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Influence of Intraventricular Taurine on the Cardiovascular System of the Rabbit

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ABSTRACT

The purpose of the present study is an attempt to investigate the effect of intraventricular taurine, which is a naturally occuring amino acid containing sulfur and has inhibitory action in brain, on heart rate and blood pressure in the urethane anesthetized rabbits and also to elucidate the mechanism of its cardiovascular actions.

Taurine (0.15~1.5 mg) injected into the lateral ventricle of anesthetized normontensive rabbits produced a dose-related fall in arterial blood pressure and heart rate, which were marked and long-lasting along with considerable respiratory depression. However, the intravenous administration of taurine at the same dose with intraventricular injection did not induce any changes in blood pressure as well as heart rate.

Depressor responses induced by taurine were inhibited significantly by pretreatment with chlorisondamine, clonidine, strychnine and bicuculline but not by atropine, vagotomy, propranolol and metoclopramide. Moreover, taurine did not affect the pressor responses of norepinephrine.

Taurine-induced bradycardic effects were blocked clearly by pretreatment with chlorisondamine, propranolol, clonidine, strychnine and bicuculline, while they were not influenced by atropine, vagotomy and metoclopramide.

These experimental results suggest that intraventricular taurine causes long-lasting hypotensive and bradycardic actions, and that these cardiovascular effects may be exerted through taurinergic (glycinergic) and GABAergic receptors which are associated with catecholaminergic neurons in brain.

Key Words: Intraventricular taurine, Hypotension, Bardycardia, Taurinergic and GABAergic Receptors

INTRODUCTION

Taurine, a sulfur-containing amino acid with a molecular weight of 125 and a molecular formula of $H_2N\text{-}CH_2\text{-}SO_3H$, occurs in high concentrations in a variety of mammalian and nonmammalian tissue and is pressent in large amounts particularly in brain, heart and muscle (Jacobsen and Smith, 1968; Guidotti *et al.*, 1972; Barbeau *et al.*, 1975; Kuriyama *et al.*, 1978; Huxtable, 1980; Kuriyama, 1980; Ida and Kuriyama, 1983). It has been also implicated as being important for arterial blood pressure control (Nara *et al.*, 1978; Kuriyama *et al.*, 1980), the neurological disorder called Friedreich's ataxia (Barbeau *et al.*, 1982), retinal functions (Urban *et al.*, 1976; Schmidt *et al.*, 1976; Knopf *et al.*, 1978), seizure activity (Marches; *et al.*, 1978; Van Gelder, 1978) and cardiovascular and respiratory control (Petty and Francesco, 1989; Bousquet *et al.*, 1984; Wessberg, *et al.*, 1983; Bousquet *et al.*, 1981; Gatti *et al.*, 1985).

Gatti and his coworkers (1985) have reported that taurine acts at the chemosensitive areas on the ventral surface of the medulla to produce

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cardiorespiratory depression, and these effects are due to an interaction of taurine with receptors similar to, but probably not identical with, glycine receptors. Kohasi and Katori (1983) have postulated that taurine is involved in cardiovascular control processes, since long term oral administration of taurine produces a significant hypotensive effect in patients with essential hypertension, and also a fall in blood pressure slightly in spontaneonsly hypertensive rats (SHR), moderately in stroke-prone SHR (Nara *et al.*, 1978; Horie *et al.*, 1987) and strikingly in rats with deoxycorticosterone acetate-salt hypertension (Fujita and Sato, 1984).

Yang and Lin (1983) as well as Bousquet and his colleagues (1981) have shown that intracerebroventricular administration of taurine to anesthetized rats and cats induces dose-related reduction in mean arterial pressure and heart rates.

It has been known that these cardiovascular effects are due to a reduction in peripheral sympathetic activity (Inoue *et al.*, 1985), an increase in vagal tone (Paakkari *et al.*, 1983) and a stimulation of glycine-type receptors (Bousquet *et al.*, 1981).

Recently, it is known that taurine has the antiatherosclerotic effect unrelated to a fall in blood pressure (Petty *et al.*, 1990). The depressor effects of taurine can be partially antagonized by strychnine (Gatti *et al.*, 1985; Bousquet *et al.*, 1981), an antagonist at glycine receptor and by 6-(aminoethyl)-3-methyl-4H-1.2.4-benzothiadiazine-1.1-dioxide hydrochloride (TAG), which is a specific antagonist of taurine (Bousquet *et al.*, 1984; Wessberg *et al.*, 1983).

Leach (1979) has suggested that the cardiovascular effects of far lower doses of taurine may be attributed to release of GABA. Moreover, in certain electrophysiological models, taurine is known to act as a GABA agonist (Curtis *et al.*, 1971; Okamoto and Quastel, 1976; Okamoto *et al.*, 1976; Frederickson *et al.*, 1978).

Recently, renin injected into the cerebroventricle elicited an increase in blood pressure and heart rate and the increase in blood pressure was prevented by pretreatment with [sar, Ile]-angiotensin II and also was strongly inhibited by GABA and taurine injected into the cerebroventricle.

The antagonism between angiotensin or renin, and GABA did not occur when these agents were administered peripherally. These results may suggest that activation of intrinsic renin-angiotensin system in the brain by the injection of renin involves GABAergic or taurinergic receptors in brain (Abe *et al.*, 1988). As aforementioned, there are many reports about cardiovascular effects of taurine. However, whether or not taurine function as a transmitter in the brain, especially for cardiovascular control is a matter of controversy even up to date. Therefore, the present investigation is an attempt to examine the effect of intraventricular taurine on blood pressure and heart rate in rabbits anesthetized with urethane and further to elucidate the mechanism of its cardiovascular actions.

MATERIALS AND METHODS

Experimental animals

Mature adult rabbits of both sexes, weighing 1.8 ~2.5 kg, were used in the present experiment. The animals were housed individually in separate cages, and food (Cheil Animal Chow) and tap water were allowed ad libitum for at least a week to adapt to experimental circumstances. On the day of experiment, a rabbit was anesthetized with urethane (g/kg) subcutaneously. The animal was tied in supine position on fixing panel to insert a T-formed cannula into the tachea for securing free air passage. The rectal temperature was maintained at 37~38°C by a thermostatically controlling blanket and heating lamp throughout the course of the experiment.

Measurement of blood pressure

In order to observe the change of arterial pressure, either one of the common carotid arteries or the femoral arteries was catheterized with polyethylene tubing [outside diameter (o.d): 1.45 mm]. The tubing was connected to a pressure transducer (Gould Co.) and pulse of mean arterial blood pressure was recorded on a physiography (Beckman Co.) continuously. The chart speed was adjusted to 0.5 cm per minute. The artery tubing was filled with heparin solution (400 I.U.) to prevent the blood coagulation during the experiment. Another cannulation with polyethylene tubing (o.d.: 0.45 mm) was made into a femoral vein for the administration of drugs and supplemental anesthetic agents as needed to maintain light surgical anesthe-

sia. Each rabbit was left undisturbed for at least 30 minutes after completion of the operative procedures to permit cardiovascular paramenters to be stabilized and drugs under investigation were administered at intervals of 60 minutes.

Heart rate was measured continuously by digitalized heart rate counter connected to physiograph with beats per minute, triggered by arterial pulses.

Administration of drugs

For the intracerebroventricular (i.v.t.) administration the cerebrum was cannulated. After fastening the animal in prone position, a hole was drilled on the skull at a point 1.5 cm rostal to the occiput tubercle and 0.5 cm lateral to the midline, and a cannula made of polyethylene tubing (2 cm long of 1.0 mm, o.d.) was introduced obliquely until the clear cerebrospinal fluid appeared in the cannula, and then it was kept in place by cementing with instant strong bond to the bone. The volume administered during experiment did not exceed 0.2 ml. At the end of each experiment. 0.1 ml of methylene blue was injected intraventriculary and the location of cannula tip was checked by dissection. Intravenas administration was given into a femoral or an ear vein.

Drugs

The sources of the drugs used in the present investigation are as follows: taurine, metoclopramide hydrochloride, bicuculline methiodide, norepinephrine bitartrate (Sigma Chemical Co., U.S.A.), strychnine nitrate (Merk Co., West Germony), atropine sultate (Aldrich Chemical Co., U.S.A), propranolol hydrochloride (I.C.I., Co., U.K.), clonidine hydrochloride (Beheringer Ingelheim Co., R.O.K.) and chlorisondamine chloride (CIBA Co., U.S.A.). All drugs were prepared in 0.9% sodium chloride solution on the day of experiment and stored in a refrigerator, except norepinephrine which was dissolved in 0.9% acid saline (pH=4.0). Doses were expressed as the base.

Statistical analysis

The statistical significance between groups was determined by utilizing the Student's t-test. Data obtained from animals which served as their control were analyzed for the significance using t-test for paired observation. A P-value of less than 0.05 was considered to represent statistically significant changes unless otherwise noted in the text. Values given in the text refer to means with standard errors of the mean (S.E.M.). The statistical analysis of the present experimental results was made by computer statistic program of described previously by Tallarida and Murray (1987).

RESULTS

Cardiovascular effects of intraventricular taurine in the urethane-anesthetized rabbits

All of rabbits used in this study were allowed to be stabilized least for 60 min before experimental protocols were initiated. When cardiovascular parameters were stabilized, taurine (0.15~1.50 mg) was injected into a lateral brain ventricle of the normotensive rabbit anesthetized with urethane. There was a dose-related and long-lasting fall in both arterial blood pressure and heart rate at all

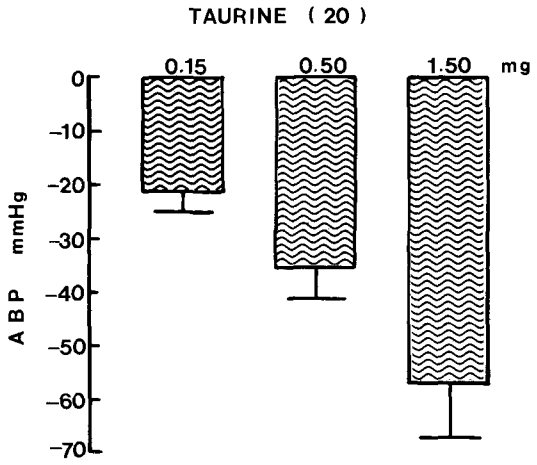

Fig. 1. Influence of intraventricular taurine on the responses of arterial blood pressure in urethane-anesthetized rabbits. Taurine was administered into the lateral brain ventricle at 60 min intervals. Ordinate: changes of blood pressure in mmHg. Abscissa: doses of taurine in mg. A numeral in the upper parenthesis indicates a number of rabbits used in the experiment. Vertical bars on the top of column denote standard errors of the mean (S.E.M.). ABP: arterial blood pressure

doses of taurine. These depressor and bradycardic effects lasted for more than at least 30 min.

However, an equivalent volume of 0.9% saline given into a lateral ventricle did not produce any changes in cardiovascular variables of the rabbits. When taurine was administered intracerebroventricularly three times consecutively, cardiorespiratory depression was observed. Therfore, in the present study, taurine was not administered consecutively more than two times.

As shown in figure 1 and 12, intracerebroventricular 0.15 mg of taurine induced a fall of mean arterial pressure by 21.5±3.62 mmHg from the original baseline of 115.8±8.46 mmHg and also a decrease of heart rate by −19.6±4.53 beats per minute from the original baseline of 322.6±15.2 beats/min. Increasing i.c.v. doses of taurine to 0.50 and 1.50 mg showed the decreased mean arterial pressure of −35.1±5.95 and −56.8±9.23 mmHg, respectively from the preinjection level of the baseline, and the fall in heart rate by −34.7±7.12 and −55.2±9.25 beats/min, respectively from 20 rabbits. All of the above experimental results were statistically significant from the corresponding preinjection values ($P<0.001$).

Before every administration of taurine, 0.2 ml of 0.9% saline was administered i.v.t. and the arterial blood pressure and heart rate determined. This was followed by the i.c.v. injection of increasing doses of taurine (0.15~1.50 mg) or an equivalent volume of saline. Arterial blood pressure and heart rate were recorded or counted during more than 30 min.

Increasing doses of taurine were injected intracerebroventricularly at about 60 minutes intervals or when the cardiovascular parameters have returned to their predose baseline. However, intravenous administration of taurine at cumulative doese from 0.15 to 1.5 mg per kilograms of body weight did not provoke any cardiovascular modifications comparable to those when the drug was administered into the central nervous system.

In the present work, the depressor and bradycardic effects of intraventricular taurine were similar with results described previously in rats or cats (Yang and Lin, 1983; Bousquet *et al.*, 1981).

Influence of atropine and vagotomy on taurine-induced depressor and bradycardic effects

In 6 experimental animals, the effect of atropine on the cardiovascular responses to i.c.v. injection of taurine was studied. Injection of atropine (3.0 mg/kg, i.v.) along with bilateral vagotomy was made in the present investigation to block cholinergic muscarinic receptors. Preliminary studies revealed that this dose of atropine blocked vasodepressor effect of muscarine. In the presence of atropine effect, taurine administered intraventricularly at all of the aforementioned doses (0.15, 0.5 and 1.50 mg) elicited nonsignificant changes in arterial blood pressure of −24.1±6.35, −33.5±5.42 and −55.1±9.74 mmHg, respectively by comparing with their control responses of −22.6±5.1, −35.9± 6.92 and −57.2±8.14 mmHg, respectively prior to injection atropine as shown in figure 2. Prior treatment of atropine did not also affect taurine-induced bradycardic effect at any doses of taurine. Following atropinization, taurine-evoked changes of heart rate at 0.15, 0.50 and 1.5mg of i.v.t. injection were −20.5±7.02, −35.5±8.25 and −57.4± 10.36 beats/min, respectively as compared with their corresponding control beats per minute, respectively (Fig. 12).

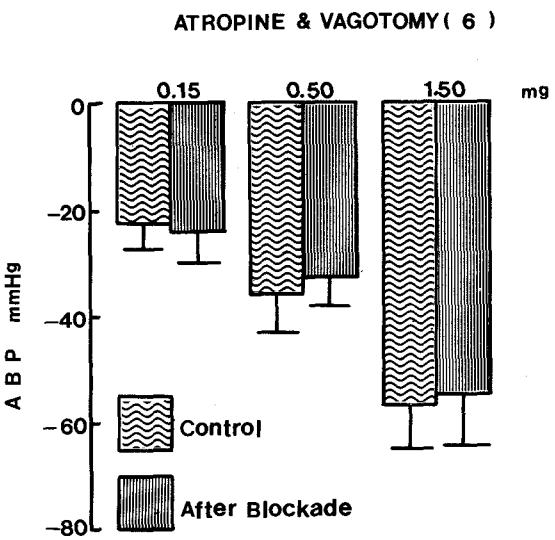

Fig. 2. Influence of atropine and vagotomy on taurine-induced depressor responses. Atropine (3.0 mg/kg, i.v.) and bilateral vagotomization were made following obtaining the control responses. Taurine was given intraventricularly at least 60 min after bilateral vagotomization was made. There was no statistical difference between groups of control and atropinization.

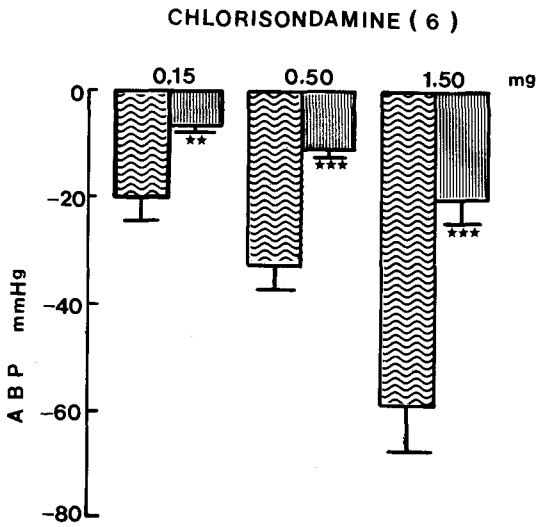

Fig. 3. Influence of chlorisondamine on taurine-induced depressor responses. Chlorisondamine (1.0 mg/kg) was given intravenously after obtaining control responses. Other legends and methods are as in Fig. 1 and 2.
**: $P<0.01$, ***: $P<0.001$

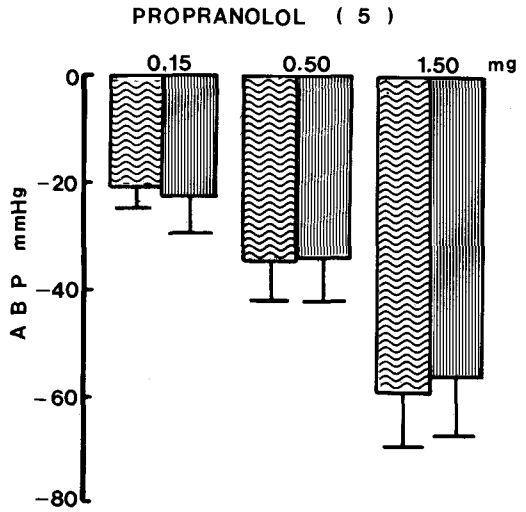

Fig. 4. Influence of propranolol on taurine-induced depressor responses. Propranolol (500 ug) was given intraventricularly after obtaining the corresponding control responses of taurine. Other legends and methods as in Fig. 1 and 2.

Bilateral vagotomy was made at the height of cervical level after completion of control responses of taurine-induced cardiovascular effect. Under bilateral vagoatomized condition, taurine-evoked changes of blood pressure and heart rate were without any alteration (data not shown).

Influence of chlorisondamine on taurine-induced depressor and bradycardic effects

Chlorisondamine (1.0 mg/kg), an autonomic ganglionic blocking agent was given intravenously into a femoral vein of the rabbit to examine the mechanism of cardiovascular effects of taurine.

Following the administration of chlorisondamine, the baseline of blood pressure was reduced from 115.8 ± 8.46 mmHg to 75.3 ± 6.94 mmHg and the baseline of heart rate also declined from 322.6 ±15.2 to 294.5 beats/min.

In 6 rabbits, responses of arterial blood pressure at 0.15, 0.50 and 1.5 mg, i.v.t. of taurine were -19.7 ± 3.51, -32.5 ± 4.03 and -58.1 ± 8.15 mmHg, respectively but the responses after chlorisondamine pretreatment were markedly inhibited by -6.9 ± 0.72 ($P<0.01$), -11.6 ± 1.05 ($P<0.001$) and -20.4 ± 3.58 ($P<0.001$) mmHg, respectively as shown in figure 3.

Furthermore, before pretreatment with chlorisondamine taurine-induced bradycardic responses at 0.15, 0.50 and 1.50 mg, i.v.t. were -19.6 ± 4.53, -34.7 ± 7.12 and -55.2 ± 9.25 beats/min, respectively while the changes after chlorisondamine were greatly attenuated by -6.5 ± 0.75 ($P<0.01$), -16.8 ± 4.50 ($P<0.01$) and -30.5 ± 5.18 ($P<0.01$) beats/min from the preinjection baseline, respectively (Fig. 12).

Influence of propranolol on taurine-induced depressor and bardycardic effects

In order to examine the relationship between taurine-induced cardiovascular effects and adrenergic beta receptors, propranolol (500 ug) was administered intracerebroventricularly. Prior to administration of propranolol, taurine-induced hypotensive responses at cumulative doses from 0.15 to 1.5 mg, i.c.v. were -20.9 ± 4.21, -34.2 ± 7.04, -58.7 ± 10.26 mmHg from the preinjection level, respectively. However, following pretreatment with propranolol taurine-induced depressor responses (which were -22.4 ± 5.68, -33.9 ± 8.05 and -56.0 ± 11.55 mmHg) were not altered as com-

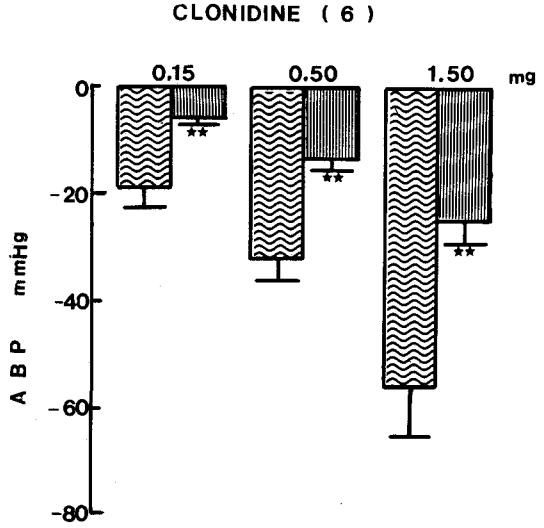

Fig. 5. Influence of clonidine on taurine-induced depressor responses. Clonidine (20 ug) was administered into an lateral ventricle following obtaining the control responses of taurine. Other legends and methods are the same as in Fig. 1 and 2. **: P<0.01

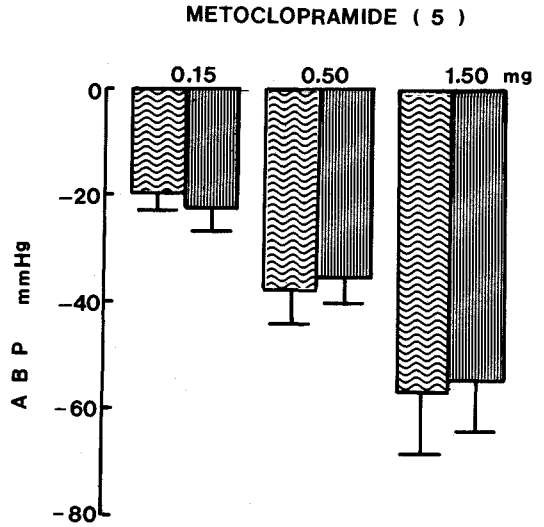

Fig. 6. Influence of metoclopramide on taurine-induced depressor responses. Metoclopramide (800 ug) was injected intraventricularly after obtaining the control responses of taurine. Other legends and methods are the same as in Fig. 1 and 2.

pared with their corresponding control responses, shown as in figure 4.

On the other hand, when propranolol (500 ug) was administered i.c.v. 15min before taurine the bradycardic responses of taurine were significantly inhibited by -4.2 ± 0.39 ($P<0.001$), -11.3 ± 1.85 ($P<0.001$) and -19.6 ± 2.63 ($P<0.001$) beats/min, respectively by comparing with their control responses of -19.6 ± 4.53, -34.7 ± 7.2 and $-55.2\pm$ 9.25 beats per minutes, respectively from 5 rabbits (Fig. 12).

Influence of clonidine on taurine-induced depressor and bradycardic effects

Clonidine (20 ug), presently employed as an antihypertensive agents by stimulating both central and peripheral adrenergic alpha$_2$-receptors (Langer *et al.*, 1982; Issac, 1982) was injected intraventricularly in order to observe the interrelationship between taurine-induced cardiovascular effects and adrenergic alpha$_2$-receptors stimulation.

After pretreatment with clonidine, depressor responses of intraventricular taurine at all of the cumulative doses from 0.15 to 1.50 mg were greatly inhibited by -6.1 ± 0.85 ($P<0.01$), -13.5 ± 2.16 ($P<0.01$) and -25.2 ± 3.95 ($P<0.01$) mmHg, respectively as compared with control responses of -18.7 ± 3.52, -31.9 ± 4.17 and -55.6 ± 9.02 mmHg from 6 rabbits, respectively as shown in table 3 and figure 5. Moreover, after administration of clonidine, bradycardic effects induced by taurine at the same cumulative doses of i.c.v. injection were clearly attenuated by -6.8 ± 0.82 ($n=6$, $P<0.01$), -15.2 ± 2.04 ($n=6$, $p<0.01$) and -27.4 ± 3.05 ($n=6$, $P<0.01$) beats/min, respectively by the corresponding control beats (Fig. 12).

Influence of metocloprmaide on taurine-induced depressor and bradycardic effects

Since it is known that metoclopramide is a dopaminergic receptor antagonist employed presently in treating vomiting and gastroparesis (Albibi *et al.*, 1983; Besancon *et al.*, 1964; pinder *et al.*, 1976) and that it causes depressor response through adrenergic alpha-receptor blocking action in rabbits (Lim *et al.*, 1989), it is likely of particular interest to investigate the effect of metoclopramide on taurine-induced cardiovascular effects. Taurine-induced hypotensive responses at 0.15, 0.50

and 1.50 mg i.v.t. before treatment with metoclopramided (800 ug, i.v.t.) were -20.3 ± 3.15, -37.5 ± 6.26 and -56.4 ± 11.02 mmHg from the original arterial pressure baseline, respectively while following prior intraventricular injection of metoclopramide their depressor were -22.5 ± 4.05 (n=5, ns), -35.2 ± 5.17 (n=5, ns) and -54.2 ± 9.96 (n=5, ns) mmHg, respectively (Fig. 6).

Furthermore, prior administration of metoclopramide also failed to alter taurine-induced bradycardic responses at all of the above same doses. Figure 13 shows the influence of metoclopramide on intraventricular taurine-induced cardiovascular reponses of heart rate.

Influence of strychnine on taurine-induced depressor and bradycardic effects

Since strychnine is generally considered as a potent and selective glycine antagonist (Curits *et al.*, 1968b; Curtis and Johnston, 1974; Muller and Snyder, 1978) and also known to prevent the taurine-evoked hypotensive and bradycardic effects in

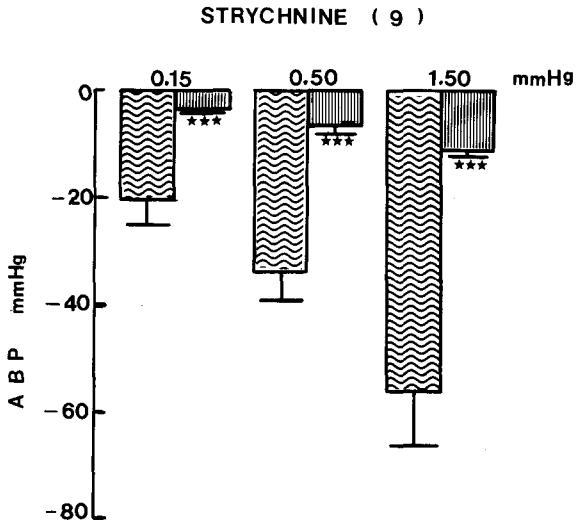

Fig. 7. Influence of strychnine on taurine-induced depressor responses. Strychnine (100 ug) was given intraventricularly after obtaining the control responses of taurine. Other legends and methods are the same as in Fig.1 and 2. ***: $P<0.001$

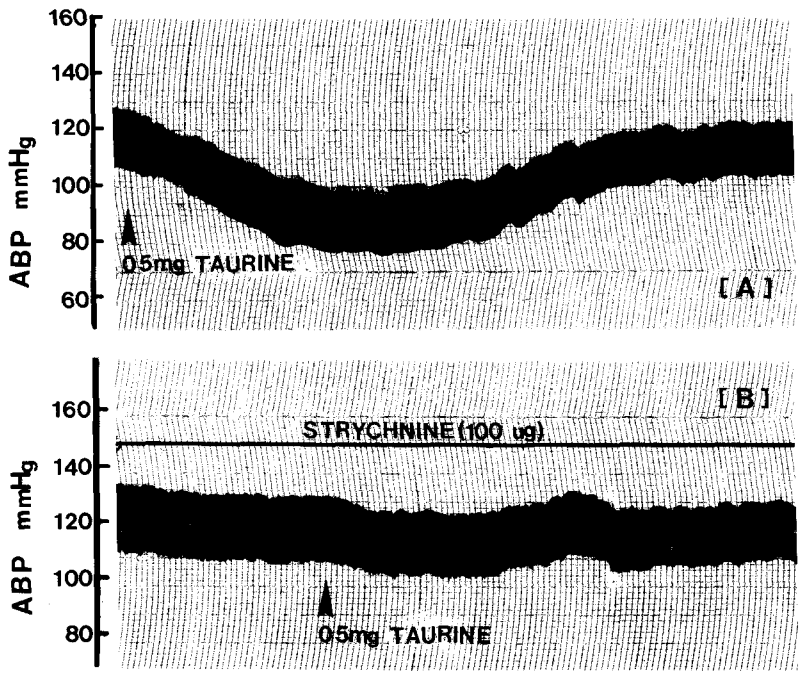

Fig. 8. The representative tracing of strychnine effect on intraventricular taurine-induced depressor response in the urethane-anesthetized rabbit (Expt. 458. body wt. 2.0 kg). At arrow mark, taurine (0.5 mg) was administered into a lateral ventricle. Between (A) and (B), strychnine (100 mg) was injected intraventricularly 15 min before taurine. Upper: Taurine-induced depressor only in a nontreated rabbit. Lower: Taurine-induced response in strychnine pretreated rabbit. ABP: Arterial blood pressure in mmHg. The chart speed was 0.25 mm/sec.

cats (Bousquet *et al.*, 1981), it seems to be interesting to investigate intrrelationship between glycinergic receptor stimulation and taurine-induced cardiovascular effects.

The rabbits were pretreated with strychnine at a dose of 100 ug 15 min before taurine. In the presence of strychnine effect, taurine-induced hypotensive responses at doses of 0.15, 0.50 and 1.5 mg, i.v.t. were greatly blocked by -3.7 ± 0.25 ($n=9$, $P<0.001$), -6.5 ± 0.71 ($n=9$, $P<0.001$) and -11.2 ± 1.04 ($n=9$, $P<0.001$) mmHg from the pre-injection level, respectively as compared with their corresponding control responses of -20.4 ± 4.15, -33.9 ± 5.02 and -56.2 ± 9.36mmHg, respectively as shown in figure 7 and 8. In 9 rabbits, bradycardic effects evoked by taurine at doses of 0.15, 0.50 and 1.5 mg, i.v.t. were -19.6 ± 4.53, -34.7 ± 7.12 and -55.2 ± 9.25 beats/min from the original baseline of heart rate, respectively. However, pretreatment with strychnine at a dose of 100 ug, i.v.t. led to the significant inhibition by -3.0 ± 0.25 ($P<0.001$), -7.8 ± 0.55 ($P<0.001$) and -13.9 ± 1.26 ($P<$

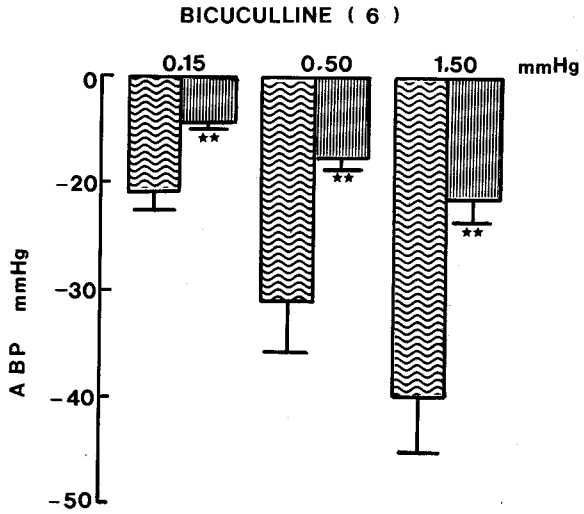

Fig. 9. Influence of bicuculline on taurine-induced depressor responses. Bicuculline (30 ug) was adminstered into a lateral ventricle after obtaining the control responses of taurine. Other legends and methods are the same as in Fig. 1 and 2. **P: 0.01

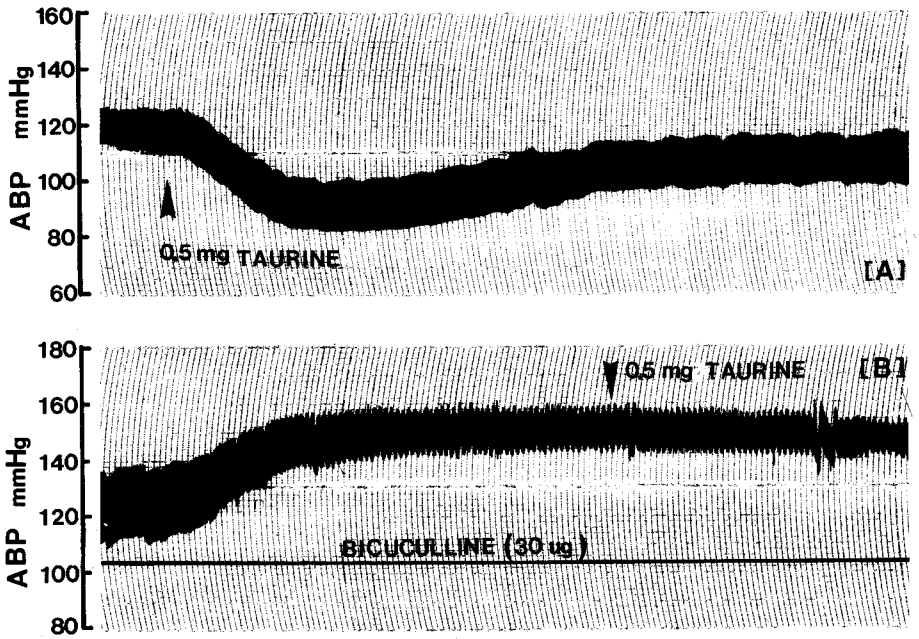

Fig. 10. The representative tracing of bicuculline effect on intraventricular taurine-induced depressor response in the rabbit anesthetized with urethane (Expt No. 462, body wt. 2.1 kg). Between (A) and (B), bicuculline (30 ug) was given intracerebroventricularly 15 min before taurine. At arrow mark, taurine (0.5 mg) was injected into a lateral brain ventricle. Other legends and methods are the same as in Fig. 8.

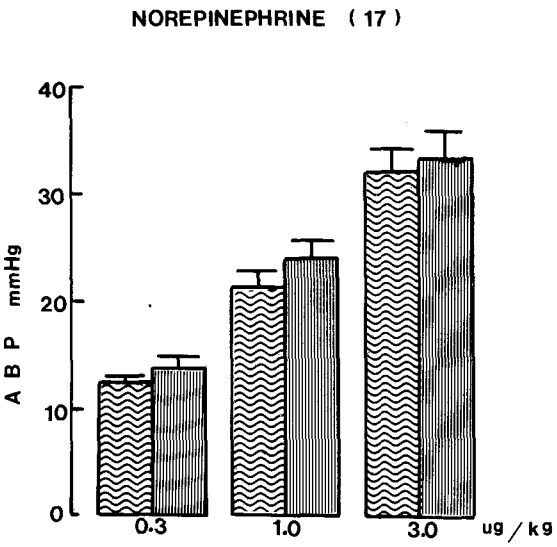

Fig. 11. Influence of intraventricular taurine on norepinephrine-induced pressor responses. Taurine (0.5 mg) was given into a lateral ventricle after obtaining the control pressor responses of norepinephrine. Other legends and methods are as in Fig. 1 and 2.

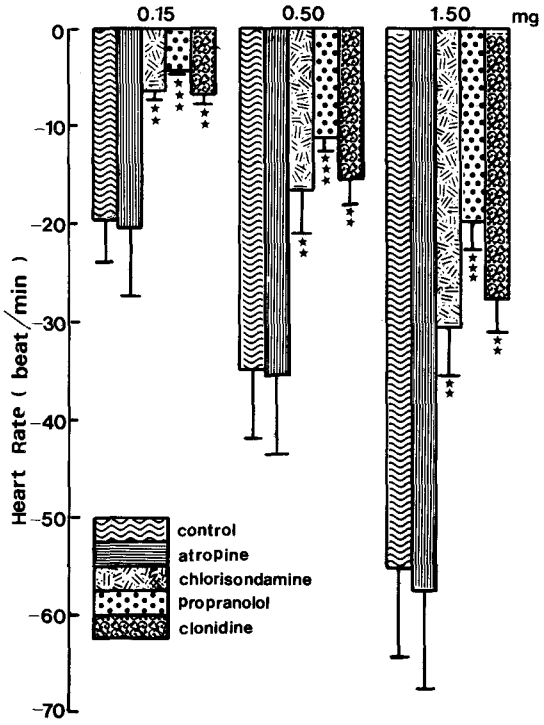

Fig. 12. Influence of atropine with bilateral vagotomy, chlorisondamine, propranolol and clonidine on taurine-induced bradycardic responses. Atropine (3.0 mg/kg, i.v.) with bilateral vagotomization at the height of cervical level, chlonisondmine (1.0 mg/kg, i.v.), propranolol (500 ug, i.v.t.) and clonidine (20 ug, i.v.t.) were administered, respectively after obtaining the corresponding control beats of taurine. Asterisks represent statistical significance between the control and each blockade group. **: $P<0.01$, ***: $P<0.001$

0.001) beats/min at the above same doses of inatrventricular taurine, respectivley (Fig. 13).

Influence of bicuculline on taurine-induced depressor and bradycardic effects

Since it has been shown that bicuculline is a specific antagonist of the GABA receptors (Curtis *et al.*, 1971a,b: Andrews and Johnston, 1979), it was tried to determine the effect of bicuculline on intraventricular taurine-evoked cardiovascular effects. Taurine-induced hypotensive responses at doses of 0.15, 0.50 and 1.50 mg, i.v.t. prior to administration of bicuculline were -21.6 ± 3.44, -42.0 ± 9.12 and -60.1 ± 9.68 mmHg from the orignininal baseline, respectively while following the pretreatment with bicuculline at dose of 30 ug i.v.t. they were markedly attenuated by -9.0 ± 0.98 ($P<0.01$), -15.4 ± 2.04 ($P<0.01$) and -23.1 ± 4.19 ($P<0.01$) mmHg at the above same doses of taurine from 6 rabbits, respectively (Fig. 9 and 10).

Changes of heart rate evoked by taurine at 0.15, 0.50 and 1.5 mg, i.v.t. after prior injection of bicuculline (30 ug, i.v.t.) were clearly diminished by -8.7 ± 1.22 ($n=6$, $P<0.01$), -16.4 ± 2.59 ($n=6$, $P<0.01$) and -29.5 ± 3.83 ($n=6$, $P<0.001$) beats/min, respectively when compared with each corresponding control beats as shown in figure 13.

Influence of intraventricular taurine on the pressor responses of norepinephrine

Since intracerebroventricular taurine-induced cardiovascular effects were greatly inhibited by the pretreatment with chlorisondamine, clonidine, strychnine and bicuculline as shown in figure 3,5,7 and 9, taurine could cause hypotensive and brady-

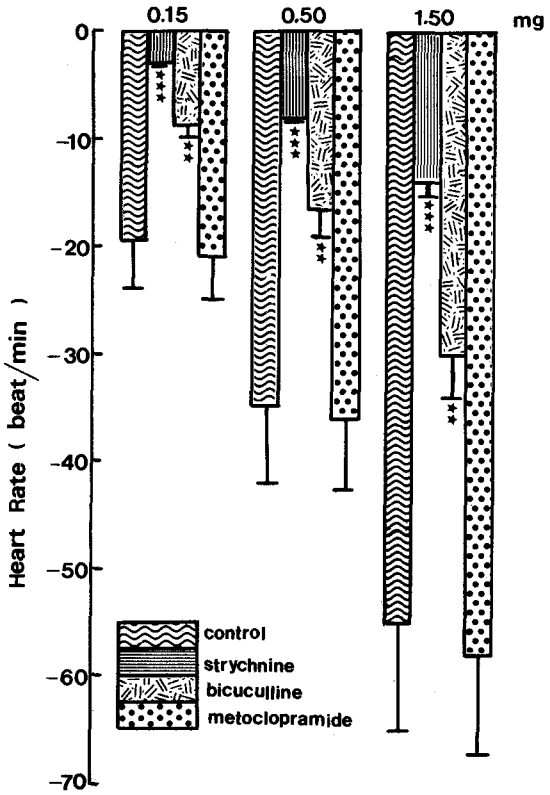

Fig. 13. Influence of strychine, bicuculline and metoclopramide on taurine-induced bradycardic responses. Strychnine (100 ug), bicuculline (30 ug) and metoclopramide (800 ug) were given into a lateral ventricle, respectively after obtaining the corresponding control beats of taurine. Other legends and methods are the same as in Fig. 12 **: $P<0.01$, ***: $P<0.001$

cardic effects through the blockade of adrenergic nerves in addition to stimulation of taurinergic (glycinergic) or GABAergic receptors in brain. It seems to be of interest to study the effect of taurine (i.v.t.) on norepinephrine-evoked pressor respon-ses.

In 17 rabbits, norepinephrine at doses of 0.3, 1.0 and 3.0 ug/kg, i.v.t. caused a dose-related hypertensive responses of 12.5 ± 1.37, 21.2 ± 3.05 and 32.1 ± 3.91 mmHg from the original baseline, respectively. However, in the presence of taurine effect they were 13.6 ± 2.04, 24.1 ± 3.51 and 33.5 ± 5.06 mmHg at the above same doses, respectively, which were not significant statistically as compared with the control responses (Fig. 11).

DISCUSSION

In the present work, it has been demonstrated that intraventricular administration of taurine, a naturally occuring amino acid, in urethane-anesthetized normotensive rabbits produced a dose-related, marked and lasting fall in arterial blood pressure as well as hear rate. These results are in agreement with previous reports by others (Inoue *et al.*, 1985; Paakrari *et al.*, 1983; Yang and Lin, 1983; Bousquet *et al.*, 1984; Petty and Di Francesco, 1989). It is also considered that these cardiovascular effects of intraventricular taurine may be caused through stimulation of taurinergic (glycinergic) and GABAergic receptors which are associated with catecholaminergic neurons in brain.

First, the present experimental results confirm that taurine produces cardiovascular effect of central origin in the urethane-anesthetized rabbits. Indeed, taurine administered intraventricularly caused a marked and lasting hypotension and bradycardia beginning with a small dose (0.15 mg). These effects were clearly of central origin since there was no effect of comparable intensity or duration when taurine was administered systemically (intravenously), even at high doses (more than 5 mg/kg). These results differ greatly from those of Sgaragli and Pavan (1972) who in rats described central hypotensive effect of taurine only at very high doses (5 mg/kg intracisternally and 10 mg/kg, i.c.v.). In support of the central cardiovascular effect evoked by taurine, it has been shown that intraventricular taurine did not affect the pressor effect of intravenous norepinephrine in the present work.

Furthermore, intracerebroventricular taurine-evoked cardiovascular effect was greatly attenuated by pretreatment with chlorisondamine, an autonomic ganglionic blockade. In terms of their results, it is considered that the action site of taurine to hypotensive and braycardic responses may be the autonomic ganglia or higher sites possibly (brain).

Second, in the light of the fact that the pretreatment with strychnine, which is known to be a potent and selective glycine antagonist (Curtis *et al.*, 1986; Curtis and Johnston, 1974; Muller and Snyder, 1978), inhibited greatly the hypotensive and bradycardic effects evoked by intraven-

tricular taurine, it is thought that i.v.t. injection of taurine causes the depressor and bradycardic in the rabbits through stimulation of glycine receptors in brain. In support of this idea, it has been reported that strychnine antagonized taurine effects under certain experimental condition, such as in frog retina (Urban *et al.*, 1976), in neurons of the spinal cord, the brain stem and the cortex (Curtis *et al.*, 1968; 1971c; Haas and Hosli, 1973; Sonhof *et al.*, 1975). Moreover, the hypotensive effects of taurine can be partially antagonized by strychnine in both cats and rats (Gatti *et al.*, 1985; Bousquet *et al.*, 1981) and by 6- (aminoethyl)-3-methyl-4H -1.2.4-benzothiadiazine-1.1-dioxide hydrochloride (TAG) (Bousquet *et al.*, 1984; Wessberg *et al.*, 1983), which is a specific antagonist of taurine in certain pharmacological models. In the present investigation, strychnine at a dose of 100 ug, i.v.t. clearly prevented taurine from having cardiovascular effects, as it did for glycine (Bousquet *et al.*, 1981).

Since strychnine antagonizes the effects of taurine, it has been suggested that the latter produces depressor and bradycardia by acting on glycinergic receptors as proposed by Haas and Hosli (1973) as well as by Bousquet and his coworkers (1981). Nevertheless, these findings do not formally rule out an action on specific taurine receptor, as suggested by Farederickson and his colleagues (1978). Anyway, the present experimental results of an antagonistic action between strychnine and taurine suggest that glycinergic receptors might be involved in the central cardiovascular actions evoked by taurine. However, the findings observed with taurine do not clearly exclude an action on separate specific taurine receptors for which a specific antagonist is not yet available so far, although TAG is introduced as antagonist of taurine. This latter hypothesis imply that taurine might act as an inhibitory neurotransmitter in central cardiovascular regulation as previously proposed by Oja and Lahdesmaki (1974) for the neurophysiological functions.

Third, prior treatment with bicuculline, which is considered as a specific antagonist of the GABA receptors (Curtis *et al.*, 1971a; b: Andrews and Johnston 1979), antagonized taurine-evoked hypotensive and bradycardic effects. These findings indicate that taurine-induced cardiovascular effects could be exerted through GABAergic receptor stimulation in brain. In support of these results, there are considerable amounts of evidences. Leach (1979) has described that taurine potentiates stimulus-evoked release of ^{3}H-GABA in rat cerebral cortex slices and this is an effect which is consistent with both a modulatory role and anticonvulsant action for this amino acid.

Moreover, bicuculline and picrotoxin also antagonize the inhibitory effect of both taurine and GABA on the cerebellar Purkinje cells (Curtis and Felix, 1971; Okamoto and Quastel, 1976; Okamoto *et al.*, 1976; Frederickson *et al.*, 1978; Okamoto and Sakai, 1980). More recentl, Kontro and Oja (1990) have demonstrated that taurine displaces binding to $GABA_B$ receptors concentration dependenly from slices of cerebral cortex of the mouse. Taurine modulates the release of GABA from slices of cerebellum through bicuculline-sensitive presynaptic receptors (Na-mina, *et al.*, 1983; Kontro and Oja, 1989) and the displacement by taurine of the binding of GABA to the GABA-benzodiazepine receptor couple has been shown with membrane-bound and solubilized preparations of receptors (Medina and DeRobertis, 1984; Malmien and Kontro, 1986; 1987).

Recent cytochemical studies have demonstrated that taurine, a inhibitory amino acid structurally related to GABA, occurs in very high concentrations in the cerebellum (Chan Palay 1982; Ottersen, 1988), and it has been localized in Purkinje cell axon terminals within the deep cerebellar nuclei where it could be colocalized with GABA (Karasawa *et al.*, 1989; Otterson *et al.*, 1988). Billard (1990) has reported that both the inhibitory action of taurine and GABA in deep cerebellar nuclei of the rat were antagonized by bicuculline and picrotoxin meaning that taurine had a "GABA-like" effect in this site. These previous results confirm and demonstrated that taurine-induced cardiovascular effects are due to the GABAergic receptor stimulation in brain.

In the present investigation, taurine-induced hypotension and bradycardia were not influenced by pretreatment with metoclopramide, which is known to be a selective dopaminergic antagonist (Albibi and Maccalum, 1983; Besancon *et al.*, 1964; Pinder *et al.*, 1976). In view of this result, it is shown that blockade of dopaminergic receptors in the brain with either receptor antagonists or by destruction of dopamine neurones causes a significant reduction in the reflex bardycardia compared to controls (Chen and Lin, 1980; Lin *et al.*, 1982). In addition, alpha$_2$-adrenergic receptor agonist, cloni-

dine was demonstrated to inhibit the cardiovascular effects of taurine in the present experiments. These results are in agreement with central effects of taurine as previously described (Bousquet *et al.*, 1981; Bousquet *et al.*, 1983; Gatti *et al.*, 1985; Petty and Di Francesco, 1989). Therefore, it can be deduced from this finding that as the inhibitory action by clonidine is generally mediated by postsynaptic alpha$_2$-adrenoceptors, the inhibitory effects of taurine when injected into a lateral ventricle may be mediated by the activation of postsynaptic alpha$_2$-receptors through taurine or GABA receptors in brain. Generally, it is konwn that clonidine is an antihypertensive agent that, paradoxically, possesses primarily alpha$_2$-adrenergic agonist property. However, clonidine owes its antihypertensive effect by a predominant action on central nerveous system, where it apparently produces a decrease in the symphathetic outflow from the CNS (Issac, 1982). Peripherally, clonidine impairs adrenergic neurotransmission by activating inhibitory presynaptic alpha$_2$-adrenoceptors (Langer *et al.*, 1982). In terms of the fact that adrenergic beta-receptor antagonist propranolol attenuated markedly taurine-induced bradycardic effect, it is thought that intraventricular taurine may provoke a decrease in heart rate via adrenergic beta-receptor blockade in brain. Since atropine and bilateral vagotomy did not affect the depressor and bradycardic responses evoked by taurine, muscarinic receptor or vagal stimulation could be exclude as the action site of taurine in brain.

In conclusion, taurine when administered intraventricularly provokes a fall in arterial blood pressure and heart rate. These hypotensive and bradycardic effects seem to be exerted through stimulation of taurinergic (glycinergic) and GABAergic receptors which are associated with catecholaminergic neurones in brain.

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=국문초록=

측뇌실내 Taurine이 가토의 혈압 및 심박에 미치는 영향

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Taurine은 유황 함유 아미노산으로서 뇌내에서 억제작용을 갖는 신경전달물질 역할을 하는것으로 알려져 있다. Taurine을 가토의 측뇌실내에 투여하여 혈압 및 심박에 미치는 영향을 검토하고 그 작용 기전을 규명코자 본 연구를 시행하여 얻은 연구결과는 다음과 같다.

Taurine (0.15~1.5 mg)은 urethane 마취 가토의 측뇌실내로 주사하였을때 혈압강하작용 및 심박감소작용이 현저하고 지속적인 용량반응 곡선을 나타내었다. 이와 동시에 상당한 호흡억제 작용도 관찰되었다.

그러나 동일량의 taurine을 정맥내에 투여시 혈압 및 심박에 아무런 영향을 미치지 못하였다.

Taurine의 혈압 하강작용은 chlorisondamine, clonidine, strychnine, bicuculline등으로 전처치시 유의하게 억제되었으나 atropine, 양측 미주신경절단, propranolol 및 metoclopramide등의 전처치로 영향을 받지 않았다. 더우기 taurine은 norepinephrine의 승압 반응에도 영향을 미치지 못하였다.

Taurine의 심박감소 작용은 chlorisondamine, propranolol, clonidine, strychnine 및 bicuculline등으로 전처리시 현저히 차단되었으나 atropine, 양측 미주신경절단, metoclopramide 등의 전처리로 영향을 받지 않았다.

이상의 연구한 결과로 보아, taurine은 가토의 측뇌실내 투여시 지속적이며 현저한 혈압하강 및 심박감소를 일으키며 이러한 작용은 뇌내의 catecholamine 뉴론과 관련있는 taurine (glycine) 및 gamma-aminobutyric acid (GABA) 수용체를 통해서 나타나는 것으로 사료된다.