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Studies on the Mechanism of the Cardiovascular Effect of Intraventricular 5-Hydroxytryptamine in Rabbits

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Abstract□An attempt was made to investigate the effect of intracerebroventricular 5-hydroxytryptamine (5-HT) on the cardiovascular system in urethane-anesthetized rabbits and to elucidate the mechanism of its action. 5-HT given into a lateral ventricle caused clearly a dose-dependent decrease in both arterial blood pressure and in heart rate. The bradycardia and hypotension induced by 5-HT were significantly attenuated by the prior injection of ketanserin, cyproheptadine or clonidine. Pretreatment of atropine with bilateral vagotomy did not affect both bradycardia and hypotension. Propranolol weakened markedly the bradycardia of 5-HT but did not influence the depressor response of 5-HT. These experimental results suggest that intraventricular 5-HT cause the hypotension and bradycardia in rabbits through the stimulation of serotonergic receptors in brain, which is seemed to be associated to inhibition of sympathetic tone.

Keywords□5-Hydroxytraptamine, hypotension, bradycardia, serotonergic receptors.

It is well-known that Salmoiraghi *et al.*[1] reported that intravenous injection of 5-hydroxytryptamine (5-HT) into anesthetized rats caused a triphasic blood pressure response consisting of a brief, but marked, initial vasodepressore response followed by a secondary increase and then a final decrease in blood pressure. Recently, base upon a variety of different studies, both *in vivo* and *in vitro,* including data from radioligand binding experiments, it has been suggested that cardivascular effects of 5-HT in anesthetized rats are mediated via at least three types of 5-HT receptors[2-4].

Dalton *et al.*[5] found that in the conscious rat, the complex cardiovascular effects of 5-HT involve stimulation of at least three different 5-HT receptors. The initial depressor reponse and bradycardia involve activation of 5-HT_3-receptors, the secondary vasopressor effect, which is significantly greater in DOCA-salt rats than that in normotensive rats results from stimulation of 5-HT_2 receptors and the late vasodepressor response is due to vasodilation via '5-HT_1-like' receptors.

With regard to the central nervous system effects of 5-HT, many studies have reported on the role of the nucleus tractus solitarius (NTS) in the central regulation of cardiovascular function[6-10]. Recently, Laguzzi and his collegues[7, 11] observed that microinjection of 5-HT into NTS elicited a transient fall in blood pressure accompanied by bradycardia, both being blocked by prior injection of 5-HT antagonists such as metergoline or ketanserin. More recently, it has been found that the putative 5-HT_1-like receptor agonist RU-24969 given intravenously in anesthetized rats induced a decrease in heart rate and blood pressure, and these cardiovascular effects of RU-24969 are mediated by central inhibition and stimulation of sympathetic and vagal tones, respectively[12].

In the present investigation an attempt was made first, to examine the cardiovascular effect of 5-HT administered intraventricularly in anesthetized rabbits, secondly to clarify the mechanism of its action and thirdly to compare intraventricular (central) effects of 5-HT with peripheral (intravenous) effects on the cardiovascular system along with its effect on nucleus tractus solitarius.

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 seprate cages and food (Cheil Animal Chow) and tap water were

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allowed ad libitum at least for a week to adapt to the environment. On the day of experiment, rabbits were anesthetized with urethane (1 g/kg) subcutaneously. The animal was tied in supine position on fixing panel to prevent the movement and a T-formed tracheal tube was inserted for securing free air passage. The body temperature was maintained at 37-38°C by a thermostatically controlled blanket and heating lamp.

Measurement of blood pressure and heart rate

The left femoral artery was catheterized with polyethylene tube (Gauge No. 21) and connected to a pressure transducer (Gould Co.) and arterial blood pressure was recorded on a physiograph (Beckan Co.) for cotinuous monitoring of arterial pressure. The artery cannula was filled with heparine-sa-line solution (400 I.U./m*l*) to prevent the blood coagulation during experiment. Another cannulation with polyethylene tube (Gauge No. 23) was made into a femoral vein for injection drugs. Each rabbit was left undisturbed for at least 30 minutes after completion of the operative procedures to permit cardiovascular parameters to be stabilized. Heart rate was measured by digitalized heart rate counter connected to physiograph with beats per minute.

Administration of drugs

For the intracerebroventricular (i.v.t.) administration of the agents a lateral ventricle of the cerebrum was cannulated. After fastening the animal in prone position, a hole was drilled on the skull at a point 1.5 cm rostral to the occiput tubercle and 0.5 cm lateral to the midline, and a cannula made of polyethylene tubing (3 cm long of 1.0 mm O.D.) was introduced obliguely until the clear cerebrospinal fluid appeared in the cannula, and then it was kept in place by cementing to the bone. The volume administered during experiment did not exceed 0.15 m*l*. At the end of each experiment the location of cannula tip was checked by injection of methylene blue.

The sources of the drugs used in the present study are as follows: 5-hydroxytryptamine creatinine sulfate and cyproheptadine HCl (Sigma Chemical Co.), atropine sulfate (Merk Co.), propranolol HCl (ICI Co), clonidine HCl (Catapress®, Boehringer Ingelheim Co.) and ketanserine tartrate (Janssen Co.). All drugs were prepared in 0.9% sodium chloride solution on the day of experiment and stored in a refrigerator.

Statistical analysis

The statistically significance between groups was determined by utilizing the Student's "t" test. Data obtained from animals which served as own control were analyzed for significance using t-test for unpaired observations. A P-value of less than 0.05 was considered to represent statistical significally noted in the text. Values are given in the text with standard errors (S.E) of means. The statistical analysis was made by computer system of Snedecor and Cochran[13].

Table I. Effect of intraventricular 5-Hydroxytryptamine (5-HT) on the of blood pressure of the rabbits

Administration route	Dose of 5-HT (ug)	Change of Blood pressure (mmHg from preinjection level)	Number of Animals
Intraventricular injection	3.0	−8.6±1.47	18
	10.0	−13.9±1.90	18
	30.0	−18.9±2.03	18

All data expressed with mean ± standard errors (S.E.). All of above results statistically significant ($p<0.001$).

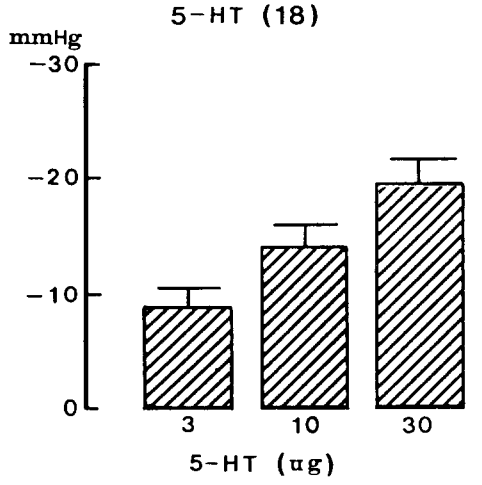

Fig. 1. Effect of 5-HT on aterial blood pressure in anesthetized normotensive rats.
The numeral in the upper bracket denotes number of animals ied in the experinent. Abscissa: Changes of blood pressure in mmHg. Ordinate: dose of 5-HT (ug/kg). 5-HT: 5-hydroxytriptamine. Vertical bars above each column indicate standard errors of means.

RESULTS

Cardiovascular effects of intracerebroventricular 5-hydroxytryptamine

The unilateral microinjection of 5-hydroxytry-

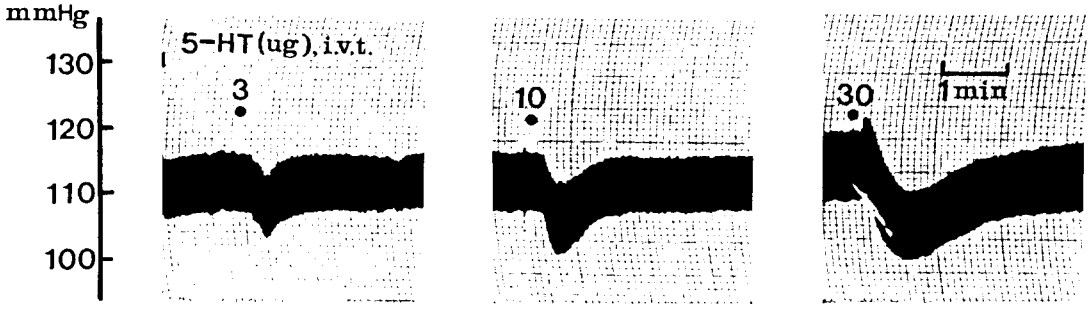

Fig. 2. The tracing of aterial blood pressure evoked by 5-HT in an anesthetized rabbit (Expt. 268, 2.1 kg).
At block dots, the indicated doses of 5-HT (3, 10 and 30 μg) were injected into the lateral ventricle, respectively. Time: 1 min.

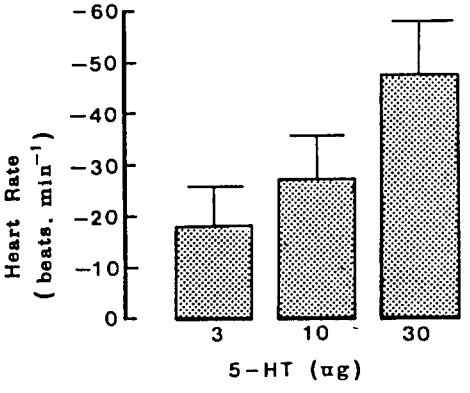

Fig. 3. The effects of 5-HT on heart rate in anesthetized normotensive rats.
The method and other legends are the same as in Fig. 1.

ptamine (5-HT) into a lateral ventricle caused a marked and immediate decrease in arterial blood pressure and heart rate in anesthetized normotensive rabbits, while the microinjection of 0.9% w/v saline elicited insignificant changes in the cardiovascular variables. The dose response curves for cardiovascular effects of 5-HT were established. The threshold dose, the dose which produced the first significant change in arterial blood pressure and heart rate when compared to the microinjection of 0.9% w/v saline was 3 μg. As shown in Table I, in rabbits, intracerebroventricular 3 μg of 5-HT produced a fall of mean arterial pressure of 8.6 ± 1.48 mmHg from the original baseline of 113.7 ± 8.4 mmHg and also decreases of 17.7 ± 8.1 beats/min from the original baseline of 376.1 ± 18.8 beats/min in heart rates. Increasing doses of 5-HT to 10 μg and 30 μg elicited fall of mean arterial pressure of 13.9 ± 1.9 and 18.9 ± 1.90 mmHg respectively from preinjection level of the baseline, and of heart rate of 26.9 ± 9.6 and 47.5 ± 11.9 beats/min from the base line, respectively. All of the above results were statistically significant from the control ($p < 0.001$) (Fig. 1 and 3). Fig. 2 illustrates the representative tracing of arterial blood pressure evoked by 5-HT. Rabbits in each group received the corresponding dose of 5-HT. Increasing doses of 5-HT were administered at about 30 min intervals or when the cardiovascular parameters had returned to their predose baseline.

Effect of atropine of 5-hydroxytryptamine-evoked cardiovascular responses

At least 3 doses of 5-HT were given to each animal, and were repeated about 15 min after the treatment with an antagonist. After completing 5-HT dose-response curves, a 5-HT receptor antagonist or other blocking agent was given to each animal in order to antagonize 5-HT blood pressure response or heart rates. This was repeated with a 5-HT antagonist or other blocking agent until cardiovascular responses of 5-HT were blocked.

Injection of atropine (3.0 mg/kg i.v.) along with bilateral vagotomy was used in the present work to block cholinergic muscarinic receptors. Preliminary studies showed that this dose of atropine blocked vasodepressor effect of muscarine. In the presence of atropin, in 6 rabbits, 5-HT administered intraventricularly at all of the aforementioned doses (3, 10 and 30 μg) elicited insignificant changes in arterial blood pressure of -8.5 ± 1.79, -12.8 ± 1.17 and -18.1 ± 1.92 mmHg, respectively, by comparing with their corresponding control responses of -7.2 ± 0.92, -12.3 ± 1.94 and -18.0 ± 1.38 mmHg prior to injection of atropine as shown in Table II.

Prior injection of atropine did not also affect 5-HT-evoked bradycardia at any dose of 5-HT

Table II. Effects of atropine and clonidine on intraventricular 5-HT-evoked changes of blood pressure

Blockade	Dose of 5-HT (μg)	Change of Blood pressure (mmHg from pre-injection level)		Statistical significance
		BEFORE	AFTER	
(6) Atropin	3.0	-7.2 ± 0.92	-8.5 ± 1.79	NS
	10.0	-12.3 ± 1.94	-12.8 ± 1.17	NS
	30.0	-18.0 ± 1.38	-18.1 ± 1.92	NS
(5) Clonidine	3.0	-7.8 ± 0.65	-3.2 ± 0.62	$p<0.02$
	10.0	-13.0 ± 1.08	-4.8 ± 0.15	$p<0.01$
	30.0	-19.1 ± 2.31	-7.8 ± 1.07	$p<0.02$

"BEFORE" and "AFTER" indicate changes of blood pressure evoked by 5-HT before and after administration of blocking agent. Atropine (3.0 mg/kg, i.v.) and clonidine (30 μg, i.v.t.) were given after obtained each corresponding control value, respectively. Statistical differences were calculated by comparing the response of "BEFORE" with that of "AFTER". Numerals in bracket denote number of animals used in the present work.

(Table IV and Fig. 9).

Fig. 4 show that pretreatment of atropine does not alter 5-HT-evoked arterial blood pressure response.

Effect of clonidine on 5-hydroxytryptamine-evoked cardiovascular responses

Clonidine[32, 33] (30 μg) presently employed as an antihypertensive agents by stimulating both central and peripheral alpha$_2$-adrenergic receptors was given intracerebroventricularly in order to observe the relationship between alpha$_2$-adrenergic stimulation of clonidine and 5-HT-evoked cardiovascular responses. After administration of clonidine intracerebroventricular 5-HT at all of the indicated doses (3, 10 and 30 μg) elicited the marked reduction in the arterial pressure to -3.2 ± 0.62 ($p<0.02$), 4.8 ± 0.15 ($p<0.01$) and -7.8 ± 1.07 ($p<0.02$) mmHg, respectively by comparing with the corresponding control values of -7.8 ± 0.65, 13.0 ± 1.08 and 19.1 ± 2.31 mmHg, respectively as in Table II. Clonidine also attenuated greatly 5-HT-induced bradycardia to -9.3 ± 2.0 ($p<0.01$), -20.7 ± 2.6 ($p<0.05$) and -28.0 ± 3.9 ($p<0.01$) beats/min at the above same doses of 5-HT, respectively (Table IV and Fig. 9).

Effect of ketanserin on 5-hydroxytryptamine-evoked cardiovascular responses

Since ketanserine which is a potent antagonist at vascular 5-HT$_2$ receptors[14] has also arpha-1 adrenoceptor blocking potency[15] and ketanserin

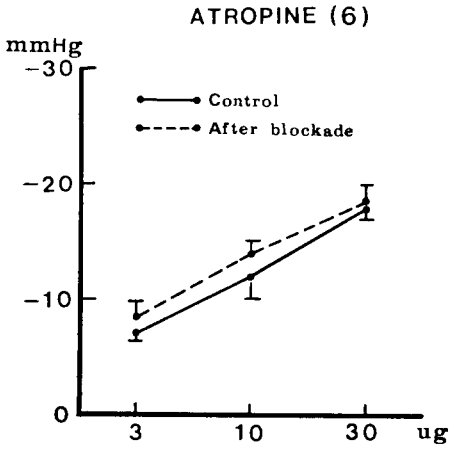

Fig. 4. Effect of atropine of 5-HT-evoked hypotensive responses.
Atropine (3.0 mg/kg) with bilateral vafotomization was given intraventricularly after obtaining control responses. The method and other legends are the same as in Fig. 1.

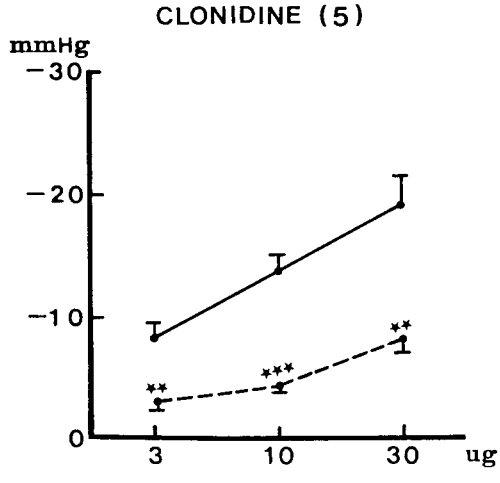

Fig. 5. Effect of clonidine of 5-HT-evoked hypotensive responses.
Clonidine (30 μg) was given intraventricularly after obtaining control responses. The method and other legends are same as in Fig. 1. **: $p<0.02$, ***: $p<0.01$

lowers blood pressure in hypertensive man as well as hypertensive animals,[16, 17] it is of interest to examine the effect of this agent (30 μg, i.v.t.) on 5-HT-evoked cardiovascular effects.

In the presence of ketanserin (30 μg, i.v.t.), changes of arterial pressure evoked by 5-HT at doses of 3, 10 and 30 μg, i.v.t. were clearly inhibited to

-2.0 ± 0.05 ($p<0.01$), -3.6 ± 0.86 ($p<0.01$) and -5.6 ± 0.93 ($p<0.001$) mmHg, respectively, by comparing with the control values of -7.3 ± 0.85, -13.6 ± 0.88 and -18.0 ± 1.51 mmHg, respectively (Table III). Pretreatment of 5 rabbits with ketanserin significantly decreased the heart rate. However, the decrease in heart rate of -6.3 ± 1.7 ($p<0.001$), -12.7 ± 1.9 ($p<0.001$) and -18.1 ± 3.6 ($p<0.001$) beats/min at each dose of 3, 10 and 30 μg of intracerebroventricular 5-HT in ketanserin-pretreated rabbits were markedly less than those induced by 5-HT in untreated rabbits (Table IV and Fig. 9). Fig. 6 shows the effect of ketanserine on 5-HT-evoked hypotensive responses.

Effect of cyproheptadine on 5-hydroxytryptamine-evoked cardiovascular responses

It is known that cyproheptadine is only a potent antagonist of 5-HT_2 and histaminergic$_1$-receptors[18] and also is an antagonist of voltage-sensitive calcium channels in pancreatic islet cells[19, 20]. Therefore, the effect of cyproheptadine (30 μg, i.v.t.) on 5-HT-induced cardiovascular responses was investigated in 6 rabbits.

As shown in Table III, prior administration of cyproheptadine produced marked inhibitory response to 5-HT-induced vasodepressor actions and also to 5-HT-evoked bradycardia (Table IV).

Hypotensive response of 5-HT at each dose of

Table III. Effects of ketanserin, cyproheptadine on intraventricular 5-HT-evoked changes of blood pressure

Blockade	Dose of 5-HT (μg)	Change of Blood pressure (mmHg from pre-injection level) BEFORE	AFTER	Statistical significance
Ketanserine (5)	0.3	-7.3 ± 0.85	-2.0 ± 0.05	$P<0.01$
	10.0	-13.6 ± 0.88	-3.6 ± 0.86	$p<0.01$
	30.0	-18.0 ± 1.51	-5.6 ± 0.93	$p<0.001$
Cyproheptadine (6)	3.0	-9.5 ± 0.32	-3.7 ± 0.42	$P<0.02$
	10.0	-14.5 ± 1.18	-7.0 ± 1.07	$p<0.02$
	30.0	-19.7 ± 1.80	-11.7 ± 1.81	$p<0.02$
Propranolol (6)	3.0	-8.5 ± 1.03	-7.9 ± 1.29	NS
	10.0	-15.5 ± 2.08	-13.6 ± 1.16	NS
	30.0	-18.3 ± 1.47	-19.1 ± 2.02	NS

Ketanserine (30 μg, i.v.t.), cyproheptadine (30 μg, i.v.t.) and propranolol (3.0 mg/kg, i.v.) were administered after obtaining each corresponding control value, respectively. Other legends and methods are the same as in Table II.

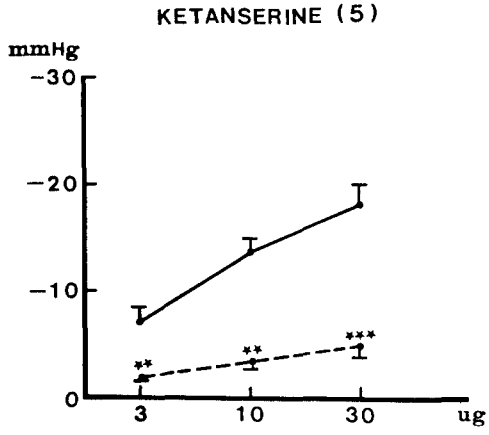

Fig. 6. Effect of ketanserin on 5-HT-evoked hypotensive responses.
Ketanserin (30 μg) was given into the lateral ventricle after obtaining control responses. The method and other legends are the same as in Fig. 1. **: $p<0.01$, ***: $p<0.001$

Table IV. Effect of some agents on changes of heart rate evoked by intraventricular 5-HT

Agents	Decrease in Heart Rate (beats per min) 5-Hydroxytryptamine 3 μg	10 μg	30 μg
Control (18)	-17.7 ± 8.1	-26.9 ± 9.6	-47.5 ± 11.9
Ketanserine (5)	-6.3 ± 1.7***	-12.7 ± 1.9***	-18.1 ± 3.6***
Cyproheptadine (6)	-4.0 ± 0.9***	-9.7 ± 2.4**	-14.8 ± 2.2**
Clonidine (5)	-9.3 ± 2.0**	-20.7 ± 2.6*	-28.0 ± 3.9**
Propranolol (6)	-5.3 ± 1.0***	-8.6 ± 1.4****	-24.6 ± 7.2**
Atropine (6)	-19.6 ± 2.5	-28.3 ± 10.1	-45.8 ± 12.6

These results are mean$\pm$S.E. of differences obtained from mean basal heart rate (376.1 ± 18.8 beats per minute) with mean$\pm$S.E. The Numeral in the bracket indicates number of animals used in each experiment. Ketanserin (30 μg) were administered into a lateral ventricle, respectively. Atropine (3.0 mg/kg) and propranolol (3.0 mg/kg) were given into a femoral vein. ***: $p<0.001$, **: $p<0.01$, *: $p<0.05$.

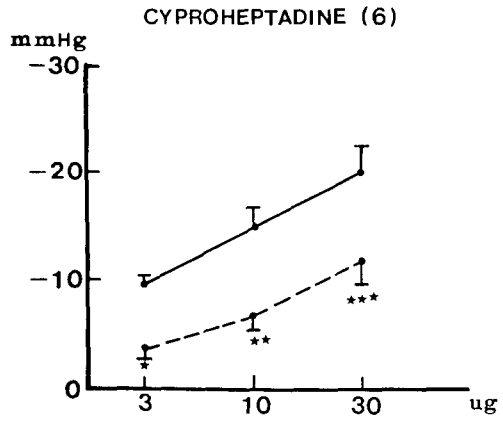

Fig. 7. Effect of cyproheptadine on 5-HT-evoked hypotensive response.
Cyproheptadine (30 μg) was given intraventricularly after obtaining control. Other legends are same as Fig. 1. **: p<0.002, ***: p<0.01

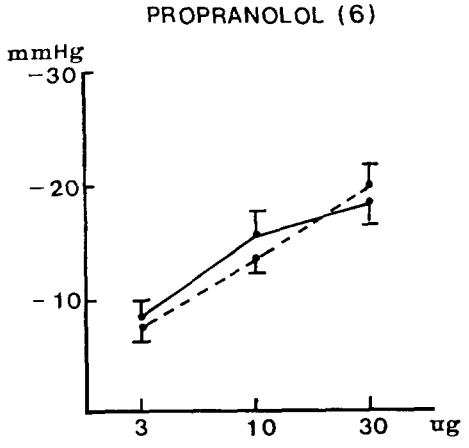

Fig. 8. Efect of propranolol on 5-HT-evoked hypotensive response.
Propranolol (3.0 mg/kg) was injected into a femoral vein after obtaining the control responses. The method and other legends are the same as in Fig. 1.

3, 10 and 30 g, i.v.t. after pretreatment of cyproheptadine (30 μg, i.v.t.) were greatly blocked by -3.7 ± 0.42 ($p<0.02$), -7.0 ± 1.07 ($p<0.02$) and -11.7 ± 1.81 ($p<0.01$) mmHg, respectively when compared to the corresponding control values of -9.5 ± 0.32, -14.5 ± 1.18 and -19.7 ± 1.80 mmHg of intraventricular 5-HT at each dose of 3, 10 and 30 μg as shown in Fig. 7. Pretreatment of cyproheptadine also inhibited significantly intracerebroventricular 5-HT-induced bradycardia to

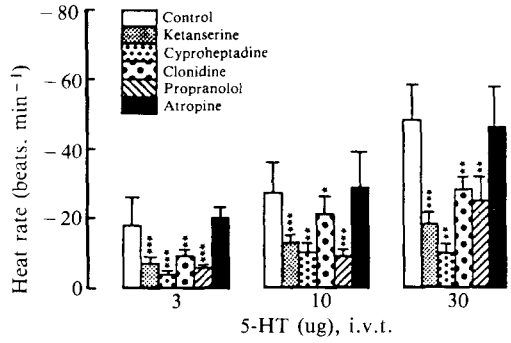

Fig. 9. Effects of some agents on changes of heart rate evoked by 5-HT.
The data were obtained from Table IV. Asterisks mean significant differences between control and test groups. ***: **p<0.001**, **: **p<0.01**, *: **p<0.05**

-4.0 ± 0.9 ($p<0.001$), -9.7 ± 2.4 ($p<0.01$) and -14.8 ± 2.2 ($p<0.01$) beats/min at 3, 10 and 30 μg of 5-HT by comparing with each corresponding control value, respectively (Fig. 9 and Table IV).

Effects of propranolol on 5-hydroxytryptamine-evoked cardiovascular responses

Intravenous propranolol (2.0 mg/kg), an adrenergic beta-receptor blocking agent was used in the present work in order to block peripheral and central adrenergic beta-receptors. In preliminary experiments, this dose of propranolol blocked vasodepressor response induced by isoproterenol. As shown Table III, prior injection of propranolol did not elicit any change in the vasodepressor response evoked by 5-HT at each dose of 3, 10 and 30 μg when compared to the corresponding control groups. Fig. 8 shows that propranolol does not affect 5-HT-evoked hypotension. However, propranolol-pretreatment attenuated significantly 5-HT-evoked bradycardia by -5.2 ± 1.0 ($p<0.001$), -8.6 ± 1.4 ($p<0.001$) and 24.6 ± 7.2 ($p<0.01$ beats/min at 3, 10 and 30 μg of 5-HT when compared to the control value before propranolol injection (Table IV and Fig. 9).

DISCUSSION

The present study demonstrates that serotonin injected into a lateral ventricle of the rabbit produced dose-dependent hypotensive activity and bradycardia which are in agreement with the expermental results of Laguzzi[7], Schvaloff and Lee *et al.*[22] in NTS.

These 5-HT-evoked hypotension and bradycardia were blocked significantly by ketanserin as well as by cyproheptadine, suggesting that 5-HT receptors in the lateral ventricle regulating the cardiovascular function may be pharmacologically identical to nucleus tractus solitarius in brain[11, 21, 22]. Nucleus tractus solitorius is known to be the major site of termination of afferents of the nineth and tenth cranial nerves[8, 23].

The most likely explanation for the inhibitory effect of ketanserin, a 5-HT_2-receptors antagonist[14], on the hypotensive response and bradycardia through stimulation of 5-HT_2-receptors in brain. On the other hand, it is reported that ketanserin itself inhibits sympathetic nerve activity. Phillips *et al.*[24]. found that the hypotensive effects of the lower does had no effect on the response to norepinephrine. The mechanism responsible for this hypotensive action of ketanserin is at present controversiable[25, 26], but in anesthetized dogs, the hypotensive effect of intravenous ketanserin involves a centrally medicated inhibition of sympathetic vascular tone[27]. Similar conclusions were reached by Mccall and Schuette[28] from their studies in anesthetized cats.

The present study suggests the hypotension and bradycardia evoked by intraventricular 5-HT may be principally due to a presynaptic inhibitory effect of 5-HT on sympathetic nerve activity, probably at the adrenergic nerve terminals in brain. In support of this hypothesis, cyproheptadine, which is 5-HT_2 and histaminergic antagonists,[18] also inhibited significantly 5-HT-evoked cardiovascular effects.

Furthermore, alpha$_2$-adrenoceptor agonist, clonidine was demonstrated to inhibit the cardiovascular effect of intraventricular 5-HT. These results are consistent with the previous reports[29-31]. Therefore, it can be deduced from this result that as the inhibitory action by clonidine is generally mediated by postsynaptic α_2-adrenoceptors the inhibitory effects of 5-HT when injected into the lateral ventricle may be mediated by the activation of postsynaptic serotonergic receptors. Thus it is suggested that the ation of serotonergic neuron may be interdigitated with α_2-adrenoceptor activation in the brain. Generally, it is known that clonidine is an antihypertensive agent that, paradoxically, possesses primarily alpha$_2$-adrenergic agonistic property. However, clonidine owes its antihypertensive effect by a predominant action on the central nervous system, where it apparently produces a decrease in the sympathetic outfow from the CNS[32]. Peripherally, clonidine impairs adrenergic neurotransmission by activating inhibitory presynaptic alpha$_2$-adrenoceptors[33]. The fact that adrenergic β-receptor antagonist propranolol weakened greatly 5-HT-induced bradycardia suggests that intraventricular-5-HT may elicit a decrease in heart rate through adrenergic β-receptors in the brain as reported for 5-HT_1-like receptor agonist 8-OH-DPAT[34-36].

Since atropine and bilateral vagotomy did not alter the cardiovascular effects induced by intraventricular 5-HT, muscarinic receptor or vagal stimulation could be ruled out as the action site of 5-HT.

However, more experiments using various antagonists and agonists of subtype receptors of 5-HT are necessary in order to check the mechanisms of action of intraventricular 5-HT.

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