Amino Acids (2000) 19: 625–634

Amino
Acids

Cardiovascular responses of the taurine-depleted rat to vasoactive agents

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Accepted January 12, 2000

Summary. The objective of this study was to assess the effect of taurine-depletion on cardiovascular responses of rat to vasoactive agents. Male Wistar-Kyoto (WKY) rats were given either tap water (control) or 3% β-alanine (taurine-depleted) for three weeks. Thereafter, mean arterial pressure (MAP) and heart rate of the freely moving animal were measured in response to vasoactive agents. Administration of phenylephine (5–40μg/kg/min; i.v.) resulted in a similar and significant increase in MAP but a reduction in heart rate in both control and taurine-depleted groups. On the other hand, administration of sodium nitroprusside (15–300μg/kg/min; i.v.) elicited a similar and significant reduction in MAP but increased heart rate in both groups. Lack of a differential response to phenylephrine and sodium nitroprusside between the two groups suggests that baroreflex regulation of cardiovascular function is not adversely affected by taurine-depletion. Administration of angiotensin II (0.1–3.0μg/kg/min; i.v.) resulted in a dose-related increase in the pressor response and a decrease in heart rate in both groups. However, angiotensin II-induced pressor response was reduced in the taurine-depleted compared to the control rats ($p < 0.05$); heart rate was similarly reduced in both groups. Acute exposure to β-alanine (3 g/kg; i.v., 30-minutes) did not alter angiotensin II-induced hemodynamic responses. Similarly, incubation of aortic rings with β-alanine (40 mM, 30 minutes) did not affect the contractile responses to angiotensin II. The results suggest that β-alanine, *per se*, does not affect angiotensin II-induced responses in rat. However, β-alanine-induced taurine depletion is associated with a reduction in the pressor response to angiotensin II without impairing baroreflex function.

Keywords: Amino acids – Taurine – Blood pressure – Phenylephrine – Sodium nitroprusside – Angiotensin II – Rat

Introduction

Taurine supplementation elicits an antihypertensive response in several animal models of hypertension. These include the spontaneously hypertensive rat, the Dahl salt-sensitive rat, the deoxycorticosterone-acetate NaCl-treated rat, and the fructose-induced hypertensive rat (Abe et al., 1987; Ideishi et al., 1994; Sato et al., 1987; Anuradha and Balakrishnan, 1999). The mechanism(s) for the blood pressure lowering effect of taurine is not established although renal mechanism as well as taurine-induced sympatholytic and vasorelaxant effects have been proposed (Ideishi et al., 1994; Sato et al., 1987; Inoue et al., 1985; Abebe and Mozaffari, this volume).

The aforementioned reports have primarily dealt with the influence of exogenous taurine administration on blood pressure and vascular reactivity. In contrast, the influence of endogenous taurine on regulation of cardiovascular function has received less attention. Singewald and colleagues (1997) have demonstrated that stimulation of the baroreceptors alters taurine release in the hypothalamus; phenylephrine infusion increases blood pressure and hypothalamic taurine release while sodium nitroprusside decreases blood pressure and the rate of hypothalamic taurine release. These observations led the authors to suggest that hypothalamic release of taurine plays an important role in counteracting fluctuations in blood pressure. As a corollary, it is plausible to suggest that taurine depletion would result in a more labile cardiovascular system thus impairing the ability of the organism to adequately cope with fluctuations in blood pressure. However, to our knowledge, the potential impact of a reduction in endogenous taurine levels on cardiovascular function has not been examined.

The present study utilized the β-alanine-induced taurine-depleted rat to further elucidate the role of endogenous taurine stores on cardiovascular function. β-Alanine inhibits cellular uptake of taurine and its inclusion in the drinking fluid reduces endogenous taurine stores (Jones et al., 1990; Harada et al., 1988; Mozaffari et al., 1997). Accordingly, we determined mean arterial pressure (MAP) and heart rate responses of the conscious freely moving animal to phenylephrine and sodium nitroprusside. Phenylephrine is an $\propto_1$-adrenergic receptor agonist and its administration elevates blood pressure that is accompanied by reflex bradycardia. On the other hand, sodium nitroprusside is a vasorelaxant causing hypotension accompanied by reflex tachycardia. This information, collectively, allows assessment of baroreflex regulation of cardiovascular function (Calhoun et al., 1991; Zhu et al., 1996). We conjectured that taurine-depleted rats would manifest impaired baroreflex function. Further, in light of several reports suggesting antagonism of some of the effects of angiotensin II by taurine (Abe et al., 1988; Ballard-Croft et al., 1997; Harada et al., 1988), we tested the hypothesis that angiotensin II-induced vasopressor response would be augmented by taurine depletion.

Materials and methods

Seven-week old male Wistar-Kyoto (WKY) rats were obtained from Harlan laboratories (Indianapolis, Indiana). All rats were maintained 2 per cage at constant humidity (60 ±

5%), temperature (24 ± 1°C), and light cycle (0600–1800 hr.). Two days after arrival, the animals were randomly assigned to two groups: the control group (n = 6) receiving only tap water and the taurine-depleted group (n = 6) receiving tap water containing 3% β-alanine for three weeks (Harada et al., 1988; Mozaffari et al., 1997). Animals had free access to food and drinking fluid throughout the study.

In preparation for measurements of hemodynamic parameters, each rat was implanted, under ether anesthesia, with femoral arterial and venous catheters (PE-10 fused with PE-50) which were tunneled under the skin with the aid of a stylet and held in position between the scapulae with dental acrylic resin (Mozaffari et al., 1997). One day after surgery, hemodynamic parameters were measured in the freely moving rat with a computerized Blood Pressure Analyzer (MicroMed, Louisville, KY). Hemodynamic responses to phenylephrine and sodium nitroprusside were assessed for determination of baroreflex function (Calhoun et al., 1991; Zhu et al., 1996). Baseline mean arterial pressure (MAP) and heart rate were stable for at least 15 minutes prior to the intravenous administration of escalating doses of phenylephrine (5, 10, 20, 30, and 40 μg/kg) to achieve a ramp increase in MAP over five minutes; MAP and heart rate were allowed to return to baseline values during a 30-minute stabilization period. Thereafter, sodium nitroprusside was infused through the venous catheter in incremental doses (15, 30, 60, 150 and 300 μg/kg/min) to produce a ramp decrease in MAP over 5 minutes. The maximum changes in MAP and heart rate responses to phenylephrine and sodium nitroprusside were recorded for each rat. The animals were allowed to rest overnight and then hemodynamic responses to angiotensin II were measured. The intravenous bolus injections of angiotensin II were made to achieve doses of 0.1, 0.25, 0.5, 1.0, 2.0 and 3.0 μg/kg (Champion et al., 1998). Both MAP and heart rate were recorded continuously during angiotensin II administration; the peak hemodynamic responses to each administered dose were reported. The results indicated a reduction in angiotensin II-mediated vasopressor response in the taurine-depleted rat.

As a first attempt in establishing that the reduction in angiotensin II-induced pressor response is related to taurine-depletion rather than β-alanine, we carried out two additional experiments. First, we determined the MAP responses in rats that were acutely treated with β-alanine with the aim of avoiding the confounding influence of taurine-depletion associated with chronic β-alanine treatment. For this study, an amount of β-alanine corresponding to daily intake of rats that consumed 3% β-alanine was given prior to administering angiotensin II. Therefore, daily fluid intake was established at 28.5 ± 0.1 ml for animals with body weight of 289 ± 4 (mean ± SEM; n = 4). Since taurine depletion was achieved by inclusion of 3% β-alanine in drinking fluid, an intake of approximately 855 mg/day of β-alanine was calculated for each rat (i.e., ~3 g/kg). After obtaining baseline MAP and heart rate, each rat was given an intravenous administration of β-alanine at a dose of 3 g/kg body weight; this dose was administered in isotonic saline over 30 minutes at a rate of 50 μl/min while measuring the hemodynamic parameters. Thereafter, the animals underwent the angiotensin II injection protocol as described earlier; MAP and heart rate responses to angiotensin II were recorded for each rat. Second, three WKY rats were sacrificed by decapitation and aortic rings were prepared as described in detail, elsewhere (Abebe and Mozaffari, this volume). Aortic rings (n = 5) were incubated with 40 mM β-alanine (Franconi et al., 1982) for 30 minutes prior to determining the angiotensin II-induced contractile responses (10^{-9}–10^{-7} M). Responses of aortic rings (n = 5) that were incubated in the bathing solution of Krebs buffer served as control.

At the conclusion of the *in vivo* experiments, the animals were sacrificed by the administration of pentobarbital (50 mg/kg; i.v.).

All drugs were dissolved in isotonic saline in appropriate concentrations such that a total of 420, 740 and 250 μl of solutions containing phenylephrine, sodium nitroprusside and angiotensin II were administered, respectively.

Statistics

The data were analyzed using one-way analysis of variance (ANOVA) for repeated measurements. This was followed by Duncan's multiple comparison test to establish differences among the mean values (significance of criteria of $p < 0.05$). Data are reported as mean ± SEM.

Results

Body weight was similar between the groups prior to β-alanine treatment (163 ± 3 and 161 ± 2 g). After three weeks of β-alanine treatment, taurine-depleted rats weighed slightly less than the control animals (245 ± 3 vs. 252 ± 2 g, respectively). Baseline MAP and heart rate were similar between the control and taurine-depleted rats (121 ± 2 mm Hg and 342 ± 10 beats/minute vs. 127 ± 3 mm Hg and 338 ± 8 beats/min, respectively).

Intravenous administration of phenylephrine resulted in a significant increase in MAP (Fig. 1A) and a significant reduction in heart rate (Fig. 1B) in both the control and taurine-depleted rats. As expected, administration of

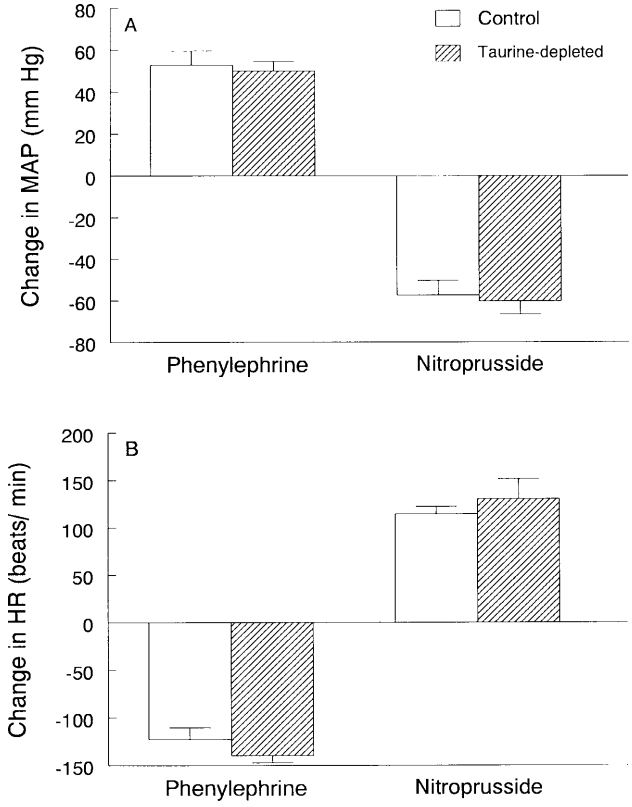

Fig. 1. Maximal changes in mean arterial pressure (*MAP*; **A**) and heart rate (*HR*; **B**) responses to phenylephrine and sodium nitroprusside in the control and taurine-depleted rats. No differences were noted between the groups in the magnitude of the response to either vasoactive agent. Data are mean ± SEM of 6 rats in each group

sodium nitroprusside caused a significant reduction in MAP (Fig. 1A) accompanied with a significant increase in heart rate (Fig. 1B) in both groups. However, no differences were noted between the control and taurine-depleted rats in the magnitude of the changes in either the MAP or heart rate responses to either phenylephrine or sodium nitroprusside administration (Fig. 1).

Intravenous administration of angiotensin II resulted in a significant increase in MAP and a significant reduction in heart rate in both groups (Figs. 2A–B). The most prominent changes in MAP and heart rate occurred at a dose of 0.25μg/kg of angiotensin II. Subsequent increases in angiotensin II dosage were associated with minimal changes in MAP or the heart rate. Interestingly, however, the pressor, but not the heart rate, response to angiotensin II (i.e., $\geq$0.25μg/kg) was significantly lower in the taurine-

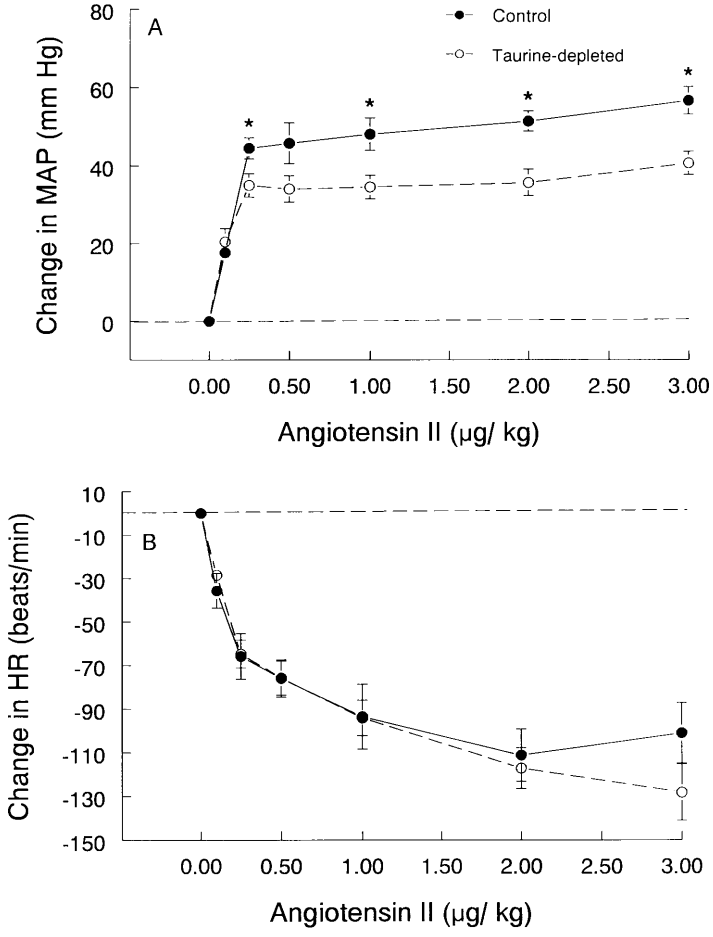

Fig. 2. Maximal changes in mean arterial pressure (*MAP*; **A**) and heart rate (*HR*; **B**) responses during administration of increasing doses of angiotensin II in the control and taurine-depleted rats. Taurine-depleted rats manifested significantly lower elevation in mean arterial pressure compared to the control rats. Data are mean ± SEM of 6 rats in each group. *$p < 0.05$ compared to the taurine-depleted rats

Table 1. *In vivo* and *in vitro* assessment of the effect of β-alanine on angiotensin II-induced changes in mean arterial pressure (MAP) of the rat and contractile responses of the aortic rings, respectively. Animals received β-alanine (3 g/kg over 30 minutes, n = 4) prior to determination of MAP responses to angiotensin II. For the *in vitro* study, aortic rings (n = 5) were incubated with 40 mM β-alanine for 30 min prior to measurements of contractile response to angiotensin II; aortic rings (n = 5) incubated in Krebs buffer were used as control

Angiotensin II dose (μg/kg)	Change in MAP (mm Hg)	Angiotensin II Concentration (M)	Contractile response (g/mg tissue wt.)	
			Control rings	β-alanine-treated rings
0.1	19.2 ± 2.8	1×10^{-9}	0.36 ± 0.08	0.30 ± 0.07
0.25	35.0 ± 3.5*	3×10^{-9}	0.58 ± 0.11	0.56 ± 0.07
0.5	41.0 ± 2.7*	1×10^{-8}	0.84 ± 0.05**	0.90 ± 0.14**
1.0	46.0 ± 2.7*	3×10^{-8}	0.82 ± 0.07**	0.96 ± 0.18**
2.0	50.8 ± 5.4*	1×10^{-7}	0.56 ± 0.02	0.72 ± 0.13**
3.0	59.8 ± 5.2*			

* $p < 0.05$ compared to the response obtained at 0.1 μg/kg dose of angiotensin II, ** $p < 0.05$ compared to the responses obtained at a concentration of 1×10^{-9} M angiotensin II in the same group.

depleted than control rats. As a result, the ratios of the changes in heart rate to MAP (i.e., index of baroreflex response) were greater in the taurine-depleted than the control rats (e.g. -3.5 ± 0.5 vs. -2.2 ± 0.2 [2 μg/kg] and -3.3 ± 0.4 vs. -1.8 ± 0.3 [3 μg/kg] beats/min/mm Hg; $p < 0.05$).

Animals that were acutely treated with β-alanine (3 g/kg body weight over 30 minutes) displayed maximal angiotensin II-induced changes in MAP that were similar to those observed for the control rats (Table 1 and Fig. 2). Consistent with the *in vivo* observations, incubation of aortic rings with 40 mM β-alanine did not affect concentration-related contractile responses induced by angiotensin II (Table 1).

Discussion

This study demonstrates that β-alanine-induced taurine depletion does not affect MAP or heart rate responses to phenylephrine or sodium nitroprusside. By contrast, angiotensin II-mediated pressor response is reduced in the taurine-depleted compared to the control rats.

An important neuronal mechanism for regulation of blood pressure is the baroreflex mechanism, the impairment of which contributes to the pathophysiology of some forms of hypertension (Victor et al., 1986; Miyajima and Bunag, 1987; Calhoun et al., 1991). The baroreflex is initiated by stimulation of the stretch receptors (e.g. baroreceptors) that are, primarily, located in the carotid sinus and the wall of the aortic arch. A rise in blood pressure stretches the baroreceptors causing transmission of signals into the central nervous system. Subsequently, feedback signals are sent through the

autonomic nervous system to the circulatory system resulting in downward adjustment of blood pressure to control levels.

It has been suggested that hypothalamic release of taurine, an inhibitory neuromodulator/neurotransmitter, is influenced by signals that originate from the peripheral baroreceptors. In this regard, Guo and Athineos (1995) reported that the pressor response to intravenous administration of levarterenol (i.e., norepinephrine) produces an increase in hypothalamic taurine release. Conversely, hypothalamic taurine release is reduced in response to a controlled hemorrhagic hypotension or intravenous administration of sodium nitroprusside. Similarly, Singwald and colleagues (1997) have shown that stimulation of the baroreceptors by phenylephrine increases blood pressure and augments hypothalamic taurine release. In contrast, baroreceptor unloading evoked by sodium nitroprusside decreases blood pressure accompanied by attenuation of hypothalamic taurine release. Therefore, we hypothesized that a reduction in endogenous taurine stores would cause a more labile cardiovascular system that would not adequately cope with acute changes in blood pressure. However, we did not observe any differences in MAP or heart rate responses to either phenylephrine or sodium nitroprusside between the control and taurine-depleted rats. Therefore, it is unlikely that the baroreflex mechanism is adversely affected in the taurine-depleted rat under these conditions. In this study, taurine-depletion was achieved by provision of 3% β-alanine in the drinking fluid. This method results in a reduction of about 40% of tissue taurine content (Harada et al., 1988; Mozaffari et al., 1997). Thus, it is possible that greater reduction in endogenous taurine stores is required to detect any alterations in baroreflex function. It is noteworthy that lack of a differential in either the MAP or the heart rate responses between the control and taurine-depleted rats also suggests lack of an effect of β-alanine, *per se*, on the baroreflex function.

In contrast to the lack of an effect of either phenylephrine or sodium nitroprusside, taurine-depleted rats manifested a significant reduction in angiotensin II-induced elevation in MAP than the control rats. Again, it is unlikely that the reduction in responsiveness to angiotensin II is due to β-alanine for the following reasons. First, MAP responses to angiotensin II were not affected by pre-treatment of the animal with β-alanine (Table 1 and Fig. 2). Second, incubation of aortic rings in 40 mM β-alanine did not affect angiotensin II-induced contractile responses (Table 1). It should be noted that β-alanine concentration in rat plasma is about 1.8 nmol/ml (e.g., 0.0018 mM), nearly 20,000 fold lower than that used in our *in vitro* studies (Korang et al., 1996). Although, we did not measure β-alanine concentration in this study, it is unlikely that plasma concentration of β-alanine in the taurine-depleted rats would be greater than those used in our *in vitro* studies. Therefore, the observations made with angiotensin II in the rats chronically treated with β-alanine were likely to be the result of taurine-depletion.

The differential response to angiotensin II between the control and taurine-depleted groups is manifested as a reduction in the maximal response without a shift in the dose-response curve thereby suggesting similar sensitivity to angiotensin II in the two groups. Thus, alterations in receptor

number or affinity for angiotensin II may not underlie the differential between the taurine-depleted and control rats, an assertion that requires receptor binding studies to confirm. Rather, the data suggest some alteration in the post-receptor signaling mechanism for angiotensin II in the taurine-depleted rat. However, it is noteworthy that a common signaling pathway is involved in mediating the pressor effects of phenylephrine and angiotensin II. Activation of the vascular $\propto_1$-adrenergic receptors (i.e., phenylephrine) and the angiotensin type 1 receptors (i.e., angiotensin II; Champion et al., 1998) results in stimulation of the phospholipase C and generation of inositol phosphates and diacylglycerol. The net effect of both agents is protein kinase C activation and an elevation in cytosolic calcium level, which result in muscle contraction (Davis and Hill, 1999). Therefore, the attenuated angiotensin II pressor response of taurine-depleted rat may relate to the lack or impairment of some taurine-dependent mechanism(s) that mediates the vascular effect of angiotensin II. Alternatively, one can also speculate that the attenuated pressor effect of angiotensin II may relate to enhancement of the vasodilatory mechanism(s). Thus, unlike the reported antagonism between angiotensin II and taurine under other conditions (Abe et al., 1988; Ballard-Croft et al., 1997; Harada et al., 1988), taurine may exert a permissive role in the pressor response of angiotensin II. However, it is perplexing to us that the taurine-supplemented rat displays enhanced acetylcholine-mediated vasorelaxation (Abebe and Mozaffari, this volume) while taurine-depleted rat manifests attenuated pressor response to angiotensin II. Thus further studies are needed to resolve these paradoxical observations.

It is noteworthy that a marked reduction in heart rate accompanied the angiotensin II-induced increase in MAP in both the control and the taurine-depleted rats. Indeed, the taurine-depleted rats manifested a similar reduction in heart rate despite significantly lower elevation in MAP at higher angiotensin II doses, thereby suggesting enhanced baroreflex-mediated bradycardia compared to the control rats. This observation is in contrast to our stated hypothesis that taurine depletion would impair baroreflex function but is in general agreement with our data obtained using phenylephrine and sodium nitroprusside. Interestingly, our observation of a marked reflex bradycardia with systemic administration of angiotensin II in rat is consistent with another report in this species (Coleman, 1980) but in contrast to impairment of reflex bradycardia in rabbit, dog, cat and sheep (see Reid, 1992; Reid and Chou, 1990). The inability of angiotensin II to impair reflex bradycardia in the rat is attributed to lack of involvement of area postrema in mediating a central action of angiotensin II in this species (Haywood et al., 1980; Guo and Abboud, 1984).

In conclusion, β-alanine-induced taurine depletion in the rat does not impair baroreflex function. However, the taurine-depleted rat displays a reduction in the pressor, but not heart rate, response to systemic administration of angiotensin II. The mechanism(s) for the impaired angiotensin II-induced pressor response in the taurine-depleted rat remain(s) to be established.

Acknowledgments

The authors thank Mrs. Champa Patel for her expert technical assistance. This study was supported by a grant from the Medical College of Georgia School of Dentistry.

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Received December 17, 1999