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Effect of Third Ventricle Administration of L-694,247, a Selective 5-HT1$_D$ Receptor Agonist, on Water Intake in Rats

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DE CASTRO-E-SILVA, E., C. SARMENTO, T. A. NASCIMENTO, C. P. LUZ, T. SOARES, C. A. MARINHO, M. CUNHA, C. BULCÃO, I. R. DE OLIVEIRA AND J. B. FREGONEZE. *Effect of third ventricle administration of L-694,247, a selective 5-HT1D receptor agonist, on water intake in rats.* PHARMACOL BIOCHEM BEHAV **57**(4) 749–754, 1997.—L-694,247, a selective 5-HT1$_D$ receptor agonist, injected directly into the third ventricle (2.5, 5.0, and 10.0 μg/rat) of dehydrated rats induced a dose-dependent partial blockade of water intake. Injected in this way, the compound abolishes drinking behavior induced by third ventricle administration of carbachol (2 μg/rat), angiotensin II (5 ng/rat), and isoproterenol (40 μg/rat). In addition, intraventricular injections of L-694,247 did not modify water intake in normohydrated rats. The effects of L-694,247 are due to a specific interaction with 5-HT1$_D$ receptors, because its inhibitory effect on water intake in dehydrated rats is blocked by the previous administration of a 5-HT1$_D$ antagonist, GR 127935 (5 μg/rat), directly into the third ventricle. It is concluded that central 5-HT1$_D$ receptor activation disrupts the functional integrity of central pathways related to drinking behavior. © 1997 Elsevier Science Inc.

5-HT1$_D$ receptors Serotonin Angiotensin II Adrenoceptors Cholinergic receptors Drinking behavior

A MULTITUDE of different 5-HT receptors mediate serotonin physiological and pharmacological actions in the central nervous system. Serotonin receptors comprise several families (5-HT1–5-HT7), possessing, in some cases, various subtypes (15,22). The 5-HT$_1$ family consists of six subtypes (5-HT1$_A$–5-HT1$_F$). 5-HT1$_D$ receptors are further subdivided into 5-HT1$_{D\alpha}$ and 5-HT1$_{D\beta}$ (16).

In the rat brain, 5-HT1$_D$ receptors were only recently demonstrated (5, 6). Both 5-HT1$_D$ and 5-HT1$_B$ receptors seem to be autoceptors regulating 5-HT synthesis and release (15). It has also been demonstrated that these receptors may function as heteroceptors present in nonserotoninergic fibers controlling the function of other neurotransmitters, such as glutamate and acetylcholine (15,22).

The absence of adequate pharmacological probes has hampered investigation of the physiological and pharmacological responses generated by some classes of serotonin receptors. This is particularly true where 5-HT1$_D$ receptors are concerned, because selective and potent 5-HT1$_D$ agonists and antagonists only recently became available. These novel pharmacological agents allowed the demonstration of physiological responses related to brain 5-HT1$_D$ receptors, such as motor control (13) and thermoregulation (25).

The prominent role of serotonin in the regulation of food intake is well established. However, brain 5-HT involvement in control of water intake is not clear, and the available studies are inconclusive. Some papers suggest that brain serotonin exerts a negative input on drinking behavior (19,23), whereas others indicate that peripheral serotonergic activation elicits the opposite effect (21).

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In the central nervous system, multiple integrated neurochemical signals control water intake. In mammals, the balance between the positive and negative drives exerted by the central aminergic and peptidergic pathways controlling water intake generates the animal's drinking behavior (8).

Among the many brain circuits for the control of drinking, the angiotensinergic and the cholinergic play a pivotal role. Angiotensin II (AII) mostly stimulates water intake in hypovolemic dehydration, when sodium intake is required, whereas cholinergic systems set drinking during osmotic dehydration (14,27,30). There are also several lines of evidence that brain catecholaminergic circuits play a role in the control of water intake. In this case, a dualistic control is observed, wherein water intake is stimulated by β- and α1-adrenoceptor activation and inhibited by α2 agonists (7,9).

In the present study, we investigated the effects of brain 5-$HT1_D$ receptor activation by the selective agonist L-694,247 on water intake in normohydrated and dehydrated rats. The effect of the compound on the dipsogenic response elicited by third ventricle injections of AII, carbachol, and isoproterenol was also studied.

METHODS

We used adult male Wistar rats (220 ± 20 g) kept under controlled light (lights on from 0600 to 2000 h) and temperature (26 ± 2°C) conditions. The animals had free access to tap water and laboratory chow (Nuvital Nutrientes Ltda., Curitiba, Brazil).

Surgical Procedure

Under sodium pentobarbital anesthesia (40 mg/kg intraperitoneally), the third ventricle of the animals was cannulated as described elsewhere (2). Briefly, the animals were fixed to a stereotaxic apparatus and a chronic cannula was implanted according to the following coordinates: anteroposterior, 0.5 mm behind the bregma; lateral, 0 mm; vertical, 8.0 mm below the skull. Two screws fixed to the skull were embedded in dental acrylic and held the cannula. After surgery, the rats were housed in individual cages for 7 days before the experiments.

Drugs and Microinjections

The following drugs were used: carbachol and AII (Asp^1-$Ileu^5$-AII) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Isoproterenol was acquired from Aldrich Chemical Co. (Milwaukee, WI, USA). L-694,247 [2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indole-3-yl] ethylamine], a 5-$HT1_D$ receptor agonist (3), was a generous gift from Merck Sharp and Dohme Research Laboratories (Harlow, Essex, UK). GR 127935 [*N*[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl) [1,1′biphenyl]-4-carboxamide oxalate], a 5-$HT1_D$ receptor antagonist (17, 26), was donated by Glaxo Research and Development Ltd. (Hertfordshire, UK).

The drugs were dissolved in saline solution, and the volume injected was always 2 μl. Third ventricle injections were made using a Hamilton microsyringe connected to a Mizzy-Slide-Pak needle by a polyethylene extension (PE 10). Following the experiments, a small amount of blue Evans dye was injected through the cannula. After sacrifice and brain removal, the position of the cannula was carefully verified. Only animals whose cannulas were correctly placed into the third ventricle were taken into consideration.

Experimental Design

We studied the effect of intracerebroventricular (ICV; third ventricle) injections of L-694,247, a 5-$HT1_D$ receptor agonist, on drinking behavior in five main experimental sets of rats: a) normohydrated, b) dehydrated, c) normohydrated AII-treated, d) normohydrated carbachol-treated, and e) normohydrated isoproterenol-treated rats. An additional experimental set comprised dehydrated animals pretreated with GR 127935, a 5-$HT1_D$ receptor antagonist, 30 min before receiving a third ventricle injection of L-694,247.

In the first experimental set, we investigated the effect of 5-$HT1_D$ receptor activation on water consumption in normohydrated rats using third ventricle injections of L-694,247 and monitoring water intake for the next 60 min. Control animals received saline solution by the same route and under the same conditions.

In the second experimental set, dehydrated animals were submitted to an overnight (14 h) water deprivation period, then graduated bottles were reintroduced into the cages immediately after L-694,247 injections in different doses. Control animals received ICV saline injections under similar conditions. With this group, we studied the participation of 5-$HT1_D$ receptors on dehydration-induced water intake.

Three experimental sets were performed to study the role of central 5-$HT1_D$ receptors on the dipsogenic effects of central cholinergic, angiotensinergic, and β-adrenergic stimulation. In these sets, different groups of normohydrated animals were pretreated ICV with several doses of L-694,247 30 min before third ventricle injections of three distinct dipsogenic agents: carbachol (2 μg/rat), AII (5 ng/rat), or isoproterenol (40 μg/rat). These doses are commonly used by investigators dealing with mechanisms of thirst regulation. Control animals received saline solution instead of L-694,247. In these groups, graduated bottles were always present in the cages. Each dose of L-694,247 was tested in a different group of animals.

An additional experimental set was designed to test whether the inhibitory effect of L-694,247 on water intake in dehydrated rats was due to a specific interaction with 5-$HT1_D$ receptors. Here, each dehydrated rat was pretreated with 5 μg of GR 127935, a 5-$HT1_D$ receptor antagonist, 30 min before receiving a third ventricle injection of L-694,247 (10 μg/rat).

All experiments were performed between 0700 and 0900 h. Water intake was monitored for 60 min in all experimental groups except those receiving isoproterenol. In this case, as the onset of isoproterenol-induced water intake is delayed in time, we recorded water intake during 90 min.

Statistical Analysis

We used computer software (GBSTAT, Dynamic Microsystems Inc., Silver Spring, MD, USA) that performs analysis of variance followed by the Scheffé multiple comparisons test. Differences were considered significant at $p < 0.01$. The cumulative water intake is presented as ml/100 g of body weight and expressed as mean ± SEM.

RESULTS

Third ventricle injections of L-694,247 did not modify drinking behavior in normohydrated rats. The water intake values after 60 min of saline or L-694,247 third ventricle injections in both control and experimental groups are similarly low (saline = 0.11 ± 0.02; L-694,247 = 0.10 ± 0.03).

As seen in Fig. 1, central injections of L-694,247 significantly attenuated water intake in dehydrated rats in a dose-

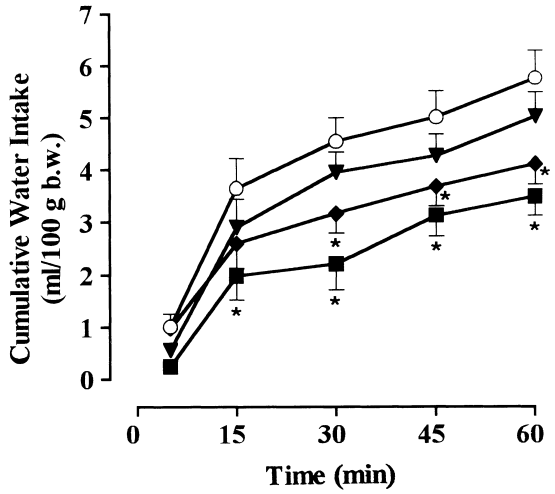

FIG. 1. Cumulative water intake (ml/100 g body weight) of dehydrated animals (overnight, 14 h of water deprivation) receiving third ventricle injections of saline (○; $n = 10$) or L-694,247 in different doses: 2.5 μg/rat (▼; $n = 10$); 5.0 μg/rat (◆; $n = 9$); 10.0 μg/rat (■; $n = 11$). Data are presented as mean ± SEM. Asterisks indicate a statistically significant difference ($p < 0.01$) of groups receiving L-694,247 compared with saline-treated controls.

dependent way. In the lowest dose employed (2.5 μg/rat), the compound was ineffective. Upon increasing the dose, a reduction of water intake as compared with saline-treated controls was observed. This inhibition was proportional to the magnitude of the dose employed. Doses higher than 10.0 μg/rat (data not shown) were unable to yield a greater inhibitory effect.

Figure 2 depicts the effects of central injections of different doses of L-694,247 on water intake of normohydrated rats induced by third ventricle administration of AII (5 ng/rat). As expected, control animals pretreated with saline and receiving AII (saline + AII) displayed a fast and potent dipsogenic response when compared with controls (saline + saline). In the groups pretreated ICV with L-694,247 30 min before receiving third ventricle injections of AII (L-694,247 + AII), the 5-HT1$_D$ antagonist caused a dose-dependent inhibition of AII-induced water intake. The magnitude of the dipsogenic response induced by AII in the group of animals pretreated with the lowest dose of L-694,247 (1.25 μg/rat) was indistinguishable from that of saline-treated controls (saline + AII). The other doses (2.5, 5.0, 10.0, and 20.0 μg/rat) significantly blocked the AII-induced dipsogenic response.

The effect of L-694,247 on the dipsogenic response of normohydrated animals to central carbachol (2 μg/rat) administration is shown in Fig. 3. Predictably, saline-pretreated animals receiving carbachol (saline + carbachol) showed a significant increase in water intake as compared with controls (saline + saline). In the groups pretreated ICV with L-694,247 30 min before receiving third ventricle injections of carbachol (L-694,247 + carbachol), L-694,247 promoted a dose-dependent blockade of carbachol-induced drinking behavior. At the lowest dose employed (1.25 μg/rat), L-694,247 attenuated drinking, at one time significantly. The other doses used (2.5 and 5.0 μg/rat) partially blocked carbachol-induced drinking.

Figure 4 shows the effect of L-694,247 on water intake induced by isoproterenol (40 μg/rat) in normohydrated rats. The group of animals pretreated with saline and receiving iso-

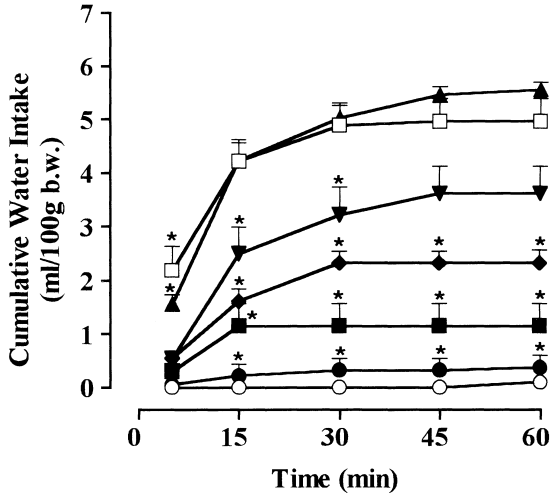

FIG. 2. Cumulative water intake (ml/100 g body weight) of normohydrated animals receiving third ventricle injections of saline (controls) or L-694,247 in different doses before third ventricle administration of AII (5.0 ng/rat). A group receiving a double injection of saline is also included. Sal + Sal (○; $n = 12$); Sal + AII 5 ng/rat (□; $n = 11$); L-694,247 1.25 μg/rat + AII 5 ng/rat (▲; $n = 10$); L-694,247 2.5 μg/rat + AII 5 ng/rat (▼; $n = 13$); L-694,247 5.0 μg/rat + AII 5 ng/rat (◆; $n = 9$); L-694,247 10.0 μg/rat + AII 5 ng/rat (■; $n = 11$); L-694,247 20.0 μg/rat + AII 5 ng/rat (●; $n = 12$). Data are presented as mean ± SEM. Asterisks indicate a statistically significant difference ($p < 0.01$) of groups pretreated with L-694,247 before receiving AII (L-694,247 + AII) compared with groups pretreated with saline (saline + AII).

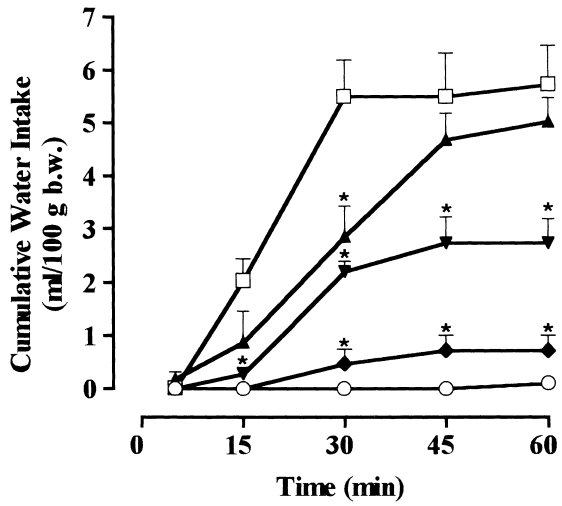

FIG. 3. Cumulative water intake (ml/100 g body weight) of normohydrated animals receiving third ventricle injections of saline (controls) or L-694,247 in different doses before third ventricle administration of carbachol (2.0 μg/rat). A group receiving a double injection of saline is also included. Sal + Sal (○: $n = 12$); Sal + carbachol 2 μg/rat (□; $n = 11$); L-694,247 1.25 μg/rat + carbachol 2 μg/rat (▲; $n = 10$); L-694,247 2.5 μg/rat + carbachol 2 μg/rat (▼; $n = 11$); L-694,247 5.0 μg/rat + carbachol 2 μg/rat (◆; $n = 11$). Data are presented as mean ± SEM. Asterisks indicate a statistically significant difference ($p < 0.01$) of groups pretreated with L-694,247 before receiving carbachol (L-694,247 + carbachol) compared with groups pretreated with saline (saline + carbachol).

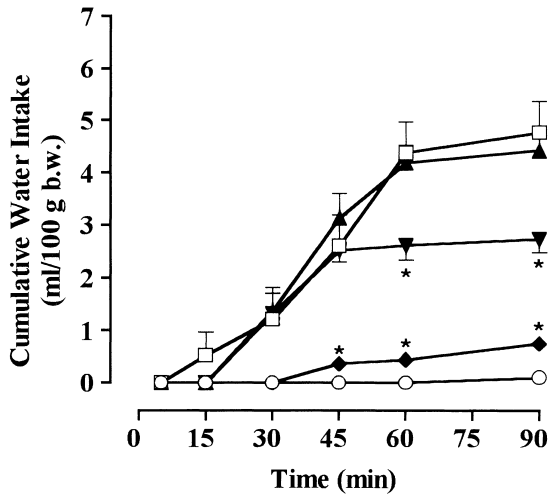

FIG. 4. Cumulative water intake (ml/100 g body weight) of normohydrated animals receiving third ventricle injections of saline (controls) or L-694,247 in different doses before third ventricle administration of isoproterenol (40.0 μg/rat). A group receiving a double injection of saline is also included. Sal + Sal (○; $n = 12$); Sal + isoproterenol 40.0 μg/rat (□; $n = 11$); L-694,247 1.25 μg/rat + isoproterenol 40.0 μg/rat (▲; $n = 10$); L-694,247 2.5 μg/rat + isoproterenol 40.0 μg/rat (▼; $n = 11$); L-694,247 5.0 μg/rat + isoproterenol 40.0 μg/rat (◆; $n = 11$). Data are presented as mean ± SEM. Asterisks indicate a statistically significant difference ($p < 0.01$) of groups pretreated with L-694,247 before receiving isoproterenol (L-694,247 + isoproterenol) compared with groups pretreated with saline (saline + isoproterenol).

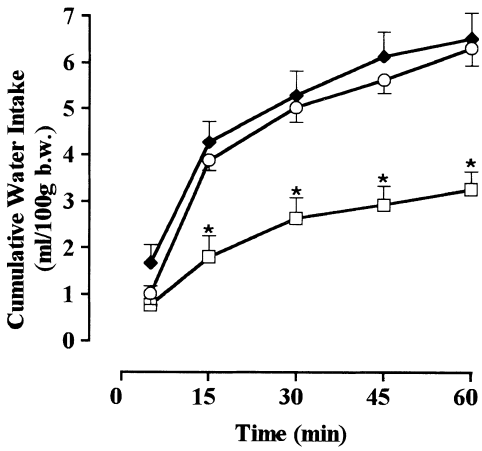

FIG. 5. Cumulative water intake (ml/100 g body weight) of dehydrated animals (overnight, 14 h of water deprivation) receiving third ventricle injections of L-694,247 and pretreated with GR 127935. A group receiving a double injection of saline is also included. Sal + Sal (○; $n = 12$); Sal + L-694,247 10.0 μg/rat (□; $n = 13$); GR 127935 5.0 μg/rat + L-694,247 10.0 μg/rat (◆; $n = 10$). Data are presented as mean ± SEM. Asterisks indicate a statistically significant difference ($p < 0.01$) of the group pretreated with GR 127935 before receiving L-694,247 (GR 127935 + L-694,247) compared with groups pretreated with saline (saline + L-694,247).

proterenol (saline + isoproterenol) exhibited a high water intake as compared with controls (saline + saline). In the groups pretreated ICV with L-694,247 30 min before receiving third ventricle injections of isoproterenol (L-694,247 + isoproterenol), a dose-dependent inhibitory effect the 5-$HT1_D$ antagonist on isoproterenol-induced water intake was observed. In this case, the lowest dose tested was ineffective. The other doses of L-694,247 (2.5 and 5.0 μg/rat) significantly inhibited isoproterenol-induced water intake.

As depicted in Fig. 5, the inhibitory effect of L-694,247 (10 μg/rat) on water intake of dehydrated rats was no longer observed in the group of dehydrated animals pretreated with GR 127935 (5 μg/rat), a 5-$HT1_D$ receptor antagonist (GR 127935 + L-694,247). In this experiment, GR 127935 was administered 30 min before L-694,247. Both drugs were injected into the third ventricle.

DISCUSSION

The present data show that third ventricle administration of L-694,247, a potent and selective 5-$HT1_D$ agonist, is able to attenuate water intake induced by dehydration and blocks the dipsogenic response elicited by central angiotensinergic, cholinergic, and β-adrenergic stimulation. In addition, the compound, injected by the same route, does not modify water intake in normohydrated rats. The effects of L-694,247 observed here seem to be specifically due to an interaction with 5-$HT1_D$ receptors, because the inhibitory effect of the drug on water intake in dehydrated rats is manifested in a dose-dependent fashion and is blocked by a previous administration of GR 127935, a 5-$HT1_D$ antagonist. This compound does not modify basal or electrically evoked central 5-HT release and is devoid of behavioral effects (17).

Central serotonergic participation in water intake control is a quite unexplored matter. Nonetheless, the scarce material available in the literature strongly suggests an inhibitory role of brain serotonin pathways in drinking behavior. Indeed, in rats, electrolytic lesions of the dorsal raphe nucleus caused a significant increase in water intake (28,29). Pharmacological depletion of brain serotonergic transmission by a selective neurotoxic agent, *p*-chlorophenylalanine, produced a significant and sustained increase in drinking behavior (23). Also, MK-212, a serotonergic agonist, injected directly into the third ventricle, significantly reduced water intake in rats (20). Peripheral administration of serotonin or serotonergic agonists seems to produce an opposite effect (an increase in drinking) that is probably mediated by peripheral release of AII (21,24).

Activation of 5-$HT1_D$ receptors did not modify water intake in normohydrated rats. This may simply mean that normohydrated rats display a very low water intake in the morning, so it is difficult to observe any further inhibitory effect.

L-694,247 attenuates, but does not abolish, drinking behavior in dehydrated rats. However, the compound elicits a total blockade in water intake due to cholinergic, angiotensinergic, and β-adrenergic central stimulation. Dehydration is a potent physiological stimulus inducing drinking behavior, a response generated by complex multifactorial integrated systems in the brain. Thus, it is not unreasonable to suggest that, under dehydration, mechanisms not influenced by 5-$HT1_D$ receptor activation maintain some input on drinking. This input, or a sum of parallel or sequential inputs, prevents the expression of the total blockade in drinking behavior observed in the groups of animals under central cholinergic, angiotensinergic, and β-adrenergic stimulation pretreated with L-694,247.

Central cholinergic, angiotensinergic, and β-adrenergic pharmacological stimulation are nonphysiological procedures

that induce drinking behavior and represent a valuable approach to studying thirst-controlling mechanisms (8,18). Certainly, each one of these treatments individually triggers a mechanism that leads to drinking motivation and water consumption. It seems that, whatever the mechanism(s) activated under each of these particular situations, it is blocked by central 5-HT1$_D$ activation.

In mammals, the maintenance of osmotic and volemic conditions within very narrow limits is essential, and thirst regulation is part of the body strategies involved with this goal. Peripheral and central data are analyzed at central regions specially represented by the hypothalamus, the septum, and the amygdala (1). These regions must transmit signals to those structures responsible for the motivation and motor events that translate a sensation (thirst) into a behavior (drinking) (8,18). Thus, it is possible that 5-HT1$_D$ receptor activation totally disrupts a necessary functional integrity between these areas during pharmacologically induced water intake, whereas during dehydration some mechanism(s) escape(s), making a residual water intake still possible even in the presence of 5-HT1$_D$ stimulation.

The dose of L-694,247 necessary to abolish water intake in rats receiving AII is fourfold higher than that required to abolish water intake induced by carbachol and isoproterenol. This only reinforces the fact that AII is a more powerful dipsogenic agent as compared with the other two drugs used.

5-HT1$_D$ receptors do exist in rat brain, although their concentration is low (6,12). Their distribution is very diffuse, and they seem to function as: a) terminal autoceptors mediating inhibition of 5-HT release in many brain areas (15) or b) postsynaptic heteroceptors mediating neurotransmitter release in nonserotoninergic nerves (10). Considering the first situation, the inhibitory effect of L-694,247, a 5-HT1$_D$ agonist, should be due a diminished 5-HT release, indicating a stimulatory role of brain 5-HT on drinking behavior. As most evidence suggests that central serotonergic pathways inhibit water intake (as mentioned above), it is possible that the effects observed here after 5-HT1$_D$ receptor stimulation are due mainly to a preferential activation of postsynaptic heteroceptors. In agreement with this interpretation, it was very recently demonstrated that 5-HT1$_D$ receptor stimulation by a selective agonist, SKF 99101H, induces a hypothermic response in rodents that is maintained even after the destruction of central serotonergic pathways by the specific neurotoxic agent *p*-chloroamphetamine (11). It should also be considered that we injected the compound directly into the third ventricle. This site is far from the raphe nuclei containing the cell bodies of serotonergic neurons, where autoceptors are mainly expressed. However, considering the experimental protocol used here, the involvement of 5-HT$_{1D}$ autoceptors cannot be safely excluded. Selective antagonists for 5-HT1$_{D\alpha}$ and 5-HT1$_{D\beta}$ receptors are not available. Thus, it is impossible to ascertain whether the inhibitory effect of L-694,247 on drinking behavior is due to an action on one, or both, of these receptor subtypes.

As compared with saline-treated controls, animals receiving L-694,247 in the doses used here did not present motor disturbances that could explain diminished water intake. Circling, hyperactivity, or sickness-like postures or behaviors were not observed. In addition, preliminary results from our laboratory show that latencies to initiate food intake after L-694,247 and saline were indistinguishable. This clearly demonstrates that motor impairment or a general depressive behavior induced by L-694,247 does not explain our results.

Blockade of 5-HT autoceptors has been suggested as an alternative approach to the treatment of depressive illness because it could reproduce the beneficial effects of 5-HT reuptake inhibitors in a shorter time (4). Thus, study of the physiological effects of serotonin 5-HT1$_D$ receptors represents a valuable contribution not only to the understanding of brain serotonin function as a whole but also to predicting possible side effects of new therapeutic approaches concerning serotonin and psychiatric diseases.

In summary, the present paper clearly demonstrates that central 5-HT1$_D$ receptor activation by L-694,247, a selective 5-HT1$_D$ agonist, partially blocks water intake in dehydrated animals and abolishes drinking behavior induced in normohydrated rats by pharmacological stimulation of cholinergic, angiotensinergic, and β-adrenergic pathways in the brain. The same procedure is unable to modify basal (nonpharmacologically stimulated) water intake in normohydrated rats. L-694,247 seems to interact specifically with 5-HT1$_D$ receptors, because GR 127935, a 5-HT1$_D$ receptor antagonist, is able to block its effect. Taken together, the data presented here suggest that acute activation of 5-HT1$_D$ receptors disrupts the functional integrity of central pathways related to drinking behavior. Further investigation into the mechanism(s) whereby 5-HT1$_D$ inhibits water intake is being conducted at present in our laboratory.

ACKNOWLEDGEMENTS

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