Pharmacology Biochemistry & Behavior, Vol. 14, pp. 385–391. Printed in the U.S.A.

L-5-Hydroxytryptophan-Induced Drinking in Rats: Possible Mechanisms for Induction[1]

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Received 15 August 1980

THREATTE, R. M., M. J. FREGLY, T. M. CONNOR AND D. C. KIKTA. *L-5-Hydroxytryptophan-induced drinking in rats: Possible mechanisms for induction.* PHARMAC. BIOCHEM. BEHAV. **14**(3) 385–391, 1981.—Administration of L-5-hydroxytryptophan (25 mg/kg body weight, SC) to female rats resulted in copious drinking. The dipsogenic response to administration of L-5-hydroxytryptophan (5-HTP) was blocked by propranolol (6 mg/kg body weight, IP), a β-adrenergic antagonist, and captopril (35 mg/kg body weight, IP), an angiotensin converting enzyme inhibitor. In addition, clonidine (12.5 and 25 μg/kg body weight, IP), a central α-adrenergic agonist known to inhibit renin release, attenuated drinking during 1, 2 and 3 hours after 5-HTP was administered. These results suggest that 5-HTP-induced drinking is mediated by way of the renin-angiotensin system. Haloperidol (150 μg/kg body weight, IP), a dopaminergic antagonist, also attenuated the dipsogenic response to administration of 5-HTP. In addition, incremental reductions in 5-HTP-induced drinking with increasing doses of spiperone (37.5 to 150 μg/kg body weight, IP), a more potent dopaminergic antagonist, were demonstrated. Thus, the dipsogenic response to administration of 5-HTP to rats is dependent on both the renin-angiotensin system and an intact dopaminergic pathway.

Drinking Renin-angiotensin system Captopril Propranolol Haloperidol Spiperone Clonidine

ACUTE subcutaneous administration of graded doses of L-5-hydroxytryptophan (5-HTP), the precursor of serotonin, to rats was accompanied by graded increases in water intake [11]. Other tryptophan derivatives, including *l*-tryptophan, d-tryptophan and acetyltryptophan, failed to stimulate drinking in rats at a dose at which 5-HTP was maximally effective (25 mg/kg body weight, SC).

Since activation of the renin-angiotensin system is well known to initiate drinking in rats, an objective of the studies described below was to determine whether 5-HTP-induced drinking might be mediated by way of the renin-angiotensin system [6–8]. Present experimental evidence also suggests that the drinking response of rats to central administration of angiotensin II is mediated by dopaminergic pathways [7,9]. Hence, an additional objective of these studies was to determine whether administration of dopaminergic antagonists could inhibit the drinking response to acute administration of 5-HTP.

METHOD

Experiment 1: Effect of Acute Administration of Propranolol on 5-HTP-Induced Drinking in Female Rats

Twenty-four female rats of the Blue Spruce Farms (Sprague-Dawley) strain weighing 230 to 250 g were used. The rats were housed 3 to a cage in a room maintained at 26 ± 1°C and illuminated from 7 a.m. to 7 p.m. The rats were given Purina Laboratory Chow and tap water ad lib. All experiments were begun between 9 and 10 a.m.

The rats were divided into 4 groups with 6 animals in each group. All animals were weighed and placed in individual stainless steel metabolic cages and allowed to become accustomed to their cages for 1 hour prior to the study. During this time water, but not food, was available. Propranolol (Inderal®, Ayerst laboratories), a β-adrenergic antagonist, was administered IP at a dose of 6 mg/kg body weight to 12 rats 15 minutes prior to the beginning of the experiment. The other 12 animals received the vehicle. Fifteen minutes later, 6 rats of the propranolol-treated group and 6 rats which received the vehicle were given 25 mg 5-HTP/kg body weight, SC (Calbiochem, San Diego, CA). The 5-HTP was solubilized in isotonic saline. The remaining 6 propranolol- and 6 distilled water-treated rats were administered saline (1 ml/kg body weight, SC). Each rat was then given a preweighed water bottle which consisted of an infant nursing bottle with a cast bronze spout as described by Lazarow [19]. Water intake was measured during the first, second and third hours after administration of either 5-HTP or its vehi-

[1]Supported by grant HL-14526-08 from the National Heart, Lung and Blood Institute.
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[4]Post doctoral Trainee supported by Institutional Endocrine Training Grant AM-07164-04 from NIH.

cle. No food was available to the rats during the experiment. Data were analyzed statistically using a two way analysis of variance [3]. Comparison between individual groups was made by means of a t-test using the pooled variance from the analysis of variance [4].

Experiment 2. Effect of Acute Administration of Captopril on 5-HTP-Induced Drinking in Female Rats

The same 24 female rats used in Experiment 1 were also used in this study. The rats were housed and maintained prior to each study as described above. Twelve of the rats were administered the angiotensin converting enzyme inhibitor, captopril, at a dose of 35 mg/kg body weight, IP while the remaining animals received the vehicle, distilled water IP (1 ml/kg body weight). Fifteen minutes later, half of both the captopril- and distilled water-treated groups received a subcutaneous injection of 5-HTP (25 mg/kg body weight) solubilized in isotonic saline. The remaining 12 animals were administered isotonic saline (1 ml/kg body weight SC). Water intake was measured during the first half hour, hour and second hour after administration of either 5-HTP or its vehicle. Data were analyzed statistically as in Experiment 1. (Captopril was kindly provided by Dr. Z. Horowitz, Squibb Research Institute, Princeton, NJ 08540.)

Experiment 3. Effect of Graded Doses of Clonidine on Water Intake of Female Rats Administered 5-HTP

Twenty-four female rats of the Blue Spruce Farms (Sprague-Dawley) strain, weighing 250 to 290 g, were used in these studies. These animals were different from those used in Experiments 1 and 2 but were housed and maintained as described in Experiment 1. The experimental design for this study was the same as that used in Experiment 1.

The rats were divided into 4 groups with 6 rats per group. Twelve rats were administered the central α-adrenergic agonist, clonidine (25 μg/kg body weight, IP), and the remaining 12 animals received saline IP (1 ml/kg body weight) 15 minutes prior to beginning the study. One half of the clonidine-treated and one half of the saline-treated groups were injected SC with 25 mg 5-HTP/kg body weight, solubilized in saline. The remaining 12 animals were given isotonic saline (1 ml/kg body weight SC). Water intake was measured at hourly intervals for 3 hours. Data were analyzed statistically as described in Experiment 1. (Clonidine was kindly provided by Dr. P. B. Steward, Boehringer Ingelheim, Ltd., Ridgefield, CT 06877.)

One month later, the same animals were divided into 3 groups with 8 animals in each group. One group was administered 6.25 μg clonidine/kg body weight and another, administered 12.50 μg/kg body weight, IP. The remaining group was injected with isotonic saline (1 ml/kg body weight). Fifteen minutes later, all 24 rats were administered 5-HTP at a dose of 25 mg/kg body weight, SC. Water intake of each animal was measured at 1, 2 and 3 hours after administration of 5-HTP. A one way analysis of variance was performed to determine the effects of treatments [4]. Comparison between individual groups was made by means of a t-test using the pooled variance from the analysis of variance [4].

Experiment 4: Effect of Haloperidol and Spiperone on the Dipsogenic Response to 5-HTP in Female Rats

Twenty-four female rats of the Blue Spruce Farms strain weighing 240 to 280 g, housed and maintained as described previously, were used in these studies. These animals were not used in any of the studies described above. They were divided into 4 equal groups. Haloperidol (Haldol®, McNeil Lab., Ft. Washington, PA, 150 μg/kg body weight), a dopamine receptor blocker, was administered IP to 12 of the rats 1 hour prior to administration of 5-HTP. The other 12 rats were injected IP with the vehicle, saline (1 ml/kg body weight). 5-HTP (25 mg/kg body weight) was administered SC to 6 of the haloperidol- treated and 6 of the saline-treated groups at the beginning of the experiment. The remaining 6 rats from each group were administered isotonic saline (1 ml/kg body weight). Water intake by each rat was measured at hourly intervals for 3 hours. The data were analyzed statistically as in Experiment 1.

One month later, the same rats (260 to 300 g) were divided into 4 groups with 6 rats per group. Three of the 4 groups of animals received the dopamine receptor blocker, spiperone, dissolved in 0.50% lactic acid. Each group of rats was administered IP a different dose of spiperone one hour prior to the administration of 5-HTP. The doses of spiperone used were 37.5, 75, and 150 μg/kg body weight. The fourth group of rats was injected with the vehicle, lactic acid (1 ml/kg body weight). The experiment was initiated by the subcutaneous administration of 5-HTP to all groups at a dose of 25 mg/kg body weight. Water intake was measured at 1, 2 and 3 hours after administration of 5-HTP. The data were analyzed by one way analysis of variance and comparisons between groups were made with a t-test using the pooled variance from the analysis of variance [4]. (Spiperone was kindly provided by Dr. C. Kadzielawa, Dept. of Pharmacology and Therapeutics, Univ. of Florida.)

RESULTS

Experiment 1

The effect of propranolol (6 mg/kg body weight) alone, and in combination with 5-HTP, on water intake during the first, second and third hours after administration of 5-HTP is shown in Fig. 1. Administration of 5-HTP resulted in a significant increase in water intake ($p<0.01$) at all 3 periods as described previously [11]. Propranolol given alone had no effect on water intake but attenuated the dipsogenic effect of 5-HTP. A two way analysis of variance revealed a significant interaction between the effects of the 2 drugs on water intake at two ($p<0.05$) and three ($p<0.05$) hours after administration of 5-HTP.

Experiment 2

Captopril alone had no effect on water intake during any period while 5-HTP induced its characteristic dipsogenic effect (Table 1). Captopril prevented the dipsogenic response to 5-HTP. In addition, there was significant interaction between the effects of the 2 drugs at one-half ($p<0.05$), one, and two hours ($p<0.01$) after administration of 5-HTP.

Experiment 3

The highest dose of clonidine (25 μg/kg body weight) used in this study had no effect on water intake by itself at any period (Table 2). However, this dose prevented the dipsogenic effect of 5-HTP from being manifested. In addition, a significant interaction was observed between the effects of the 2 drugs at all periods.

The lowest dose of clonidine (6.25 μg/kg body weight) affected 5-HTP-induced drinking only during the first hour

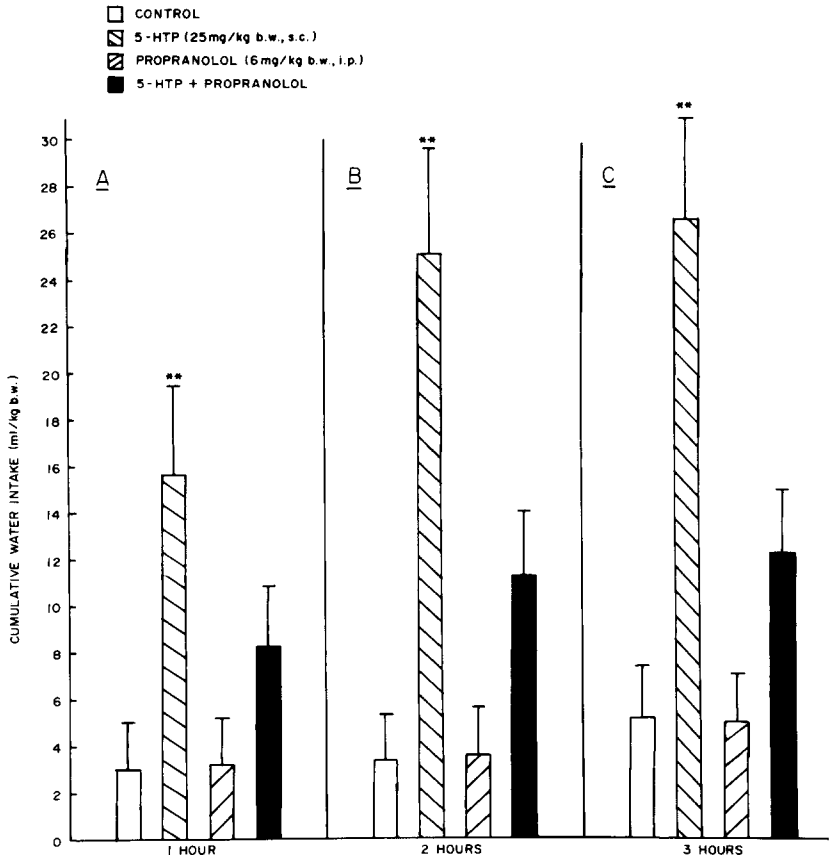

FIG. 1. Effect of the acute administration of propranolol, 6 mg/kg body weight, IP, on 5-HTP-induced drinking (25 mg/kg body weight, SC) in female rats. Propranolol (P) was administered 15 minutes prior to the administration of 5-HTP. The height of each bar represents the mean water intake of 6 rats. One S.E. is set off at each mean. Panels A, B, and C show accumulative mean intakes during the first, second and third hours of the experiment, respectively, **Significantly different from control ($p<0.01$).

after treatment (Fig. 2). An intermediate dose of clonidine (12.5 μg/kg body weight) significantly reduced 5-HTP-induced drinking at 1, 2 and 3 hours after the administration of 5-HTP ($p<0.01$).

Experiment 4

Haloperidol alone had no effect on water intake but attenuated the drinking response two and three hours after the administration of 5-HTP (Table 3). A two way analysis of variance indicated no significant interactions between the effects of the 2 drugs on water intake at any period.

Increasing doses of spiperone resulted in incremental reductions in drinking characteristically induced by the administration of 5-HTP alone (Fig. 3).

DISCUSSION

Administration of 5-HTP resulted in copious drinking in female rats. This confirms previous studies from this laboratory [11]. The dipsogenic response to 5-HTP was attenuated by administration of the β-adrenergic antagonist, propranolol (Fig. 1). Captopril, an angiotensin converting enzyme inhibitor, also attenuated 5-HTP-induced drinking (Table 1). These results are of interest when compared to previous studies in which isoproterenol was the dipsogenic agent [16–18, 20, 21]. The initiation of drinking by isoproterenol has been attributed to its ability to release renin via stimulation of β-adrenergic receptors leading ultimately to the formation of angiotensin II [1, 6–8, 10, 14]. Since 5-HTP-induced drinking is blocked by administration of either propranolol or captopril, it appears that the dipsogenic effect of 5-HTP may be mediated by way of the renin-angiotensin system. Support for this hypothesis also derives from previous findings that 5-HTP increases renin secretion when injected into phenobarbital-anesthetized dogs [25]. In addition, preliminary studies from this laboratory confirm that the plasma renin activity of rats measured one hour after administration of 25 mg 5-HTP/kg body weight, IP was elevated more than 9 fold above that of controls administered 1 ml isotonic saline/kg body weight, IP.

Clonidine, an α-adrenergic agonist which penetrates brain tissue [15], attenuated the drinking response of rats administered 5-HTP (Table 2). There is evidence to demonstrate that

TABLE 1

EFFECT OF CAPTOPRIL* ON 5-HTP-INDUCED DRINKING IN FEMALE RATS

Experimental Group	No. of Rats	Mean Body Weight (g)	Cumulative Water Intake (ml/kg body weight) during 0.5	1.0	2.0 hr
Control	6	216 ± 6†	0.3 ± 0.2	0.6 ± 0.4	6.9 ± 4.6
5-HTP (25 mg/kg body weight, SC)	6	208 ± 4	9.5 ± 3.3‡	12.8 ± 4.1‡	26.8 ± 2.5‡
Captopril (35 mg/kg body weight, IP)	6	221 ± 8	0.0 ± 0.0	0.9 ± 0.4	2.7 ± 1.3
5-HTP + Captopril	6	212 ± 3	0.2 ± 0.2¶	0.5 ± 0.3¶	5.7 ± 1.5¶
2 Way Analysis of Variance					
5-HTP			<0.01	<0.05	<0.005
Captopril			<0.01	<0.05	<0.005
Interaction			<0.05	<0.01	<0.01

*Captopril administered 15 min prior to administration of 5-HTP.
†One standard error of the mean.
‡Significantly different from controls ($p<0.01$).
¶Significantly different from 5-HTP alone ($p<0.01$).

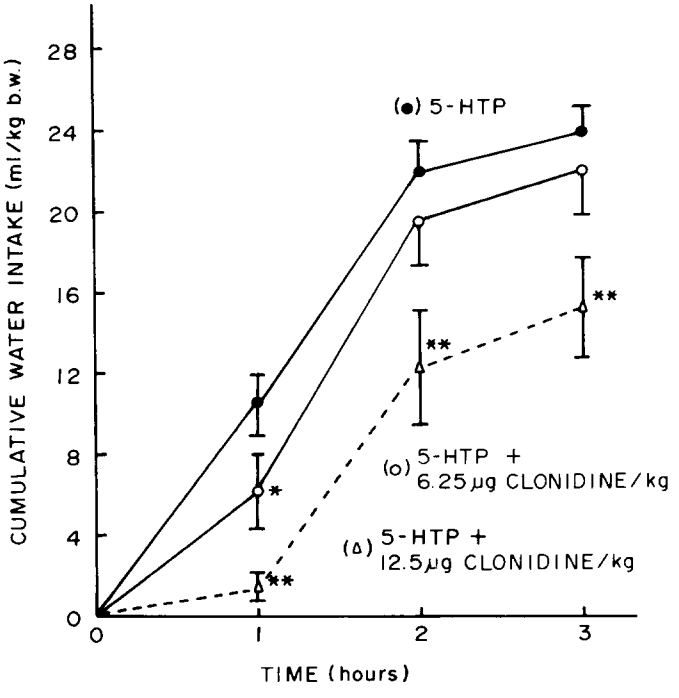

FIG. 2. The effect of 0 (○), 6.25 (0), and 12.5 (△) μg clonidine/kg, IP on the accumulative water intake of female rats at 1, 2, and 3 hours after subcutaneous administration of 5-HTP. Rats were administered clonidine, 15 min prior to 5-HTP. Each point is the mean of 6 rats. One S.E. is set off at each mean. * Significantly different from 5-HTP alone ($p<0.05$). ** Significantly different from 5-HTP alone ($p<0.01$).

clonidine depresses renin secretion via a central action which is mediated by the renal nerves [23]. The decrease in renin release is mediated via presynaptic α-adrenergic neurons which inhibit the release of catecholamines from renal nerve endings terminating on intrarenal β-adrenergic receptors [13]. It has been suggested that serotonergic neurons in the brain are part of a neural pathway with an excitatory effect on renin secretion [13]. Since 5-HTP increases renin secretion and is the precursor of serotonin, the possibility arises that the effect of 5-HTP may be mediated through its conversion to serotonin. There is evidence from previous work that clonidine acts by way of α-adrenergic neurons to inhibit serotonergic neurons which, in turn, leads to a reduction in renin secretion [24]. Therefore, clonidine may exert its inhibitory effect on 5-HTP-induced drinking in rats through this pathway. However, clonidine prevented drinking in response to administration of isoproterenol as well [12]. Thus, the possibility also arises that clonidine inhibits both isoproterenol- and 5-HTP-induced drinking via stimulation of α-adrenergic receptors within the kidney or activation of α-adrenergic receptors at a central site.

The dipsogenesis accompanying administration of 5-HTP was markedly reduced by prior treatment with the dopamine antagonist, haloperidol (Table 3), which has some blocking action on noradrenergic neurons as well. It is, however, considered to be more potent as a dopamine antagonist [2]. Another more specific dopamine antagonist [3], spiperone, gave similiar results (Fig. 3). Spiperone is 5 to 10 times more active than haloperidol as a neuroleptic and its affinity for dopamine receptors in brain tissue is much more potent than haloperidol [3]. These data suggest that dopaminergic path-

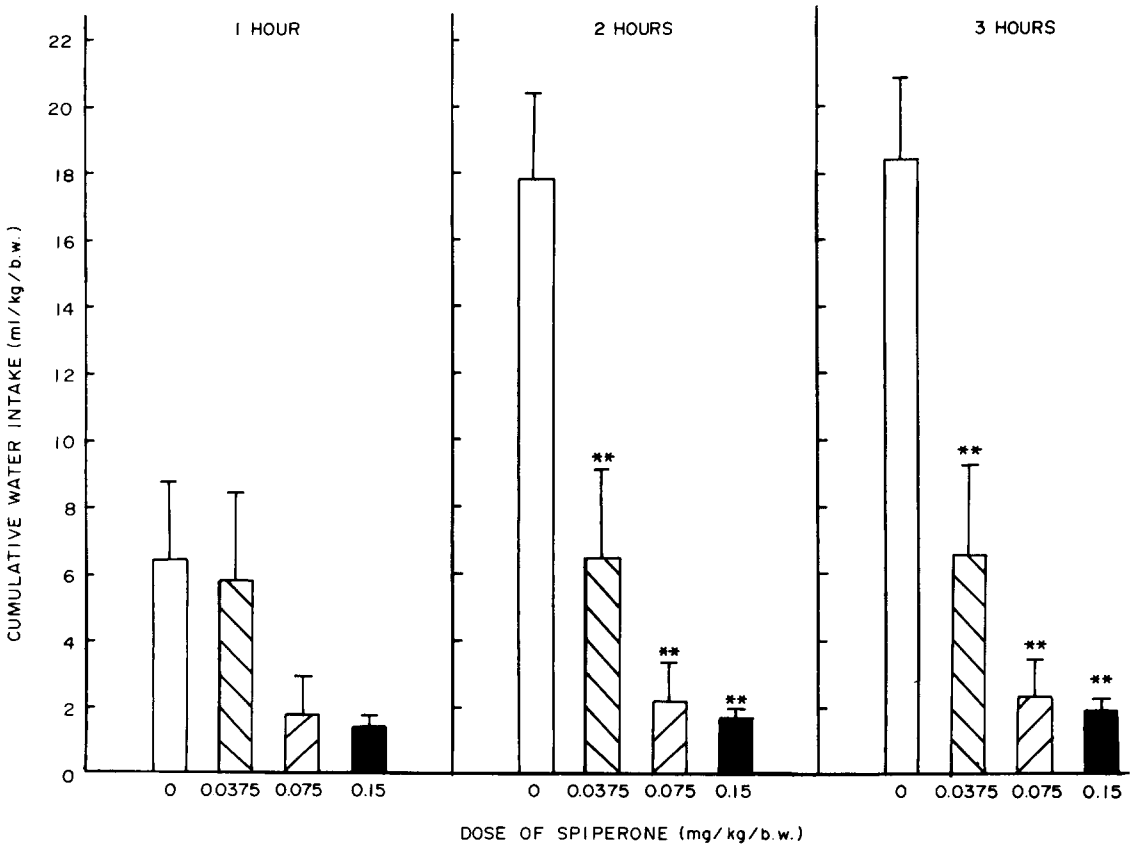

FIG. 3. Effect of 0, 0.0375, 0.075 and 0.15 mg spiperone/kg body weight, IP on the dipsogenic response to 5-HTP (25 mg/kg body weight, SC) in female rats. Spiperone was administered 1 hour prior to administration of 5-HTP. The height of each bar represents the mean of 6 rats. One S.E. is set off at each mean. Panels A, B, and C show accumulative mean water intakes during the first, second and third hours of the experiment for each dose of spiperone used. **Significantly different from 5-HTP alone ($p<0.01$).

TABLE 2

EFFECT OF CLONIDINE* ON WATER INTAKE FOLLOWING ADMINISTRATION OF 5-HYDROXYTRYPTOPHAN TO FEMALE RATS

Experimental Group	No. of Rats	Mean Body Weight (g)	Cumulative Water Intake (ml/kg body weight) during		
			1 hour	2 hours	3 hours
Control	6	264 ± 5†	1.5 ± 0.5	2.9 ± 0.6	2.9 ± 0.6
5-HTP (25 mg/kg, body weight, SC)	6	294 ± 5	13.5 ± 3.4‡	20.5 ± 2.9‡	21.5 ± 3.2‡
Clonidine (25 μg/kg, body weight, IP)	6	294 ± 2	0.6 ± 0.1¶	1.1 ± 0.1¶	1.4 ± 0.2¶
5-HTP + Clonidine	6	285 ± 6	0.7 ± 0.3	5.2 ± 1.9	7.9 ± 3.4
Significance:					
5-HTP			<0.005	<0.005	<0.005
Clonidine			<0.005	<0.005	<0.005
Interaction			<0.005	<0.005	<0.05

*Clonidine administered 15 minutes prior to the administration of 5-HTP.
†One standard error of the mean.
‡Significantly different from control ($p<0.01$).
¶Significantly different from 5-HTP alone ($p<0.01$).

TABLE 3

EFFECT OF HALOPERIDOL* ON 5-HTP-INDUCED WATER INTAKE IN FEMALE RATS

Experimental Group	No. of Rats	Mean Body Weight (g)	Cumulative Water Intake (ml/kg body weight) during		
			1 hour	2 hours	3 hours
Control	6	245 ± 5†	3.3 ± 1.6	3.7 ± 1.7	4.3 ± 1.6
5-HTP (25 mg/kg, body weight, SC)	6	256 ± 4	8.8 ± 3.0	13.4 ± 3.4‡	15.4 ± 2.8‡
Haloperidol (150 μg/kg, body weight, IP)	6	276 ± 11	0.6 ± 0.1	1.4 ± 0.1	2.1 ± 0.2
5-HTP + Haloperidol	6	265 ± 11	3.2 ± 1.7	4.3 ± 1.6¶	5.2 ± 2.7‖
Significance:					
5-HTP			<0.05	<0.01	<0.005
Haloperidol			<0.05	<0.05	<0.05
Interaction			NS	NS	NS

*Haloperidol administered 1 hour prior to the administration of 5-HTP.
†One standard error of the mean.
‡Significantly different from controls ($p<0.01$).
¶Significantly different from 5-HTP alone ($p<0.01$).
‖ ‖Significantly different from 5-HTP alone ($p<0.05$).

ways play a role in the control of 5-HTP-induced drinking. Interestingly, it has been shown that angiotensin II-induced drinking requires an intact central dopaminergic neuronal system as well [9].

The results of these studies suggest that the drinking response to 5-HTP is mediated by way of the renin-angiotensin system since blockade at any of three levels prevented the dipsogenic response to 5-HTP; the release of renin from the kidney by propranolol and clonidine; the conversion of angiotensin I to angiotensin II by captopril; and the central mediation of the dipsogenic response by treatment with the dopaminergic receptor antagonists, haloperidol and spiperone. Visual inspection of the animals during the experiments in which the pharmacological agents were administered, did not reveal any change in gross motor activity that could account for the attenuation of 5-HTP-induced drinking observed in these studies.

The dipsogenic effect of 5-HTP in rats cannot be explained by an increase in body temperature. Preliminary data from this laboratory showed no significant effect of administration of 25 mg 5-HTP/kg body weight, IP on colonic temperature of rats 30 minutes after treatment.

Whether 5-HTP acts directly to stimulate renin release, or whether it does so after conversion to serotonin, is unknown at present but is currently under study in this laboratory. It is known that serotonin can stimulate renin release in the rat but release is postulated to be an indirect effect of the fall in blood pressure accompanying its administration [22]. Additional studies are required to determine the mechanism by which 5-HTP activates the renin-angiotensin system.

ACKNOWLEDGEMENTS.

We thank Mrs. Charlotte Edelstein for the graphic illustrations and Dr. Christopher Barney for valuable advice.

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