuma, J., H. Hasegawa, A. Sawamura, N. Awata, H. Harada, K. Ogura and S. Kishimoto, 1982, Taurine for treatment of congestive heart failure, Int. J. Cardiol. 2, 303.

Azuma, J., A. Sawamura, N. Awata, H. Ohta, H. Hamaguchi, H. Harada, K. Takihara, H. Hasegawa, Y. Yamagami, T. Ishiyama, H. Iwata and S. Kishimoto, 1985, Therapeutic effect of taurine in congestive heart failure: a double-blind cross-over trial, Clin. Cardiol. 8, 276.

Azuma, J., A. Sawamura and N. Awata, 1992, Usefulness of taurine in chronic congestive heart failure and its prospective application, Jpn. Circ. J. 56, 95.

Chapman, R.A., M.S. Suleiman and Y.E. Earm, 1993a, Taurine and the heart, Cardiovasc. Res. 27, 358.

Chapman, R.A., M.S. Suleiman, G.C. Rodrigo, K.K. Minazaki, K.R. Chatamra, C.R. Little, D.K. Mistry and T.J.A. Allen, 1993b, Intracellular taurine, intracellular sodium and defense against cellular damage, in: Ionic Channels and Effect of Taurine on the Heart, eds. D. Noble and Y.E. Earm (Kluwer Academic Publishers, Boston, MA) p. 73.

Crass, M.F. III and J.B. Lombalsini, 1977, Loss of cardiac muscle taurine after acute left ventricular ischemia, Life Sci. 21, 951.

Earm, Y.E., W.K. Ho, I. So, C.H. Leem and J. Han, 1993, Effect of taurine on the activation of background current in cardiac myocytes of the rabbit, in: Ionic Channels and Effect of Taurine on the Heart, eds. D. Noble and Y.E. Earm (Kluwer Academic Publishers, Boston, MA) p. 119.

Hamaguchi, T., J. Azuma and S. Schaffer, 1991, Interaction of taurine with methionine: inhibition of myocardial phospholipid methyltrasferase, J. Cardiovasc. Pharmacol. 18, 224.

Huxtable, R.J. and R. Bressler, 1974, Elevation of taurine in human congestive heart failure, Life Sci. 14, 1353.

Kimura, J., S. Miyamae and A. Noma, 1987, Identification of sodium-calcium exchange current in single ventricular cells of guinea-pig, J. Physiol. 384, 199.

Kramer, J.H., J.P. Chovan and W. Schaffer, 1981, Effect of taurine on calcium paradox and ischemic heart, Am. J. Physiol. 240, H238.

Milei, J., R. Ferreira, S. Lesuy, P. Forcada, J. Cavarrubias and A. Boveris, 1992, Reduction of reperfusion injury with preoperative rapid intravenous infusion of taurine during myocardial revascularization, Am. Heart J. 123, 339.

Pion, P.D., M.D. Kittleson, Q.R. Rogers and J.G. Morris, 1987, Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy, Science 237, 764.

Satoh, H. and N. Sperelakis, 1992, Taurine inhibition of fast Na^+ current in embryonic chick ventricular myocytes, Eur. J. Pharmacol. 218, 83.

Satoh, H. and N. Sperelakis, 1993, Effects of taurine on Ca^{2+} currents in young embryonic chick cardiomyocytes, Eur. J. Pharmacol. 231, 443.

Sawamura, A., N. Sperelakis and J. Azuma, 1986a, Protective effect of taurine against decline of cardiac slow action potentials during hypoxia, Eur. J. Pharmacol. 120, 235.

Sawamura, A., N. Sperelakis, J. Azuma and S. Kishimoto, 1986b, Effects of taurine on the electrical and mechanical activities of embryonic chick heart, Can. J. Physiol. Pharmacol. 64, 649.

Sawamura, A., H. Sada, J. Azuma, S. Kishimoto and N. Sperelakis, 1990, Taurine modulates ion influx through cardiac Ca^{2+} channels, Cell Calcium 11, 251.

Schanne, O.F. and R. Dumaine, 1992, Interaction of taurine with the fast Na-current in isolated rabbit myocytes, J. Pharmacol. Exp. Ther. 263, 1233.

Sperelakis, N. and H. Satoh, 1993, Taurine effects on ion channels of cardiac muscle, in: Ionic Channels and Effect of Taurine on the Heart, eds. D. Noble and Y.E. Earm (Kluwer Academic Publishers, Boston, MA) p. 93.

Sperelakis, N., H. Satoh and G. Bkaily, 1992, Taurine effects on ionic currents in myocardial cells, Adv. Exp. Med. Biol. 315, 129.

Steele, D.S., G.L. Smith and D.J. Miller, 1990, The effects of taurine on Ca^{2+} uptake by the sarcoplasmic reticulum and Ca^{2+} sensitivity of chemically skinned rat heart, J. Physiol. 422, 499.

Suleiman, M.S. and R.A. Chapman, 1993, Calcium paradox in newborn and adult guinea-pig hearts: changes in intracellular taurine and the effects of extracellular magnesium, Exp. Physiol. 78, 503.

Suleiman, M.S., G.C. Rodrigo and R.A. Chapman, 1992, Interdependence of intracellular taurine and sodium in guinea pig heart, Cardiovasc. Res. 26, 897.

Waldenström, A., G. Wiksstrom, G. Ronquist and A. Holmgren, 1995, Taurine a new low molecular weight marker for myocardial injury, Circulation (Suppl. 92), I-458.

Yamauchi-Takihara, K., J. Azuma, S. Kishimoto, S. Onishi and N. Sperelakis, 1988, Taurine prevention of calcium paradox-related damage in cardiac muscle: its regulatory action on intracellular cation contents, Biochem. Pharmacol. 37, 2651.