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Effects of Taurine on Cardiovascular Response in the Rat

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ABSTRACT

The cardiovascular effects of administration of taurine into the lateral cerebral ventricle of conscious rats were examined. Rats were divided into three groups: intact, catecholamine (CA)-depleted and serotonin (5−HT) - depleted, each group receiving 30, 100 and 300 μg of taurine. At these doses, taurine caused a dose-dependent decrease in both heart rate and mean arterial pressure, and an increased sensitivity of the baroreflex to change in heart rate. Pretreatment of intact rats with taurine did not change the adrenaline-induced pressor response, but enhanced adrenaline-induced reflex bradycardia. The ability of taurine to induce hypotension and bradycardia and to enhance adrenaline-induced reflex bradycardia were significantly attenuated by pretreatment of rats with drugs which deplete either brain CA (e.g.α-MT) or 5-HT (e.g. PCPA). Therefore, the present data indicate that taurine regulate cardiovascular functions through a central mechanism involving monoaminergic systems.

Key words: Taurine, Catecholamine, Serotonin, Cardiovascular functions.

In recent years, sufficient evidence has accumulated which suggests that taurine (2-aminoethanesulphonic acid) is one of the major inhibitory neurotransmitters in the central nervous system[1,2]. Present data has indicated that taurine is involved both directly and indirectly, in the pathogenesis of several behavioral disorders[1,2,3]. Animal studies have demonstrated that intraperitoneal or intracerebroventricular (i.c.v.) administration of taurine into rats, caused hypothermia[4,5]. Intraperitoneal administration of taurine was additionally shown to depress the conditioned response to food and water in genetically obese mice and water-deprived mice, respectively[6] However, investigations of the influence of taurine on cardiovascular function in conscious rats have been relatively few. Therefore, in the present study, the effects of taurine on heart rate, arterial pressure and adrenaline-induced reflex bradycardia were studied in intact conscious rats. In addition, to ascertain whether the regulation of cardiovascular function by taurine may be mediated by central monoaminergic systems, we also performed our study on rats which were deplected of either brain catecholamine (CA) or

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serotonin (5-HT).

MATERIALS AND METHODS

Adult male Wistar rats, weighing about 250 g were used in all experiments. One week before used in experiments, rats were put under general anesthesia (sodium pentobarbital 60 mg/kg i.p.) and implanted with cannulae. Implantation of cerebroventricular cannulae was carried out according to the De Groot[7] coordinates: AP 7.0; Lat. 1.0; and Hor. 0.1 mm. The cannulae were constructed by connecting a 50 μl Hamilton syringe via PE 10 tubing. During surgery, the correct positioning of each guide tube was verified by the rapid flow of saline into the lateral cerebral ventricle under gravity[8]. To monitor blood pressure and to administer adrenaline intravenously, rats were reanesthetized with ether twenty four hours before experiments and implanted with polyethylene catheters (PE-50 tubing) into the left femoral vein and artery. The catheters were passed subcutaneously and exteriorized posterior to the ear at the midline. Patency of the catheter was maintained with heparin[9]. Before experiments the animals were kept individually in wire-mesh cages at room temperature (25 ± 1.0°C) under natural light-dark cycles. The animals were given free access to tap water and granular chicken feed.

EXPERIMENTAL DESIGN

The individual effects of central administration of taurine on cardiovascular function were studied in three groups of animals: (1) intact control rats, (2) CA-depleted rats (tested 4 hr after intraventricular administration of 120 μg α-methyl-p-tyrosine methyl ester), (3) 5-HT-depleted rats (tested 72 hr after intraperitoneal administration of 250 mg/kg p-chlorophenylalanine ethylester). The vasopressor and bradycardiac responses of these groups of animals to i.v. doses of adrenaline were assessed[10].

DRUG SOLUTIONS

Drugs (taurine, adrenaline, α-MT and PCPA) used in this research were obtained from Sigma Chemical Co. (St. Louis, MO). Drug solutions were prepared in pyrogen-free glass-ware which was baked at 180°C for 5 hr before use. All solutions were freshly prepared in 0.9% saline on the day of testing.

MEASUREMENTS OF CARDIOVASCULAR FUNCTION

On the day of experiment, animals were placed holders and implanted arterial lines were attached to blood pressure transducers (Gould, type P23XL) for continuous recording of blood pressure. Heart rate was monitored with a Gould Biotach amplifier. The rats were then left undisturbed until steadystate conditions were returned. All recordings were performed with a four-channel Gould 2400S polygraph. Taurine and α-MT were administered to rats through the intracerebroventricular cannulae. p-Chlorophenylalanine was administered to rats by intraperitoneal injection. Adrenaline was used as a vasopressor substance and was administered by way of the femoral vein. Appropriate vehicle-injected controls were always run simultaneously with drug-treated animals.

Table 1. Effects of intracerebroventricular administration of taurine on cardiovascular responses in intact conscious rats

Treatment	Control values	Minimum values	Difference	Time to maximum fall(min)	Time of recovery (min)
Mean arterial pressure (mmHg)					
0.9% saline	115±17	112±16	- 3±0.5	0.2±0.1	0.5±0.3
Taurine 30 ug	108±12	96±20	-12±1.9 *	2.5±0.4 *	4.2±0.9 *
Taurine 100 ug	113±14	90±21	-23±3.5 *	4.4±0.7 *	6.8±1.5 *
Taurine 300 ug	106±14	70±19	-36±5.1 *	6.9±1.0 *	11.5±1.8 *
Heart rate, beats/min					
0.9% saline	405±51	400±49	5±1.2	0.5±0.3	0.7±0.4
Taurine 30 ug	409±53	394±68	-15±2.4 *	3.1±0.5 *	5.0±1.1 *
Taurine 100ug	410±59	382±50	-28±4.1 *	4.7±0.9 *	8.3±1.9 *
Taurine 300ug	411±65	372±52	-39±8.9 *	9.0±1.4 *	13.7±2.5 *

* Significantly different from control value (0.9% saline), p value less than 0.05 (Student's t-test). The values are expressed as the mean± S.E. of 6 animals.

Table 2. Effects of intracerebroventricular administration of taurine on cardiovascular responses induced by intravenous injection of adrenaline in intact conscious rats

Treatment	Mean arterial pressure, mmHg			Heart rate, beasts/min		
	Control	After adrenaline	Difference	Control	After adrenaline	Difference
Adrenaline 1.25 μg/kg i.v.						
0.9% saline	112±24	163±29	51± 7	409±66	347±63	- 62±16
Taurine 30 ug	117±15	166±24	49±10	402±75	327±82	- 75±13
Tauine 100 ug	115±23	165±32	50± 7	403±67	317±70	- 86±23
Taurine 300 ug	117±20	166±28	49±11	398±81	289±57	-109±29 *
Adrenaline 2.5 μg/kg i.v.						
0.9% saline	106±19	174±30	68±15	411±70	337±64	- 74±15
Taurine 30 ug	113±25	178±33	65±10	409±76	329±79	- 80±18
Taurine 100 ug	107±13	176±39	69±14	417±59	321±52	- 96±25
Taurine 300 ug	113±26	184±36	71±18	418±85	306±65	-112±20 *

* Significantly different from control values (0.9% saline group), at $p < 0.05$ (Student's t-test). The values are expressed as the mean ± S.E. of 6 animals.

RESULTS

Effects of taurine on heart rate, arterial blood pressure and adrenaline-induced reflex bradycardia in intact conscious rats

As shown in Table I, after direct administration of doses of taurine ranging from 30-300 μg, into the lateral cerebral ventricle of intact conscious rats, a dose-related fall in both heart rate and arterial pressure occurred. For example, after an intracerebroventricular injection of 100 μg of taurine both heart rate and mean arterial pressure fell almost immediately, and reach their minimum levels (i.e., 28 beats/min and 23 mmHg, respectively) within 5 min. The cardiovascular responses recovered within 9 min after injection with taurine. In control animals, administration of saline vehicle caused a rapid, transient drop in mean arterial pressure which recovered at 0.7 min. This drop in arterial pressure however was not significant. Administration of varying doses of taurine to animals which had received intravenous injection of either 1.25 or 2.5 μg adrenaline/kg body weight, resulted in a dose-dependent enhancement of

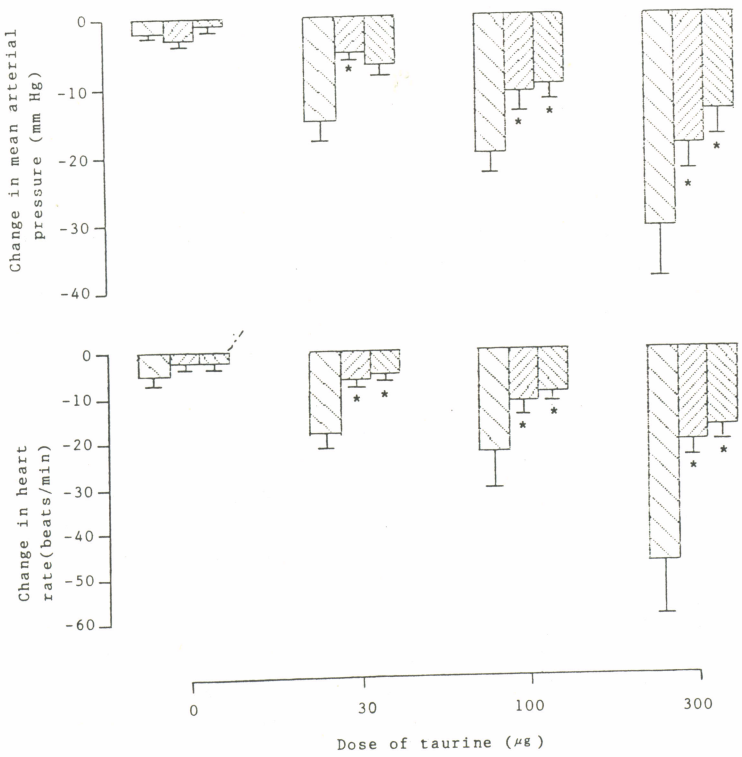

Fig. 1. Effects of intracerebroventricular administration of taurine on cardiovascular responses in catecholamine or serotonin depleted conscious rats. Each column indicated mean ±S.E. of 6 rats. * Significantly different from vehicle-treated group, at $P<0.05$.

: vehicle-treated : α-MT-treated

: PCPA-treated

reflex bradycardia. For example, as shown in Table 2, rats which were given adrenaline (2.5 μg/kg) subsequent to receiving 0.9% saline exhibited an average increase of mean arterial pressure of 68 mmHg and an average decrease of heart rate of 74 beats/min. However, rats which were given adrenaline 10 mins after a prior injection with taurine exhibited greater bradycardia compared to control rats. Pretreatment of animals with taurine however, did not influence the effects of adrenaline on arterial blood pressure.

Effects of taurine on cardiovascular function and adrenaline-induced reflex bradycardia in CA or 5-HT-depleted conscious rats

Four hours after i.c.v. administration of α-MT 120μg (a CA synthesis inhibitor), or seventy-two hours after i.p. administration of PCPA 250 mg/kg (a 5-HT synthesis inhibitor), animals were subjected to i.c.v. administration of taurine at doses of 30, 100 and 300 μg. As shown in the Fig. 1, the dose-related hypotensive and bradycardiac effects of taurine were significantly attenuated after CA-depletion with

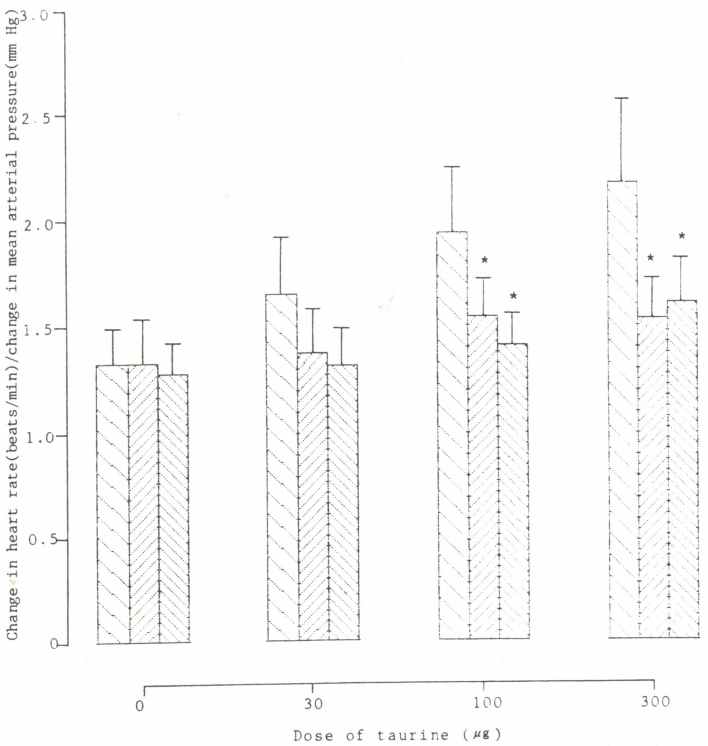

Fig. 2. Effects of intracerebroventricular administration of taurine on cardiovascular responses induced by intravenous injection of adrenaline (1.5 μg /kg) in catecholamine or serotonin depleted conscious rats. * Significantly different from vehicle-treated group, at $P < 0.05$. Each column indicates mean ± S.E. 6 rats.

: vehicle-treated : α-MT-treated

: PCPA-treated

α-MT or 5-HT-depletion with PCPA. Similarly, in the Fig. 2, shown taurine potentiation of adrenaline-induced reflex bradycardia was diminished in rats pretreated with α-MT or PCPA.

DISCUSSION

Both previous research using anesthetized rats[11] and the present study using conscious rats demonstrated that direct administration of taurine into the cerebral ventricule caused acute decreases in basal heart rate and arterial pressure. Furthermore, adrenaline-induced reflex bradycardia was greatly enhanced by pretreatment of animals with taurine. The results presented here indicate that the effects of taurine on cardiovascular function were greatly reduced after pretreatment of animals with α-MT or PCPA. α-MT is a potent inhibitor of tyrosine hydroxylase[12]. This enzyme has been implicated in the rate-limiting step in the biosynthesis of catecholamines. Thus, after treatment of rats with α-MT brain content of noradrenaline and dopamine are reduced[13]. Similarly, brain content of serotonin was reduced in rats treated with PCPA[14]. The arterial baroreflex system is regarded as one of the most powerful and rapidly acting homeostatic mechanism for regulating blood pressure. It is generally accepted that the central baroreceptor arc is polysynaptic, with the primary synapse in the nucleus of the tractus solitarius (NTS) and inhibiting neurons interposed between the NTS and the cardiovascular center[15,16]. Recently, evidence has a accumulated which indicates that, in the rat, the central baroreceptor arc contains monoaminergic synapses. For example, activation of serotonergic receptors within the brain was found to depress adrenaline induced bradycardia, whereas inhibition of these central serotonergic receptors facilitated adrenaline-induced bradycardia[17,18]. Blockade of brain dopaminergic receptors with dopamine receptor antagonists, or destruction of dopaminergic neurons caused a significant reduction in reflex bradycardia[19,20]. In contrast, activation of brain dopaminergic receptors by dopamine receptor agonists or by electrical stimulation of dopamine neurons led to an enhancement of the adrenaline-induced bradycardia in rats. In the rabbit both noradrenergic and serotonergic neurons within the brain have been shown to participate in central baroreceptor-heart rate reflex pathways[21,22]. Knowledge also indicates that taurine[3,5] act directly or indirectly on central monoaminergic neurons to influence brain neurotransmitter content and activity. So far as we know, the key to regulation of cardiovascular function lies in the reciprocal relationship between vagal tone and sympathetic efferent activity. According to the present results, it seems that, taurine act through a central mechanism to facilitate vagal efferent activity and/or inhibit preganglionic sympathetic efferent activity, which leads to hypotension, bradycardia and enhancement of adrenaline-induced bradycardia in rats. However, the effects of taruine on normal cardiovascular function and adrenaline-induced reflex bradycardia were significantly reduced after pretreatment of rats with α-MT (to deplete noradrenaline and dopamine) or PCPA (to deplete serotonin). Thus, we suggest that taurine is involved in the central regulation of cardiovascular function. Moreover, the effects of taurine on cardiovascular function appear to be mediated by central serotonergic and catecholaminergic systems. Further experiments are

need to assess the sites of action of taurine and the mechanism by which they modify cardiovascular function.

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牛磺酸對大白鼠心血管之作用

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摘　要

本實驗係探討由側腦室投予不同劑量之牛磺酸，對清醒大白鼠心血管之影響。實驗中大白鼠分爲三組：㈠對照組，㈡以 α-MT 抑制腦中兒茶酚胺含量之實驗組，㈢以 PCPA 抑制腦中血清張力素含量之實驗組。大白鼠由側腦室投予牛磺酸，劑量分別爲 30, 100 或 300 μg，結果顯示牛磺酸可導致大白鼠心跳減慢，平均血壓下降，且加強由腎上腺素所造成的反射性徐脈現象，此作用隨牛磺酸使用之劑量增加而增加。大白鼠投予牛磺酸後再投予腎上腺素，並不會改變由腎上腺素所引發的壓力反應，但牛磺酸的預先投予會加強腎上腺素所造成的反射性徐脈。若投予 α-MT 來耗竭大白鼠腦中兒茶酚胺之含量，或投予 PCPA 來耗竭大白鼠腦中血清張大素之含量，即可顯著地抑制牛磺酸所引起的心跳減慢，血壓下降，及反射性徐脈加強等作用。由實驗結果得知，牛磺酸調節心血管之功能與中樞性單胺系統有關。

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