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$[Ca^{2+}]_i$-dependent actions of taurine in spontaneously beating rabbit sino-atrial nodal cells

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Abstract

Modulation by taurine of the pacemaking activity and the underlying ionic currents in rabbit sino-atrial nodal cells was investigated at low and high cellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) using a patch-clamp technique. At both pCa 8 and 6, taurine depressed the spontaneous activity, more strongly at pCa 6 than at pCa 8. Taurine, 20 mM, markedly inhibited the L-type Ca^{2+} current: by 56.9 ± 2.8% ($n = 6$, $P < 0.001$) at pCa 8, and by 97.6 ± 3.8% ($n = 7$, $P < 0.001$) at pCa 6. Also at 20 mM, taurine decreased the delayed rectifier K^+ current by 26.8 ± 2.6% ($n = 6$, $P < 0.01$) at pCa 6, whereas taurine had less or no effect at pCa 8. The hyperpolarization-activated inward current also decreased at both pCa 8 and 6, by 18.3 ± 1.3% ($n = 8$, $P < 0.05$) and by 20.8 ± 3.3% ($n = 8$, $P < 0.05$) in 20 mM taurine, respectively. Taurine caused a more potent inhibitory effect at pCa 6. Taurine often elicited dysrhythmias, at 20 mM, in 3 of 17 cells at pCa 8 and in 12 of 16 cells at pCa 6. During washout, the incidence of dysrhythmias or arrest increased further. These results indicate that taurine exerts more potent inhibitory actions on ionic currents under Ca^{2+} overload conditions in rabbit sino-atrial nodal cells. However, taurine would possibly elicit a cellular Ca^{2+} overload, when taurine application was discontinued.

Keywords: Taurine; Automaticity; Spontaneous action potential; Ionic current; Ca^{2+} overload; Sino-atrial nodal cell

1. Introduction

Recently, many cardiac actions of taurine have been reported. Taurine is considered to play an important role in the maintenance of physiological functions such as osmoregulation, antioxidation, radioprotection and Ca^{2+} modulation (Huxtable, 1992; Lombardini, 1980; Kramer et al., 1981). Our more recent studies have also shown beneficial effects of taurine on cardiac functions (Satoh and Sperelakis, 1992, 1993, 1998). Taurine modulates the ionic channels to maintain the cellular Ca^{2+} concentration ($[Ca^{2+}]_i$); taurine inhibits the L-type Ca^{2+} current (I_{Ca}) when $[Ca^{2+}]_i$ is high, and taurine enhances I_{Ca} when $[Ca^{2+}]_i$ is low (Satoh and Sperelakis, 1993; Satoh and Horie, 1997). Taurine similarly modulates the delayed rectifier K^+ current (I_K) (Satoh, 1995a,c). Most recent voltage-clamp experiments have shown a different sensitivity of taurine with the rapidly activated and the slowly activated currents (I_{Kr} and I_{Ks}). Taurine modulates the I_{Kr}, but not I_{Ks} (Satoh, 1999).

We have already reported the modulation by taurine of the automaticity of embryonic chick cardiomyocytes and rabbit sino-atrial node multicellular preparations (Satoh, 1995a,b). However, the effects of taurine on the ionic channels and the spontaneous activity of single sino-atrial nodal pacemaker cells are still unknown. In the pacemaker cells of the sino-atrial node, spontaneous beating is regulated by the contribution of many ionic currents (Noble, 1984; Shinagawa et al., 2000). The aim of the present experiments was to examine the modulation of the chronotropic effect of taurine at low and high $[Ca^{2+}]_i$ levels in spontaneously beating rabbit sino-atrial nodal cells. Also, the alterations of the spontaneous action potentials and the underlying ionic currents, especially a hyperpolarization-activated inward current (I_f) which is found in pacemaking cells such as sino-atrial nodal cells, were examined using a patch-clamp technique.

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2. Methods

All experiments were carried out according to the guidelines laid down by the Nara Medical University animal welfare committee, and also under the terms of the Declaration of Helsinki.

2.1. Cell preparation

Rabbits, weighing 1.5–2.0 kg, were anaesthetized with sodium pentobarbital (30 mg/kg, i.v.). The chest was opened and the aorta was cannulated in situ. The heart was dissected out and perfused with normal Tyrode solution on the Langendorff apparatus. After washout of blood, the heart was perfused with Ca^{2+}-free Tyrode solution, and spontaneous beating ceased. Then, the perfusate was switched to Ca^{2+}-free Tyrode solution containing 0.4 mg/ml trypsin for 5–10 min and then 0.8 mg/ml collagenase (Wako, Osaka, Japan) for 15–20 min. The heart was washed out with high-K^+ and low-Cl^- solution (KB solution), and the sino-atrial nodal tissue was dissected out with scissors. The temperature of all solutions was maintained at 36 °C.

2.2. Whole-cell voltage- and current-clamp experiments

Whole-cell voltage-clamp recordings were performed using an Axopatch patch-clamp amplifier (Axon Instruments, Burlingame, CA, USA) and standard techniques. Patch pipettes were fabricated from borosilicate glass capillaries using a two-stage puller, and had a resistance of 5–7 MΩ. The series resistance error was less than 10 mV, and no compensation was used. The liquid junction potential between the pipette solution and the external solution (less than 10 mV) was corrected for all membrane potential recording. Experiments were carried out at a temperature of 36 °C. The data were stored and analyzed on an IBM-AT microcomputer, using the PCLAMP analysis program (Axon Instruments). Current amplitude for I_{Ca} was measured at a peak current, and for I_K and I_f, were measured at a late current. Current traces were filtered using a cut-off frequency of 2 kHz for plotting. All values are given as means ± S.E.M. The differences between mean values were evaluated by analysis of variance (ANOVA) and Student's *t*-test for paired data, and a *P* value of less than 0.05 was considered significant.

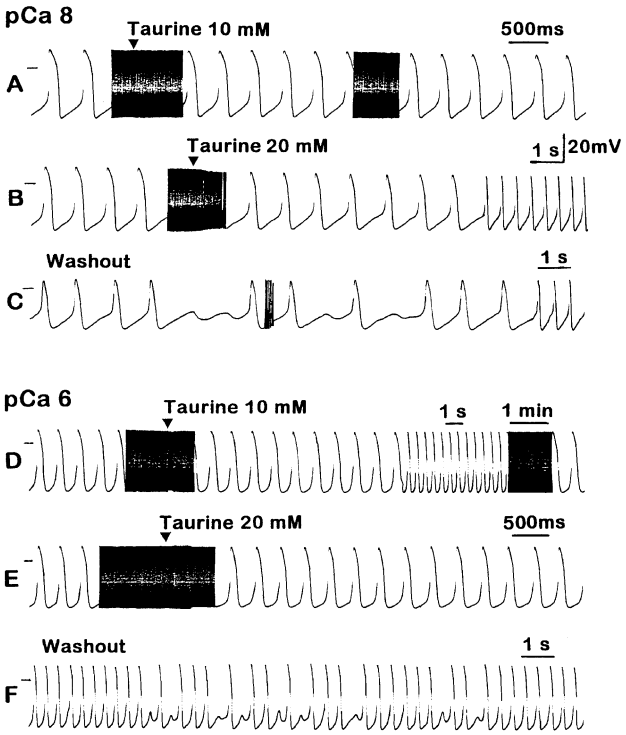

Fig. 1. Effects of taurine on a spontaneously beating rabbit sino-atrial nodal cell. A–B: Spontaneous action potentials at pCa 8 in the presence of 10 and 20 mM taurine. D–E: Applications of taurine (10 and 20 mM) at pCa 6. C and F: Abnormal action potentials during washout at pCa 8 and 6. Short line before the action potential recordings indicates 0 mV level.

Table 1
Effects of taurine on the spontaneous action potentials in rat sino-atrial nodal cells

	n	APA (mV)	APD_{50} (ms)	MDP (mV)	CL (ms)
pCa 8					
Control	8	72.4 ± 6.2	95.2 ± 9.2	−58.2 ± 4.5	310.4 ± 11
Taurine, 10 mM	8	−7.0 ± 2.1	−6.1 ± 2.2	−5.1 ± 2.5	+6.4 ± 3.0
Taurine, 20 mM	8	−19.1 ± 2.3[a]	−10.5 ± 2.7[b]	−12.6 ± 3.4[b]	+12.7 ± 3.5[b]
pCa 6					
Control	10	70.0 ± 1.8	81.3 ± 2.2[c]	−58.3 ± 1.7	321.3 ± 7.5
Taurine, 10 mM	10	−3.0 ± 1.8	+1.3 ± 2.4	−6.1 ± 2.1	+9.4 ± 2.8[b]
Taurine, 20 mM	10	−8.1 ± 2.6	+7.5 ± 3.2	−7.8 ± 3.3	+31.7 ± 4.1[d]

Values (%) are represented as control ± S.E.M.
[a] $P < 0.01$, with respect to control value.
[b] $P < 0.05$, with respect to control value.
[c] $P < 0.05$, with comparison between the values at pCa 8 and 6.
[d] $P < 0.001$, with respect to control value.

2.3. Experimental solutions

The composition of the modified Tyrode solution was (in mM): NaCl 137, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1.0, NaH_2PO_4 0.3, glucose 5.0, and HEPES [*N*-(2-hydroxyethyl)piperazine-*N*′-2-ethansulfonic acid] (Wako) 5.0. The pH was adjusted to 7.4 with NaOH. Taurine (Sigma, St.

Table 2
Incidence of occurrence of dysrhythmias and arrest in rabbit sino-atrial nodal cells

	pCa 8	pCa 6
Taurine, 10 mM	0/17	4/16
Taurine, 20 mM	3/17	12/16
Washout	14/17	16/16

Values are presented as the number of occurrences/the number of experiments.

Louis, MO, USA) was dissolved to the desired concentrations directly in the bath solution, and the solution was superfused. The pipette solution (intracellular) contained (in mM): K-aspartate 110, KCl 20, $MgCl_2$ 1, EGTA 10, Mg-ATP 5, creatine phosphate 5, and HEPES 5 (pH 7.2). In the experiments for the I_{Ca}, 2 mM tetraethylammonium (TEA) was added to the external Tyrode solution to avoid the interference of other currents. The pipette solution for the I_{Ca} current contained (in mM): CsOH-aspartate 110, CsCl 20, EGTA 10, Mg-ATP 5, creatine phosphate 5, cAMP 0.05, and HEPES 5 (pH 7.2).

The concentrations of free Ca^{2+} (pCa 8 and 6) in the internal solution were calculated on the basis of apparent stability constants for EGTA, Ca^{2+}-ATP, Ca^{2+}-creatine phosphate, Mg^{2+}-EGTA, Mg^{2+}-ATP, and Mg^{2+}-creatine phosphate, according to the calculation of Fabiato and Fabiato (1979) and the correction of Tsien and Rink (1980).

3. Results

3.1. Effects on the pacemaking activity at different pCa levels

In the absence of taurine, spontaneous beating was relatively higher at pCa 6 (but not significantly so). In comparison with the action potential parameters from pCa 8 to pCa 6, the action potential duration at 50% repolarization (APD_{50}) decreased by $14.6 \pm 1.8\%$ ($n = 8–10$, $P < 0.05$). The cycle length (CL) increased but not by a significant amount (approximately 3.5%). No changes in the effects on the other parameters occurred. The effects on the various parameters are summarized in Table 1.

At both pCa 8 and 6, taurine application depressed the spontaneous activity, and the depression was stronger at pCa 6. At pCa 8, taurine, 10 mM, did not cause any significant effects, but at 20 mM it significantly decreased the sinus rate and shortened the APD_{50} (Fig. 1A and B). Simultaneously, the action potential amplitude (APA) and the maximum diastolic potential (MDP) were also decreased. On the other hand, at pCa 6 taurine (10 and 20 mM) increased only the CL (Fig. 1D and E). Lower concentrations of taurine (1–5 mM) had less or no effect on the spontaneous action potentials.

Taurine (10 and 20 mM) often elicited dysrhythmias, as shown in Fig. 1C and F. In some cells, an arrest (with small oscillations) occurred. The incidence is summarized in Table 2. The occurrence was concentration-dependent

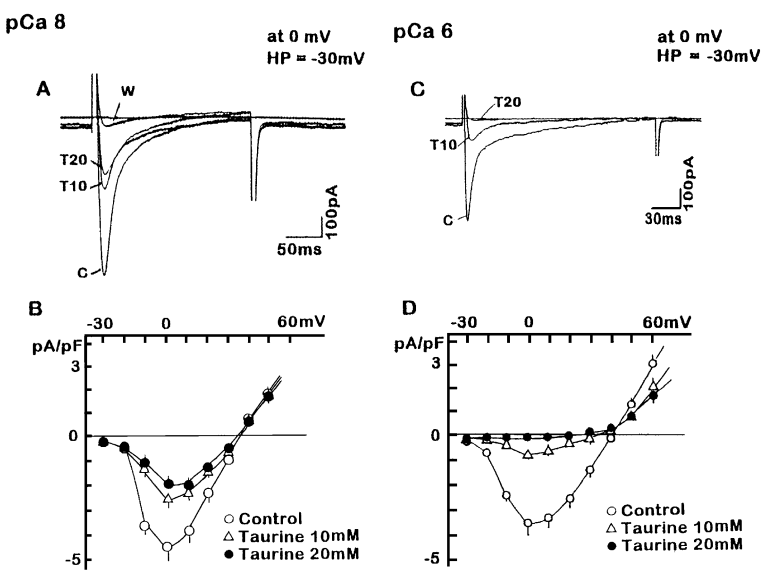

Fig. 2. Changes in L-type Ca^{2+} current at pCa 8 and 6. A: Current traces in control (C) and 10 and 20 mM taurine (T10 and T20). The current trace after 7-min washout (W). Test pulse for 300 ms was applied to 0 mV from a holding potential −30 mV. Horizontal line indicates zero current level. B: *I–V* curves in control and in 10 and 20 mM of taurine. C: Current traces in control (C) and 10 and 20 mM taurine (T10 and T20). Test pulse was applied for 200 ms to 0 mV from a holding potential −30 mV. Horizontal line indicates zero current level. D: *I–V* curves in the absence and presence of taurine. Symbols used are for control (open circles), 10 mM (triangles) and 20 mM (filled circles) of taurine. The values are represented as means ± S.E.M.

and was more frequent at pCa 6 than at pCa 8. Discontinuation of taurine elicited severer dysrhythmias. The dysrhythmias lasted for 10–15 min during washout. However, the regular rhythm as control was not restored in most sino-atrial nodal cells.

3.2. Effects on the ionic currents

Taurine markedly inhibited the L-type Ca^{2+} current (I_{Ca}) at both pCa 8 and 6 (Fig. 2). At pCa 8, the average values were $-43.3 \pm 1.9\%$ ($n = 6$, $P < 0.01$) at 10 mM and $-56.9 \pm 2.8\%$ ($n = 6$, $P < 0.001$) at 20 mM taurine. At pCa 6, taurine had a more potent inhibitory effect on I_{Ca}, by $78.5 \pm 2.4\%$ ($n = 7$, $P < 0.001$) at 10 mM and by $-97.6 \pm 3.8\%$ ($n = 7$, $P < 0.001$) at 20 mM.

Taurine at pCa 6 decreased the delayed rectifier K^+ current (I_K), whereas taurine at pCa 8 failed to affect the I_K, as shown in Figs. 3 and 4; Fig. 5 shows an I_K reduction. At pCa 6, the I_K decreased by $17.1 \pm 1.3\%$ ($n = 6$, $P < 0.05$) at 10 mM and by $26.8 \pm 2.6\%$ ($n = 6$, $P < 0.05$) in 20 mM taurine.

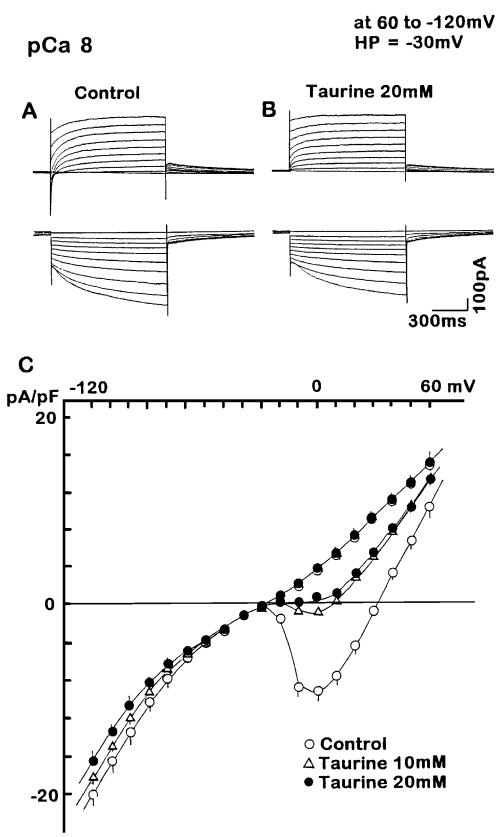

Fig. 3. Modulation by taurine of the ionic currents at pCa 8 in rabbit sino-atrial nodal cells. Holding potential was −30 mV. Test pulses were applied for 1 s from −20 to 60 mV and from −40 to −120 mV. A: Control. B: Taurine (20 mM). Horizontal line indicates zero current level. C: Current–voltage curves for the L-type Ca^{2+} current, the delayed outward K^+ current and the hyperpolarization-activated inward current. Symbols used are for control (open circles), 10 mM (triangles) and 20 mM (filled circles) of taurine. The values are represented as means ± S.E.M.

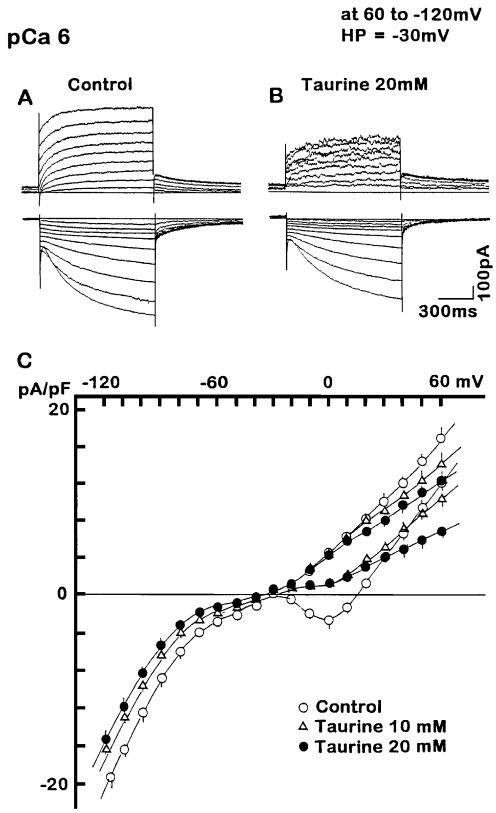

Fig. 4. Modulation by taurine of the ionic currents at pCa 6 in rabbit sino-atrial nodal cells. Holding potential was held at −30 mV. Test pulses were applied for 1 s from −20 to 60 mV and from −40 to −120 mV. A: Control. B: Taurine (20 mM). Horizontal line indicates zero current level. C: Current–voltage curves for the L-type Ca^{2+} current, the delayed outward K^+ current and hyperpolarization-activated inward current. Symbols used are for control (open circles), 10 mM (triangles) and 20 mM (filled circles) of taurine. The values are represented as means ± S.E.M.

The hyperpolarization-activated inward current (I_f) in 10 and 20 mM taurine also decreased by $9.0 \pm 1.1\%$ ($n = 8$, $P > 0.05$) and $18.3 \pm 1.3\%$ ($n = 8$, $P < 0.05$) at

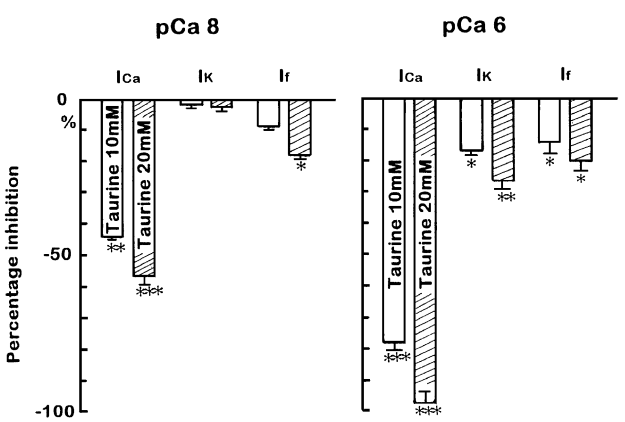

Fig. 5. Compared effects of taurine at pCa 8 and 6. Percentage inhibitions of the amplitude of peak current of I_{Ca} at 0 mV, I_K at 60 mV, and I_f at −120 mV are represented. Open column indicates 10 mM taurine, and shaded column, 20 mM taurine. The values are represented as means ± S.E.M. *: $P < 0.05$, **: $P < 0.01$, and ***: $P < 0.001$, with respect to control value.

pCa 8, respectively (Fig. 3). Taurine 10 and 20 mM decreased I_f by 14.6 ± 3.3% ($n = 8$, $P < 0.05$) and 20.8 ± 3.3% ($n = 8$, $P < 0.05$) at pCa 6, respectively (Fig. 4).

The effects of taurine on the amplitude of peak currents are summarized in Fig. 5, as a comparison between those at pCa 8 and 6. These responses to taurine did not recover even after a washout of over 20 min.

4. Discussion

The present study showed that: (1) taurine at 10 mM caused a significant negative chronotropic effect at pCa 6, and at 20 mM, at both pCa 6 and 8; (2) the I_{Ca} current decreased markedly at pCa 6 and 8; (3) taurine (10–20 mM) inhibited I_K at pCa 6, but less so at pCa 8; (4) the I_f current also decreased at both pCa levels; (5) taurine had more potent inhibitory effects on the ionic currents at pCa 6 than at pCa 8; (6) taurine often elicited dysrhythmias, and the incidence was concentration-dependent and was higher at high pCa; and (7) washout failed to restore the spontaneous action potentials and the ionic currents, and produced rather severe dysrhythmias in some cells.

Taurine is present in a small amount (10–20 mM) in cardiac muscles, and plays an important role in the maintenance of physiological functions; osmoregulation, Ca^{2+} modulation, protein interactions and metabolic actions (antioxidation, radioprotection, energy storage and anion balance) (Huxtable, 1992; Lombardini, 1980; Kramer et al., 1981). Many beneficial effects of taurine on cardiac ionic channel currents have been demonstrated (Satoh and Sperelakis, 1992, 1993, 1998). However, taurine does not stimulate the intracellular signaling cascades, cAMP, PI and cGMP mediated through receptors (Segawa et al., 1985; Lombardini, 1992). No pharmacological studies have yet demonstrated the presence of a specific taurine receptor. Thus, taurine appears to exert direct actions on the ionic channels and ionic transports (Huxtable, 1992; Satoh and Sperelakis, 1998). The responses were almost irreversible, which may show a long acting property for the drug, consistent with our previous reports (Satoh, 1999; Satoh and Sperelakis, 1993).

4.1. Chronotropic effect

The taurine-induced negative chronotropic effect would be regulated mainly by the rate of the slow diastolic potential (phase 4 depolarization) and in part by the APD prolongation of sino-atrial nodal action potentials. In our previous experiments, taurine produced a biphasic effect in rabbit sino-atrial nodal multicellular preparations; it initially enhanced the sinus rate and then decreased it (Satoh, 1995b). In spontaneously beating embryonic chick cardiomyocytes, taurine caused a positive chronotropic effect at pCa 10, and caused only a negative chronotorpic effect at pCa 6 (Satoh, 1995a). In the present experiments, however, no positive chronotropic effect occurred, not even at pCa 8. Taurine caused only a negative chronotropic effect at both pCa levels. The stronger negative effect occurred at pCa 6, as compared with pCa 8.

Regarding alterations of action potential configurations in this study, taurine shortened the APD at pCa 8, and prolonged the APD at pCa 6 but not significantly so. The results are consistent with those of previous experiments with spontaneously beating embryonic chick ventricular cardiomyocytes, in which taurine significantly shortened the APD at pCa 10 and did not affect the APD at pCa 7 (Satoh, 1995c). Taurine increased the I_K at low pCa and decreased the I_K at high pCa in embryonic chick cardiomyocytes (Satoh and Sperelakis, 1992). In guinea pig ventricular muscles and rabbit sino-atrial nodal multicellular preparations, taurine prolonged the APD at a low $[Ca^{2+}]_o$ level and shortened the APD at a high $[Ca^{2+}]_o$ level. In the present experiments, however, the APD modulation was consistent with the findings for I_K inhibition at pCa 6 but not at pCa 8. Although the discrepancy is still unexplained, it seems that the sino-atrial nodal APD is not contributed to only by I_K, and that the changes in $[Ca^{2+}]_o$ levels are not necessarily equal to the regulations of pCa levels. There might be physiological differences between single cells and multicellular tissues.

4.2. Pacemaker currents

In general, the regulation of spontaneously beating sino-atrial nodal cells is considered to be due to (1) I_{Ca} current, (2) decline of I_K conductance, and (3) I_f current (Noble, 1984; Irisawa et al., 1993). Taurine decreased all the currents (I_{Ca}, I_K and I_f) in this study. Furthermore, a T-type Ca^{2+} current has also been reported to contribute to the early part of the pacemaker current (Noble, 1984). The T-type Ca^{2+} current was stimulated by taurine (Satoh and Sperelakis, 1998). Most recently, the pacemaker mechanism in the sino-atrial nodal cells has also been reported to be involved with the rapidly activated delayed K^+ current (I_{Kr}) and the sustained inward current (I_{ST}) (Guo et al., 1995; Shinagawa et al., 2000). Taurine selectively affected the I_{Kr}, but not I_{Ks}, in guinea pig cardiomyocytes (Satoh, 1999). Taurine also inhibited potently the I_{ST}, approximately by 20–30% ($n = 4$, $P < 0.01$) at 10 mM (unpublished data). These inhibitory effects could also be related directly with the generation of the pacemaker potential.

The I_f current is "specific" in the pacemaking nodal cells. Taurine also inhibited the I_f at both pCa levels and more potently at pCa 6, but the inhibition was weaker by approximately 18–20%. It seems unlikely that this current contributes to the pacemaking activity under normal conditions, because activation needs the higher hyperpolarization (over −70 mV) and longer duration (over 1 s) of stimulation pulse. Therefore, the inhibition by taurine of the I_f current would cause a much smaller effect on spontaneous activity under the present conditions.

Thus, the pacemaker potential is not regulated by one current only. The modulation of many currents by taurine could contribute to the regulation of pacemaking activity (Satoh et al., 1989a,b). At both pCa 8 and 6 levels, taurine had inhibitory effects on the ionic currents. The inhibition was more potent at pCa 6, indicating that taurine might exhibit a kind of cardioprotective action.

4.3. Occurrence of dysrhythmias

Taurine exhibits both stimulatory and inhibitory effects, depending on the $[Ca^{2+}]_i$ level. The responses to taurine against $[Ca^{2+}]_i$-induced effects would exert cardioprotective actions. In the present experiments, however, taurine elicited dysrhythmias in a concentration-dependent fashion, in the presence of 20 mM, with an incidence of approximately 18% and 75% at pCa 8 and 6, respectively. The incidence was much higher at pCa 6. Surprisingly, their occurrence was more pronounced during washout, and the regular rhythm in almost sino-atrial nodal cells was not restored after 20- to 30-min washout. This phenomenon is similar to our previous results for taurine's actions (Satoh, 1999; Satoh and Sperelakis, 1993), and also to the results for exposure to and discontinuation of caffeine and other drugs possessing similar actions on cardiac ionic channels and Ca^{2+} stores (Satoh and Vassalle, 1985, 1989, 1996). The resultant cellular calcium overload was demonstrated with a Ca^{2+} detecting dye (fura 2) (Sperelakis et al., 1992; Satoh, 1997). Once severe disease such as calcium overload occurs, taurine and its washout would also incompletely resume control.

Thus, taurine might possess an arrhythmogenic action, although it possesses inhibitory (or protective) actions on ionic channel currents under disease conditions (Satoh and Sperelakis, 1998). The excess Ca^{2+} elevation may not only cause a negative chronotropic effect, but also elicit dysrhythmias. Under calcium overload conditions such as hypoxia, ischemia and cardiac failure, triggered activity, which is a key to causes of arrhythmias, easily occurs (Satoh et al., 1989a,b; Satoh and Vassalle, 1989). The dysrhythmias occurred with the highest incidence during washout. This is demonstrated by the appearance of a rebound (further elevation) of $[Ca^{2+}]_i$ level after the release from cellular calcium overload (Satoh and Vassalle, 1985, 1989; Satoh, 1997). This rebound would cause severe dysrhythmias and might simultaneously produce structural damage. Further experiments are needed to clarify the mechanisms.

Acknowledgements

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