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On the Mechanism of Serotonin-Induced Dipsogenesis in the Rat[1]

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KIKTA, D. C., C. C. BARNEY, R. M. THREATTE, M. J. FREGLY, N. E. ROWLAND AND J. E. GREENLEAF. *On the mechanism of serotonin-induced dipsogenesis in the rat.* PHARMACOL BIOCHEM BEHAV 19(3) 519–525, 1983.—Subcutaneous administration of *l*-5-hydroxytryptophan (5-HTP), the precursor of serotonin, to female rats induces copious drinking accompanied by activation of the renin-angiotensin system. Neither a reduction in blood pressure nor body temperature accompanied administration of 5-HTP. The objective of the present study was to determine whether serotonin-induced dipsogenesis, like that of 5-HTP, is mediated via the renin-angiotensin system. Serotonin (2 mg/kg, SC)-induced drinking was inhibited by the dopaminergic antagonist, haloperidol (150 μg/kg, IP), which also inhibits angiotensin II-induced drinking. Both captopril (35 mg/kg, IP), an angiotensin converting enzyme inhibitor, and propranolol (6 mg/kg, IP), a β-adrenergic antagonist, blocked serotonin-induced dipsogenesis. The α_2-adrenergic agonist, clonidine (6.25 μg/kg, SC), which suppresses renin release from the kidney, attenuated serotonin-induced water intake. The dipsogenic responses to submaximal concentrations of both serotonin (1 mg/kg, SC) and isoproterenol (8 μg/kg, SC) were additive rather than interactive suggesting that similar pathways mediate both responses. The serotonergic receptor antagonist, methysergide (3 mg/kg, IP), inhibited serotonin-induced drinking but had no effect on isoproterenol (25 μg/kg, SC)-induced dipsogenesis. However, neither serotonin (2 mg/kg, SC) nor isoproterenol (25 μg/kg, SC)-induced drinking was inhibited by cinanserin (25 μg/kg, IP). These data indicate that serotonin induces drinking in rats via the renin-angiotensin system. However, the results of the studies using methysergide suggest that serotonin appears to act at a point prior to activation of β-adrenoceptors in the pathway leading to release of renin from the kidneys.

Serotonin Water intake Renin-angiotensin system Captopril Propranolol Clonidine Isoproterenol Methysergide Cinanserin

PREVIOUS studies from this laboratory have shown that 5-hydroxytryptophan (5-HTP), the immediate precursor of serotonin, is a potent dipsogen when administered peripherally to rats [12, 18, 29]. The dipsogenic response to 5-HTP is inhibited by the peripheral decarboxylase inhibitor, carbidopa; by the dopaminergic antagonists, haloperidol and spiperone; by the β-adrenergic antagonist, propranolol, by the angiotensin I converting enzyme inhibitor, captopril, and by a peripheral serotonin receptor antagonist, methysergide [18,29]. The dipsogenic effect of 5-HTP is accompanied by an increase in plasma renin activity, but no significant change in either blood pressure or body temperature [3]. Attenuation of the dipsogenic response to 5-HTP by a peripheral decarboxylase inhibitor and a serotonin receptor antagonist suggests that it must be converted to serotonin peripherally to induce drinking. The results further suggest that the newly formed serotonin activates the renin-angiotensin system since the dipsogenic response to 5-HTP could be inhibited by propranolol and captopril and an increase in plasma renin activity accompanied its administration. Serotonin is known both to stimulate drinking and to increase plasma renin activity in rats [3, 21, 22] but the latter has been attributed to a reduction in blood pressure which also accompanies its administration. A fundamental difference between the responses to peripheral administration of 5-HTP and serotonin to rats is that blood pressure failed to change in the case of the former and decreased in the case of the latter [3].

The objective of the present study was to assess more thoroughly the dependence of the dipsogenic response to serotonin on the renin-angiotensin system. To this end, the effects of the dopaminergic receptor antagonist, haloperidol; the renin-angiotensin system antagonists, propranolol, captopril, and clonidine; and the serotonin receptor antagonist,

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cinanserin, on serotonin-induced thirst were studied in rats. In addition, both the interaction between serotonin and isoproterenol, a β-adrenoceptor agonist, on drinking and the effect of methysergide and cinanserin on the dipsogenic response to isoproterenol were studied. The results indicate that serotonin, like 5-HTP, induces drinking in rats via the renin-angiotensin system. However, serotonin appears to act at some step prior to activation of the β-adrenoceptors in the kidneys.

METHOD

A total of sixty-eight female rats of the Blue Spruce Farms (Hooded) strain were used for all the experiments described here. Forty of the rats weighing 230 to 330 g, were used for the first 4 experiments. The remaining rats, weighing 270 to 320 g, were used for Experiments 5, 6 and 7. The rats were housed 4 per cage in a room maintained at 24± 1°C and illuminated from 7 a.m. to 7 p.m. All rats were provided with Purina Laboratory Chow and tap water ad lib prior to all experiments.

For each experiment, 24 of the rats were divided randomly into 4 groups of 6 each. At least 7 days were allowed between experiments. One hr prior to the beginning of an experiment, the 24 rats were weighed and placed in individual stainless steel metabolism cages equipped with water bottles which consisted of infant nursing bottles with cast bronze spouts as described by Lazarow [19]. The temperature of the water was 24°C. Food was not available during the experiments. All experiments were begun between 9 and 10 a.m. All compounds tested were dissolved in saline (except captopril, which was dissolved in double-distilled water) to give 1 ml/kg of body weight. Concentrations of compounds tested are not expressed as the base compound.

Although water intake has been reported to be influenced by the phase of the estrus cycle of female rats [8], a recent study from this laboratory has shown that this effect can be masked by a moderate dose of isoproterenol [13]. Hence, the use of female rats in tests of water intake is justified under these conditions and when randomization of both treatment and animals is carried out, as it was in the present studies.

Experiment 1: Effect of Haloperidol on Serotonin-Induced Water Intake

The 4 groups of rats used for this experiment were treated as follows: Group 1 (control) received isotonic saline (1 ml/kg, IP) followed by isotonic saline (1 ml/kg, SC) 1 hr later. Group 2 received haloperidol (150 μg/kg, IP) followed by isotonic saline SC 1 hr later. Group 3 received isotonic saline IP followed by serotonin (2 mg/kg, SC) 1 hr later. Group 4 received haloperidol (150 μg/kg, IP) followed by serotonin (2 mg/kg, SC) 1 hr later. The water bottles were weighed prior to the second administration of drug and returned to the metabolism cages immediately following the second injection.

Experiment 2: Effect of Captopril on Serotonin-Induced Water Intake

The 4 groups of rats used for this experiment were treated as follows: Group 1 (control) received double-distilled water (1 ml/kg, IP) followed by isotonic saline (1 ml/kg, SC) 15 min later. Group 2 received captopril (35 mg/kg, IP) followed by isotonic saline 15 min later. Group 3 received double-distilled water followed by serotonin (2 mg/kg, SC) 15 min later. Group 4 received captopril (35 mg/kg, IP) followed by serotonin (2 mg/kg, SC) 15 min later. Water intake was measured as described for Experiment 1.

Experiment 3: Effect of Propranolol on Serotonin-Induced Water Intake

The 4 groups of rats used for this experiment were treated as follows: Group 1 (control) received isotonic saline (1 ml/kg, IP) followed by isotonic saline (1 ml/kg, SC) 30 min later. Group 2 received propranolol (6 mg/kg, IP) followed by isotonic saline (1 ml/kg, SC) 30 min later. Group 3 received isotonic saline (1 ml/kg, IP) followed by serotonin (2 mg/kg, SC) 30 min later. Group 4 received propranolol (6 mg/kg, IP) followed by serotonin (2 mg/kg, SC) 30 min later. Water intake was measured as described for Experiment 1.

Experiment 4: Effect of Clonidine on Serotonin-Induced Water Intake

The 4 groups of rats used for this experiment were treated as follows: Group 1 (control) received isotonic saline (1 ml/kg, SC) followed by isotonic saline (1 ml/kg, SC) 15 min later. Group 2 received clonidine (6.25 μg/kg, SC) followed by isotonic saline 15 min later. Group 3 received isotonic saline followed by serotonin (2 mg/kg, SC) 15 min later. Group 4 received clonidine (6.25 μg/kg, SC) followed by serotonin (2 mg/kg, SC) 15 min later. Water intake was measured as described for Experiment 1.

Experiment 5: Interaction Between Serotonin and Isoproterenol on Induction of Drinking

The 4 groups of rats used for this experiment were treated as follows: Group 1 (control) received isotonic saline (1 ml/kg, SC) followed by isotonic saline (1 ml/kg, SC) 30 min later. Group 2 received serotonin (1 mg/kg, SC) followed by isotonic saline 30 min later. Group 3 received isotonic saline followed by isoproterenol (8 μg/kg, SC) 30 min later. Group 4 received serotonin (1 mg/kg, SC) followed by isoproterenol (8 μg/kg, SC) 30 min later. Water intake was measured as described for Experiment 1, except the third hr measurement was omitted. Serotonin was administered 30 min prior to isoproterenol because the onset of drinking following serotonin [18] is slower than that for isoproterenol [4].

Experiment 6: Effect of Methysergide on Isoproterenol-Induced Water Intake

The 4 groups of rats used in this experiment were treated as follows: Group 1 (control) received isotonic saline (1 ml/kg, IP) followed by isotonic saline (1 ml/kg, SC) 15 min later. Group 2 received methysergide (3 mg/kg, IP) followed by isotonic saline (1 ml/kg, SC) 15 min later. Group 3 received isotonic saline (1 ml/kg, IP) followed by isoproterenol (25 μg/kg, SC) 15 min later. Group 4 received methysergide (3 mg/kg, IP) followed by isoproterenol (25 μg/kg, SC) 15 min later. Water intake was measured as described for Experiment 1, except the third hr measurement was omitted.

Experiment 7: Effect of Cinanserin on Isoproterenol- and Serotonin-Induced Water Intake

In the first part of this experiment, the 4 groups were treated as follows: Group 1 (control) received isotonic saline (1 ml/kg, SC) followed by isotonic saline (1 ml/kg, IP) 15 min later. Group 2 received cinanserin (25 mg/kg, IP) followed by isotonic saline (1 ml/kg, SC) 15 min later. Group 3 received

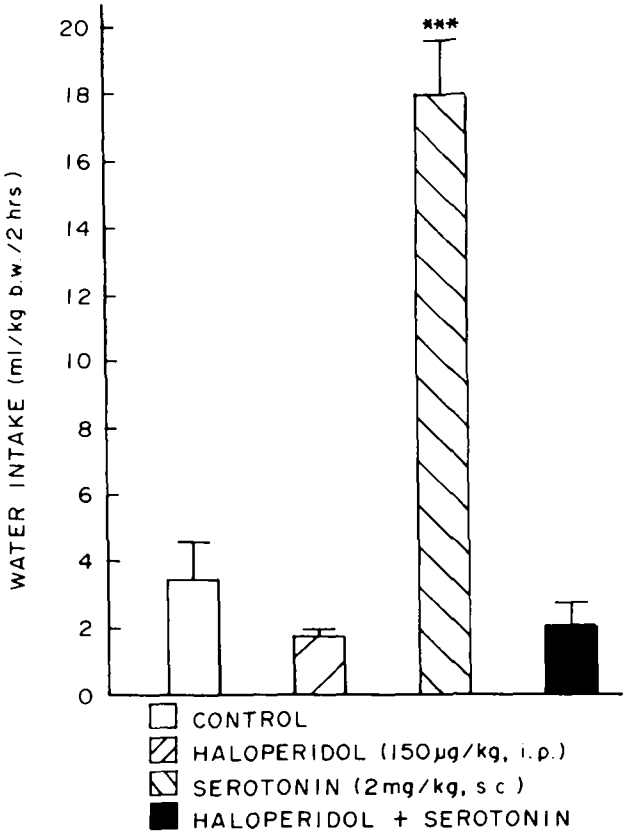

FIG. 1. Effect of pretreatment for 1 hr with haloperidol (150 μg/kg, IP) on the dipsogenic response to serotonin (2 mg/kg, SC). Cumulative water intake during the first 2 hr after administration of the dipsogen is shown. Significant difference from control is denoted: ***$p<0.001$.

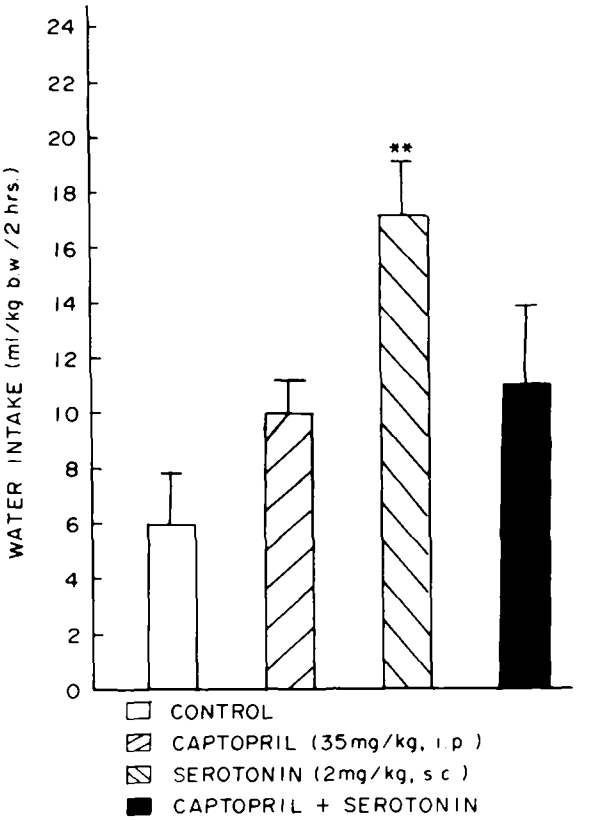

FIG. 2. Effect of pretreatment for 15 min with captopril (35 mg/kg, IP) on the dipsogenic response to serotonin (2 mg/kg, SC). Cumulative water intake during the first 2 hr after administration of the dipsogen is shown. Significant difference from control is denoted: **$p<0.01$.

isotonic saline (1 ml/kg, IP) followed by isoproterenol (25 μg/kg, SC) 15 min later. Group 4 received cinanserin (25 mg/kg, IP) followed by isoproterenol (25 μg/kg, SC) 15 min later. Water intake was measured as described for Experiment 1, except the third hr measurement was omitted.

The second part of the experiment was identical to the first, except that serotonin (2 mg/kg, SC) was used instead of isoproterenol as the dipsogen.

Drugs

The 5-hydroxytryptamine creatinine sulfate complex (serotonin) was purchased from Sigma Chemical Co., St. Louis, MO. The DL-propranolol hydrochloride (Inderal®) was purchased from Ayerst Laboratories, Inc., New York, NY. The captopril (SQ 14,225) was kindly provided by Dr. Z. Horovitz, and the cinanserin (SQ 10,643) by Dr. S. J. Lucania of Squibb Research Institute, Princeton, NJ. The haloperidol (Haldol®) was obtained from McNeil Laboratories, Ft. Washington, PA. The clonidine was a gift from Dr. P. B. Steward of Boehringer Ingelheim, LTD., Ridgefield, CT. The DL-isoproterenol hydrochlordie (Isuprel®) was purchased from Breon Laboratories, Inc., New York, NY. The methysergide maleate was a gift from Dr. C. E. Eden of Sandoz Pharmaceuticals, East Hanover, NJ.

Analysis of Data

All data are shown as the mean and standard error. The data from each experiment were analyzed statistically by means of an analysis of variance for a factorially designed experiment [5]. Differences between group means were analyzed statistically by means of a two-tailed t-test using the pooled variance from the analysis of variance [5]. A probability of less than 0.05 was considered significant.

RESULTS

Experiment 1

Administration of serotonin was associated with a significant ($p<0.01$) increase in water intake within 2 hr (Fig. 1), as described previously [18]. The dipsogenic response to serotonin was inhibited by prior administration of haloperidol (Fig. 1). Similar results were obtained at 1 and 3 hr after administration of serotonin. Haloperidol, alone, had no effect on water intake at either 1, 2 or 3 hr after administration. Using a 2-way analysis of variance, a significant ($p<0.01$) interaction between haloperidol and serotonin on water intake was observed at all 3 time periods.

Experiment 2

Administration of captopril prevented the 2 hr serotonin-induced water intake (Fig. 2) but, when administered alone, had no effect on water intake at all times measured. Two-way analysis of variance indicated a significant ($p<0.05$) interaction between captopril and serotonin on dipsogenesis.

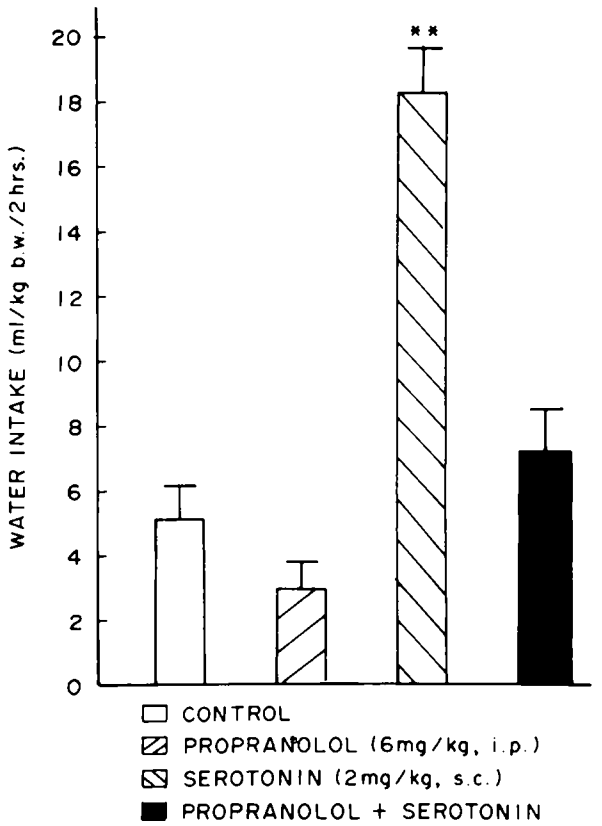

FIG. 3. Effect of pretreatment for 30 min with propranolol (6 mg/kg, IP) on the dipsogenic response to serotonin (2 mg/kg, SC). Cumulative water intake during the first 2 hr after administration of the dipsogen is shown. Significant difference from control is denoted: $^{**}p<0.01$.

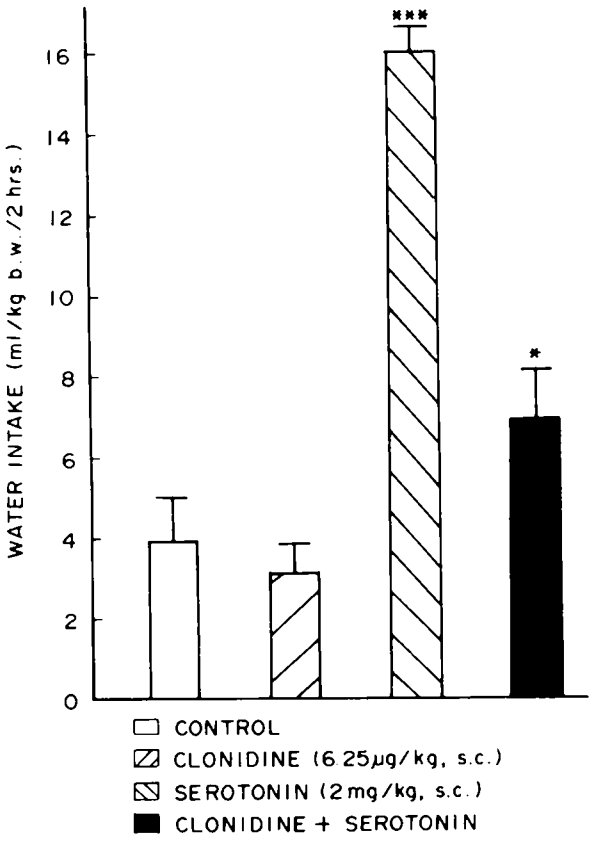

FIG. 4. Effect of pretreatment for 15 min with clonidine (6.25 μg/kg, SC) on the dipsogenic response to serotonin (2 mg/kg, SC). Cumulative water intake during the first 2 hr after administration of the dipsogen is shown. Significant differences from control are denoted: $^{*}p<0.05$, $^{***}p<0.001$.

Similar results were obtained at 1 and 3 hr after administration of serotonin.

Experiment 3

Propranolol inhibited the 2 hr serotonin-induced dipsogenic response (Fig. 3) but, when administered alone, had no effect on water intake at all times measured. Two-way analysis of variance revealed a significant ($p<0.01$) interaction between propranolol and serotonin on water intake in rats. Similar results were obtained 1 and 3 hr after administration of serotonin.

Experiment 4

Clonidine attenuated significantly ($p<0.01$), but did not abolish completely, the 2 hr serotonin-induced drinking response (Fig. 4). When administered alone, clonidine had no effect on water intake (Fig. 4). Similar results were obtained at 1 and 3 hr after administration of serotonin. Two-way analysis of variance revealed a significant interaction between clonidine and serotonin on water intake after 1 ($p<0.01$), 2 ($p<0.01$), and 3 ($p<0.05$) hr.

Experiment 5

Submaximal concentrations of the dipsogenic agents, serotonin [16] and isoproterenol [18], were used in this experiment in order to test whether water intake of rats administered both dipsogens would be either additive or interactive. Both the groups of rats receiving serotonin and those receiving isoproterenol showed significant ($p<0.01$) increases in water intake after 2 hr (Fig. 5). Rats receiving both dipsogens showed no interaction between the two compounds on water intake, but rather a dipsogenic response approximately equal to the sum of the 2 individual responses [(serotonin-treated minus control) plus isoproterenol-treated]. Similar responses were obtained 1 hr after administration of the dipsogenic agents.

Experiment 6

Methysergide had no effect either on basal water intake or on the 2 hr dipsogenic response to isoproterenol (Fig. 6). Similar results were obtained 1 hr after administration of isoproterenol. Thus, there was no interaction between methysergide and isoproterenol on water intake in rats at both times measured.

Experiment 7

Cinanserin (25 mg/kg, IP) had no effect either on basal or on isoproterenol-stimulated water intake (Table 1).

Cinanserin also had no significant effect on either 1 or 2 hr water intakes after serotonin, although there is a hint of a reduction after 2 hr (Table 1). In a follow-up experiment, the data from which are not reported, we found that a higher

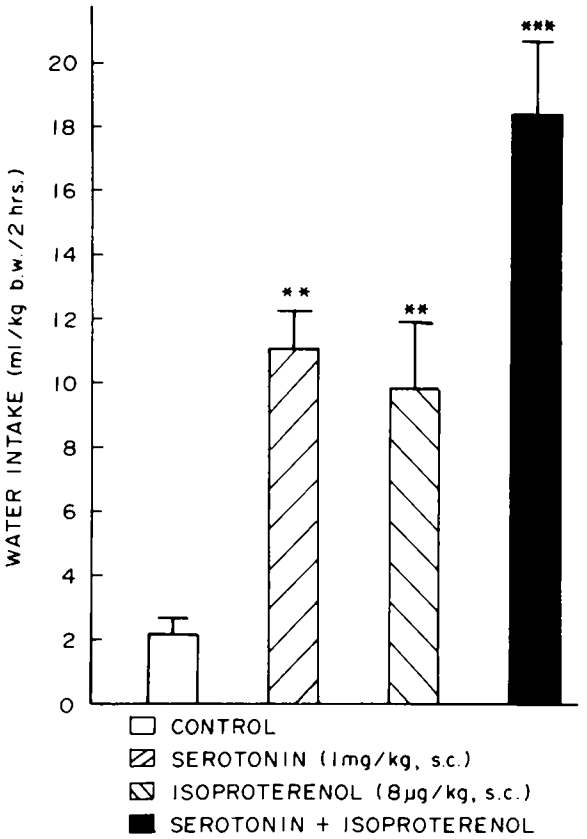

FIG. 5. Interaction between serotonin (1 mg/kg, SC) and isoproterenol (8 μg/kg, SC) on water intake. Cumulative water intake during the first 2 hr after administration of the dipsogens is shown. Significant differences from control are denoted: $^{**}p<0.01$, $^{***}p<0.001$.

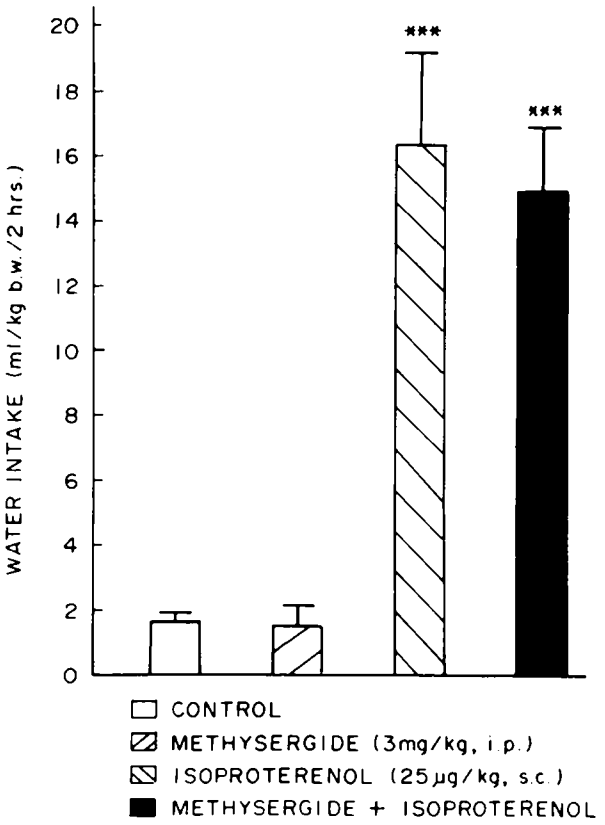

FIG. 6. Effect of pretreatment for 15 min with methysergide (3 mg/kg, IP) on the dipsogenic response to isoproterenol (25 μg/kg, SC). Cumulative water intake during the first 2 hr after administration of the dipsogen is shown. Significant differences from control are denoted: $^{***}p<0.001$.

dose of cinanserin (75 mg/kg, IP) produced apparent motor seizures which were not overcome by subsequent administration of serotonin (2 mg/kg, SC) or 5 HTP (25 mg/kg, SC). In this case the observed reduction of water intake was obviously a nonspecific effect of cinanserin.

DISCUSSION

L-5-Hydroxytryptophan, the immediate precursor of serotonin [20], is a potent dipsogenic agent in rats [12,29] only after peripheral conversion to serotonin [18]. The mechanism by which 5-HTP induces drinking in rats [3,29] is believed to be by way of the renin-angiotensin system [9, 11, 23]. Therefore, the objective of the present study was to assess the dependence of the dipsogenic response to serotonin on the renin-angiotensin system.

The dipsogenic response to serotonin was inhibited by the dopaminergic antagonist, haloperidol (Fig. 1), as was the response to 5-HTP tested in an earlier study [29]. Although haloperidol, at high concentrations, inhibits slightly central noradrenergic receptors, it is a more potent inhibitor of central dopaminergic receptors [2]. Thus, serotonin-induced dipsogenesis, like angiotensin II-induced dipsogenesis [9,10], appears to be mediated through central dopaminergic neurons. Drinking induced by central administration of carbachol, a cholinergic agonist, is unaffected by central administration of haloperidol [9,10]. Therefore, the inhibition of both angiotensin II- and serotonin-induced dipsogenesis by haloperidol suggests that both compounds initiate drinking in the rat via the same pathway.

Captopril, an angiotensin converting enzyme inhibitor, blocked the serotonin-induced water intake (Fig. 2). Similarly, drinking in response to both 5-HTP [29] and isoproterenol [17], but not to angiotensin II [17], is inhibited by captopril. In addition, propranolol, a β-adrenergic antagonist which inhibits both isoproterenol- [4,31] and 5-HTP- [21,29] induced drinking and increases in plasma renin activity, blocked serotonin-induced water intake (Fig. 3). Clonidine, an α_2-adrenoceptor agonist which suppresses renin release from the kidney in rats [25], also attenuated the dipsogenic response to serotonin (Fig. 4). Although there is some controversy as to whether clonidine depresses renin release via a central [28], as opposed to a peripheral [25,32] action, the fact remains that it inhibits both renin release and serotonin-induced drinking in rats. In addition, clonidine has been reported to attenuate angiotensin II-induced drinking [15]. Hence, clonidine may have antidipsogenic actions in addition to inhibition of renin release.

Administration of serotonin to rats is followed by a transient rise in plasma renin activity [3,21]. Chronic treatment of rats with desoxycorticosterone and isotonic saline as the sole drinking fluid is associated with both decreased levels of plasma renin activity [26] and attenuated dipsogenic responses to isoproterenol [14]. 5-HTP and serotonin (personal

TABLE 1

EFFECT OF CINANSERIN ON WATER INTAKE INDUCED BY ADMINISTRATION OF ISOPROTERENOL AND SEROTONIN

Treatment	Cumulative Water Intake (ml/kg b.w.) during: 1 hr	2 hr
Study 1		
Control	1.5 ± 0.5*	2.9 ± 0.6
Cinanserin (25 mg/kg, IP)	1.1 ± 0.2	2.6 ± 0.9
Isoproterenol (25 μg/kg, SC)	12.2 ± 0.9	15.1 ± 2.2
Cinanserin + Isoproterenol	14.6 ± 2.8	17.7 ± 1.6
Two-Way Analysis of Variance:		
Cinanserin	NS	NS
Isoproterenol	<0.01	<0.01
Interaction	NS	NS
Study 2		
Control	3.6 ± 0.7	4.2 ± 0.7
Cinanserin (25 mg/kg, IP)	4.2 ± 1.6	6.2 ± 3.0
Serotonin (2 mg/kg, SC)	9.5 ± 1.2	18.6 ± 1.1
Cinanserin + Serotonin	10.9 ± 1.7	14.7 ± 1.9
Two-Way Analysis of Variance:		
Cinanserin	NS	NS
Serotonin	<0.01	<0.01
Interaction	NS	NS

*One standard error of the mean.

communication, D. Fater) while angiotensin II-induced drinking is enhanced [14]. Therefore, the preponderance of the data presented here indicates that serotonin, like 5-HTP [29] and isoproterenol [22], probably induces drinking in rats via release of renin from the kindeys and subsequent formation of the dipsogen, angiotensin II [23].

The mechanism by which serotonin induces release of renin from the kidneys is not known. There was no interaction between serotonin and isoproterenol on the dipsogenic response when rats received both compounds at submaximal doses suggesting that arousal of drinking occurs by a similar mechanism for both compounds (Fig. 5). In fact, the volumes of water ingested by rats administered the 2 compounds was approximately equal to the sum of the dipsogenic responses to the 2 compounds when administered separately. Furthermore, the dipsogenic response to isoproterenol was unaffected by pretreatment with either methysergide (Fig. 6) or cinanserin (Table 1), both of which have been reported to block the central excitatory effects of serotonin, with methysergide being 10 times as potent on a mg basis [24]. We have previously reported that methysergide blocks serotonin-induced drinking in rats [18], suggesting that sertonin acts as a point prior to activation of the renal β-adrenoceptors and the release of renin. We do not fully understand the present failure to block serotonin-induced drinking with cinanserin. It is possible that a block would have been obtained at a dose somewhere between 25 and 75 mg/kg but the interpretation of such a result would be confounded by possible motor effects of the drug. Alternately, serotonin may act at a peripheral receptor that is not anatgonized by cinanserin.

Previous studies from this laboratory [3,18] showed that serotonin acts peripherally to induce both dipsogenesis and an increase in plasma renin activity in the rat. These findings are different from those for the dog [16,33] where serotonin acts centrally to increase both drinking and plasma renin activity. Van de Kar *et al.* [30] have suggested that the rat may be similar to the dog in this respect in that parallel decreases in both hypothalamic serotonin content and plasma renin activity occurred following central administration of several serotonin-depleting agents to rats. However, adrenal serotonin content was also reduced in their rats and could have infuenced plasma renin activity.

The present study does not elucidate the peripheral site at which serotonin acts to induce renin release. Although administration of serotonin reduces both systemic blood pressure and body temperature which could contribute to the release of renin, Barney *et al.* [3] found that neither action is responsible for the increase in renin release and subsequent dipsogenesis induced by the precursor of serotonin, 5-hdyroxytryptophan. Serotonin is believed to stimulate release of catecholamines from the adrenal medulla [6,27]. Therefore, an increase in circulating catecholamines may result in enhanced activation of the renal β-adrenoceptors and thus an increased release of renin.

Administration of serotonin is also associated with profound renal vasoconstriction [1] which results in decreased renal blood flow [1,7] even at concentrations which have no effect on systemic blood pressure [7]. A reduction in renal perfusion pressure is a potent stimulus for renin release from the juxtaglomerular cells. Thus, the possibility that serotonin may act on renal adrenergic nerve endings to release catecholamines which, in turn, stimulate the renal β-adrenoceptors should also be considered.

Data from the present study confirm the hypothesis that serotonin induces dipsogenesis in the rat via activation of the renin-angiotensin system. However, serotonin appears to act at some step prior to the activation of the β-adrenoceptors in the kidneys. Additional studies will be required to determine the site or sites at which serotonin acts to induce the release of renin in the rat.

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