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The Nucleus Accumbens Is a Site of Action for the Inhibitory Effect of Ritanserin on Ethanol Intake in Rats

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PANOCKA, I., R. CICCOCIOPPO, C. POLIDORI AND M. MASSI. *The nucleus accumbens is a site of action for the inhibitory effect of ritanserin on ethanol intake in rats.* PHARMACOL BIOCHEM BEHAV 46(4) 857–862, 1993.—The present study evaluated the effect of central injections of the 5-$HT_{2/1C}$ receptor antagonist, ritanserin, on ethanol intake in rats with developed preference for 3% ethanol. Intracerebroventricular (ICV) injections of ritanserin (10 μg/rat/day for 10 days) decreased ethanol preference, while subcutaneous (SC) treatment with the same dose was ineffective. Ritanserin ICV, 1 μg/rat/day, did not reduce alcohol preference. Bilateral injections of ritanserin into the nucleus accumbens (NAC; 0.5 μg/site/day for 10 days) produced a prompt and very pronounced suppression of ethanol preference, without affecting total fluid intake. Bilateral injections of ritanserin (0.5 μg/site/day for 10 days) into the ventral tegmental area (VTA) or into the medial prefrontal cortex (MPC) evoked only slight and variable reduction of ethanol preference. Injections of ritanserin, 5 μg/site/day, into the VTA gave a nonselective suppression of the ingestive behavior. The present results provide evidence for a central site of action for the effect of ritanserin on ethanol intake and suggest that the NAC might be a highly sensitive site for its action. Since the NAC is a major target of the mesolimbic dopaminergic system, they also suggest that the effect of ritanserin might be due to interference with this system.

Ethanol preference Ritanserin 5-HT_2 receptor antagonists Nucleus accumbens Ventral tegmental area Medial prefrontal cortex

A LARGE body of evidence indicates that serotonin (5-HT) is involved in the control of ethanol intake (2,18,31,33); however, the mechanism(s) by which it affects alcohol intake are largely unknown. In particular, the finding that suppression of alcohol intake can be obtained with 5-HT agonists and with drugs that increase the synaptic availability of 5-HT (1, 8,23,24), on the one hand, and with 5-HT antagonists such as 5-HT_3 (9,33) and 5-HT_2 antagonists (19–21,26,27,30), on the other hand, suggests that a variety of mechanisms might mediate its effect.

Several findings indicate a possible role of 5-HT in the rewarding aspects of ethanol drinking (18,22,36), possibly through interaction with the dopaminergic system, which is suggested to play a critical role in alcohol reward (6,7,10,11). In this relation, it has been shown that 5-HT_3 receptor blockers inhibit ethanol-induced release of mesolimbic dopamine (3,38), while 5-HT_2 antagonists are known to activate dopaminergic neurons in mesolimbic structures following acute administration (4,5,35,37), and to modulate tyrosine hydroxylase activity in the brain (25,32,34).

Following our previous studies on the effect of 5-HT_2 antagonists on ethanol intake (26,27), our interest was focused to determine the site(s) of action for their effect. A first attempt was made to demonstrate a central site of action for the 5-$HT_{2/1C}$ receptor antagonist, ritanserin (17), by intracerebroventricular (ICV) injection; then we moved to investigate the sensitivity of discrete brain areas to direct injection of the drug into them. In relation to the possible interaction of 5-HT_2 antagonists with the mesolimbic and mesocortical dopaminergic system (4,5,35,37), the present study evaluated the sensitivity of the nucleus accumbens (NAC), of the ventral tegmental area (VTA), and of the medial prefrontal cortex (MPC) to the direct injection of ritanserin in rats with developed preference for 3% ethanol.

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METHOD

Animals

Male Wistar rats (Charles River, Calco, Co., Italy) weighing 300–350 g were used. They were kept in individual cages on a 12L : 12D cycle. Food pellets (diet No. 4RF18, Mucedola, Settimo, Milanese, Italy) and tap water were available ad lib.

Surgery

Rats were anesthetized with Ketalar (50 mg/kg, IM) and implanted stereotaxically with one stainless steel guide cannula for ICV injection, or with two guide cannulas for microinjections into the VTA, NAC, or MPC. Cannulas were attached to the skull by means of jewelry screws and dental cement. Coordinates, taken from the atlas of Paxinos and Watson (28), were as follows: lateral ventricle—0.9 mm posterior (P) and 2 mm lateral (L) to bregma; 2 mm ventral (V) from the surface of the skull; VTA—5.3 mm P and 0.8 mm L to bregma; 7.4 mm V from the surface of the skull; NAC—1.7 mm anterior (A) and 1.5 mm L to bregma; 7 mm V from the surface of the skull; MPC—4.5 mm A and 0.8 mm L to bregma; 3.5 mm V from the surface of the skull.

After surgery rats were allowed to recover for 1 week, during which they were handled and mock injected to make them adapted to the testing procedure.

Induction of 3% Ethanol Preference

Ethanol preference was induced according to the method of Meert et al. (20). Animals were forced to drink 3% ethanol solution for a week, during which it was the only fluid offered. The following week they had access just to water; afterwards, during all the experiments, they were given free choice between 3% ethanol and water. This procedure usually develops preference for 3% ethanol solution in about 80% of the rats, when they are not implanted with intracranial cannulas. In the present study, ethanol preference was induced in about 60% of the rats employed.

Drug Solution

Ritanserin (a gift of Janssen Pharmaceutica, Beerse, Belgium) was dissolved in a vehicle containing 20% propylene glycol and a few drops of lactic acid. The pH of the solution was adjusted to 5 by adding 2 N NaOH.

Intracranial Injections

Ritanserin or its vehicle were unilaterally injected in a volume of 1 μl into the lateral cerebroventricle; injections into discrete brain areas were made bilaterally in a volume of 0.5 μl per site. Drugs were injected by means of a stainless steel injector (2 mm longer than the cannula) temporarily inserted into the guide cannula.

Peripheral Injections

Ritanserin solution or its vehicle were given SC in a volume of 1 ml/kg of body weight.

Experiment 1. Effect of ICV Ritanserin Treatment on 3% Ethanol Preference

This first experiment was carried out to evaluate whether, and at which doses, ritanserin is able to reduce ethanol intake following ICV administration. Three groups of rats were employed: one group received ICV injections of ritanserin, 10 μg/rat/day, the second received ritanserin 1 μg/rat/day, while the third received ritanserin vehicle. All the groups were treated at 6:00 p.m. for 10 days.

Experiment 2. Effect of SC Ritanserin Treatment on 3% Ethanol Preference

As ritanserin easily crosses the blood-brain barrier, the ICV injection might be expected to result in diffusion of the drug into the peripheral circulation. Therefore, Experiment 2 was designed to ascertain whether the effect observed in Experiment 1 might be due to leakage of the drug into the periphery. The rats received daily SC injections either of 10 μg/rat of ritanserin or of its vehicle at 6:00 p.m. for 10 days.

Experiment 3. Effect of Ritanserin on 3% Ethanol Preference Following Injection Into the VTA

Firstly, two groups of rats were bilaterally injected either with ritanserin 1 μg/rat/day (0.5 μg per site) or with its vehicle. Afterwards, two other groups of rats received either ritanserin 10 μg/rat/day (5 μg per site) or its vehicle. All the injections were made at 6:00 p.m. for 10 days.

Experiment 4. Effect of Ritanserin on 3% Ethanol Preference Following Injection Into the NAC

Two groups of rats, receiving bilateral injections either of ritanserin 1 μg/rat/day (0.5 μg per site) or of its vehicle, were used. All the injections into the NAC were made at 6:00 p.m. for 10 days.

Experiment 5. Effect of Ritanserin on 3% Ethanol Preference Following Injection Into the MPC

Two groups of rats, receiving bilateral injections either of ritanserin 1 μg/rat (0.5 μg per site) or of its vehicle, were injected daily at 6:00 p.m. for 10 days.

Histology

Upon completion of testing, rats were sacrificed with an overdose of anesthetic, and brains were dissected free and kept in 10% formalin for at least a week. Histology was performed to evaluate the placement of the intracranial cannulas. Frozen brain sections (50 μ) were cut and stained with hematoxylin.

Statistical Analysis

Statistical analysis of data was performed by means of split-plot analysis of variance (ANOVA) with between-group comparisons for drug treatment and within-group comparisons for time (treatment day). Individual comparisons were performed by means of *t*-test. Statistical significance was set at $p < 0.05$. Ethanol solution intake (ml/rat), total fluid intake (ml/rat), and percent ethanol preference (percentage of daily total fluid intake drank as 3% ethanol solution) were submitted to statistical analysis. Results are reported in the figures as percent ethanol preference ± SEM.

RESULTS

Histological Analysis

Figure 1 shows all the valid placements of injector tips into discrete brain areas in ritanserin-treated rats, according to the

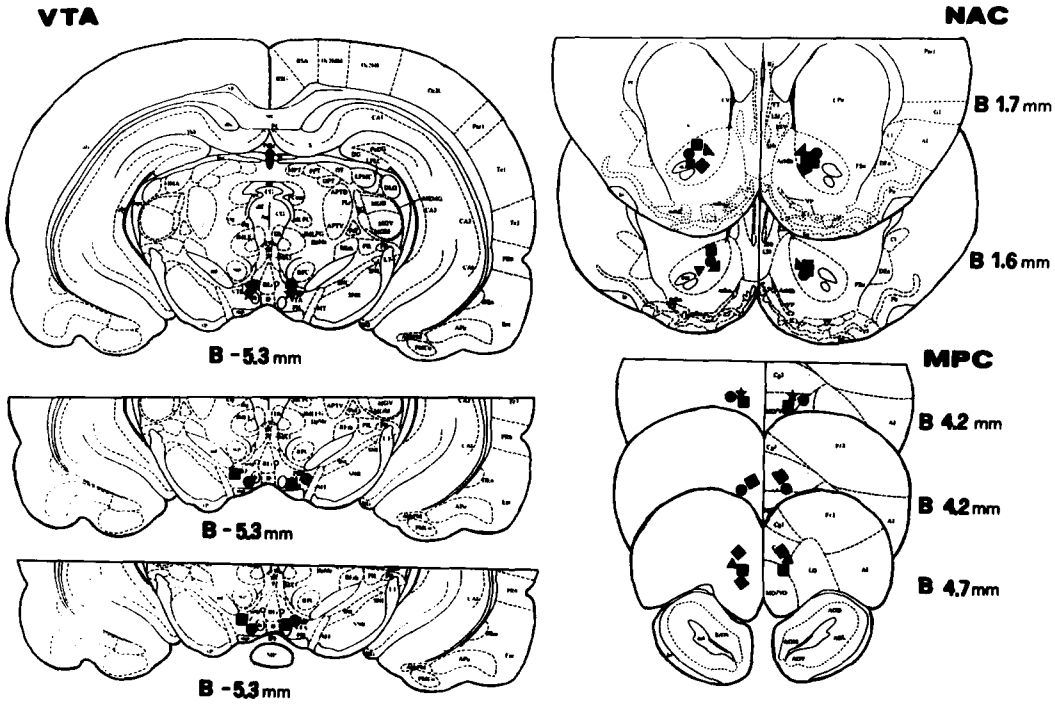

FIG. 1. The figure shows bilaterally the end of the injector track into the VTA, NAC, and MPC for all ritanserin-treated rats with valid injector tip placements. Different brain sections are identified by the antero-posterior coordinate from bregma (B), according to the Paxinos and Watson atlas (28).

Paxinos and Watson atlas (28). Successful bilateral placements were obtained in about 80% of the implanted animals. Only data from animals with valid cannula placement were included in the experimental results. The histological analysis revealed that two rats had injector tips located above the NAC and results obtained from these animals were discarded. They had proven to be only marginally sensitive to the inhibitory effect of ritanserin.

Experiment 1. Effect of ICV Ritanserin Treatment on 3% Ethanol Preference

Intracerebroventricular injection of ritanserin, 10 μg/rat/day, reduced 3% ethanol intake, $F(1, 11) = 8.39$, $p < 0.05$, as well as 3% ethanol preference, $F(1, 11) = 17.524$, $p < 0.01$, as shown in Fig. 2. Planned pairwise comparisons revealed a significant difference in the preference of the two groups from the 3rd day of treatment. On the other hand, daily ICV injections of ritanserin 1 μg/rat/day did not significantly modify ethanol preference.

Neither doses of ritanserin altered total fluid intake (water + 3% ethanol solution), which ranged between 36 and 41 ml/rat/day, both in controls and in ritanserin-treated rats (data not shown).

Experiment 2. Effect of SC Ritanserin Treatment on 3% Ethanol Preference

The results obtained following SC injection of 10 μg/rat/day of ritanserin are reported in Fig. 3. The overall ANOVA revealed no drug treatment effect on either ethanol intake or ethanol preference, in the absence of drug treatment-time interaction. Also, total fluid intake was not significantly modified by the SC ritanserin treatment.

Experiment 3. Effect of Ritanserin on 3% Ethanol Preference Following Injection Into the VTA

Ritanserin, 1 μg/rat/day (0.5 μg/site), did not significantly modify 3% ethanol intake, $F(1, 9) = 2.45$, $p > 0.05$. A slight reduction of 3% ethanol preference was observed, $F(1, 9) = 6.153$, $p < 0.05$, the effect being statistically significant only on day 8 of treatment (Fig. 4). During the treatment, total

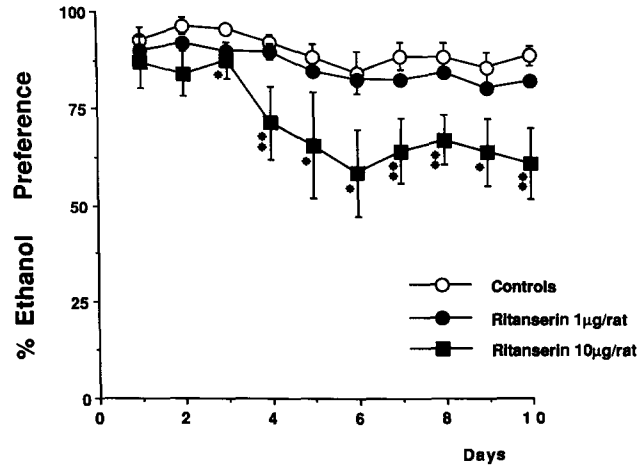

FIG. 2. Effect of ICV injections of ritanserin, 10 or 1 μg/rat/day, or of its vehicle on 3% ethanol preference. Values are mean ± SEM of seven data for controls and of six data for both ritanserin doses. Difference from controls: $*p < 0.05$; $**p < 0.01$; where not indicated, difference from controls was not statistically significant.

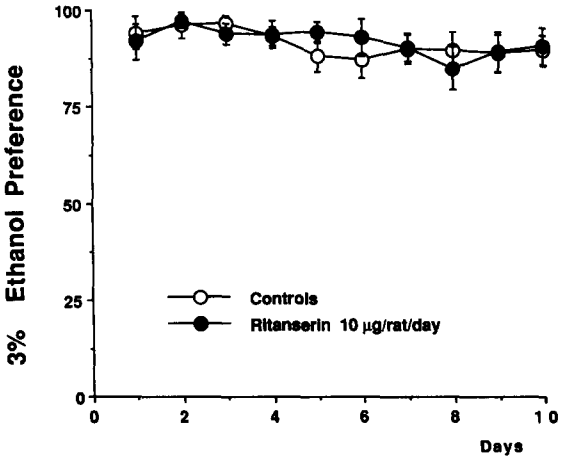

FIG. 3. Effect of SC injections of ritanserin, 10 µg/rat/day, or of its vehicle on 3% ethanol preference. Values are mean ± SEM of five data. Difference from controls was never statistically significant.

fluid intake of ritanserin-treated rats was essentially identical to that of controls.

Following injection of a higher dose, 10 µg/rat/day, ritanserin produced a marked suppression of both ethanol and water intake. On the 3rd day of treatment, total daily fluid intake of ritanserin-treated rats fell to 15.7 ± 2.7 ml/rat vs. 38.8 ± 3.4 ml/rat in controls. The treatment was interrupted.

Experiment 4. Effect of Ritanserin on 3% Ethanol Preference Following Injection Into the NAC

Ritanserin, 1 µg/rat/day (0.5 µg/site), injected into the NAC produced a marked reduction of both 3% ethanol intake, $F(1, 15) = 23.31, p < 0.001$, and of 3% ethanol preference, $F(1, 15) = 25.181, p < 0.001$ (Fig. 5A). Planned pairwise comparisons showed that the difference between groups was statistically significant from the first day of treatment.

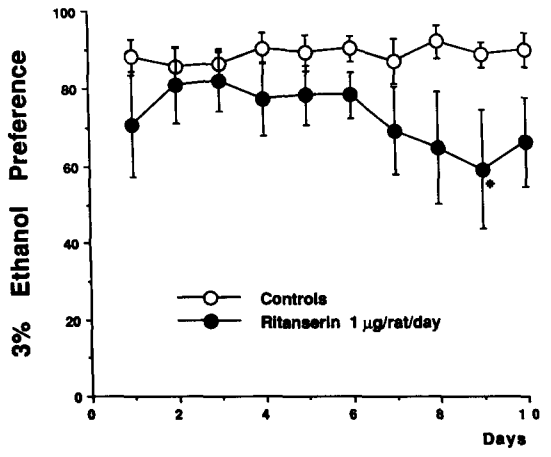

FIG. 4. Effect of bilateral injections of ritanserin, 0.5 µg/site/day (1 µg/rat/day), or of its vehicle into the VTA on 3% ethanol preference. Values are mean ± SEM of five data for controls and of six data for ritanserin. Difference from controls as in Fig. 2.

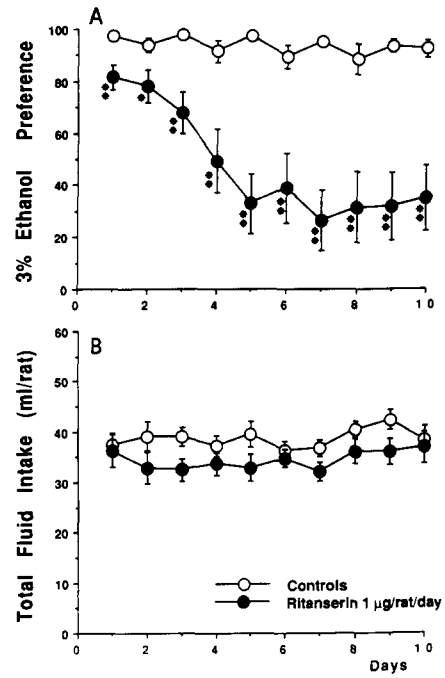

FIG. 5. Effect of bilateral injections of ritanserin, 0.5 µg/site/day (1 µg/rat/day), or of its vehicle into the NAC on: (A) 3% ethanol preference and (B) total fluid intake. Values are mean ± SEM of eight data for controls and of nine data for ritanserin. Difference from controls as in Fig. 2.

Ethanol preference gradually decreased from the first day and on the 5th day of treatment it was reduced to about 30%, remaining approximately at this value for the rest of the treatment. While suppressing ethanol intake, the injection of ritanserin, 1 µg/rat/day into the NAC, did not modify total fluid intake (Fig. 5B).

Experiment 5. Effect of Ritanserin on 3% Ethanol Preference Following Injection Into the MPC

Ritanserin treatment produced a significant decrease in 3% ethanol intake, $F(1, 14) = 12.65, p < 0.01$, and in 3% ethanol preference, $F(1, 14) = 11.933, p < 0.01$; however, the effect was modest in intensity (Fig. 6). Individual comparisons revealed that ritanserin effect was statistically significant only on the 3rd, 6th, and 8th day of treatment. Also, in this experiment total fluid intake was not affected by ritanserin, $F(1, 14) = 0.041, p > 0.05$.

DISCUSSION

The first two experiments of the present study provide clear evidence in favor of a central site of action for the effect of ritanserin on ethanol intake. In fact, 10 µg/rat/day of ritanserin reduced ethanol preference following injection into the lateral cerebroventricles, but not after SC injection, thus excluding the possibility that the effect of the central injection might have been due to leakage of the drug into the periphery.

For direct injection into discrete brain areas a rather small volume was employed (0.5 µl/site), and the dose employed was 1 µg/rat/day, which had proven to be ineffective following injection into the ventricle. These experimental conditions were adopted to reduce possible backflow of the injectate into

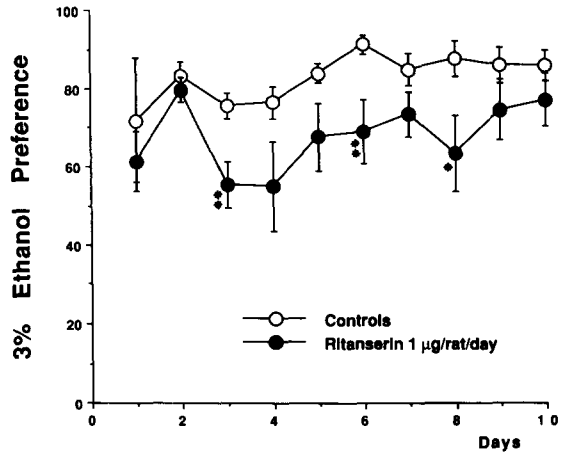

FIG. 6. Effect of bilateral injections of ritanserin, 0.5 µg/site/day (1 µg/rat/day), or of its vehicle into the MPC on 3% ethanol preference. Values are mean ± SEM of eight data. Difference from controls as in Fig. 2.

the cerebroventricle (16) and to avoid the possibility that ventricular diffusion of the drug might affect the evaluation of the sensitivity of the brain area under investigation.

The results obtained clearly show that the NAC is highly sensitive to direct microinjection of ritanserin. The effect following direct injection into this nucleus a) is prompt, being statistically significant from the first day of treatment; b) is very pronounced, lowering the ethanol preference to about 30%; c) remains stable once it is fully expressed; and d) is also behaviorally selective, as shown by the fact that total fluid intake of treated animals was essentially identical to that of controls. These findings, together with the fact that the same dose is ineffective when given by ICV injection, strongly support the idea that the NAC is a site of action for the effect of ritanserin on ethanol intake. On the other hand, neurochemical evidences showing that the NAC is rich in 5-HTergic afferent fibers originating in the dorsal raphe (12) and is also endowed with moderate density of 5-HT_2 receptors (29) are in keeping with the idea that the NAC may be a site of action for a 5-HT_2 antagonist.

In contrast, very modest results were obtained when the same dose of ritanserin was injected into the VTA or the MPC. The inhibitory effect on ethanol intake following injection of ritanserin into these areas was low in intensity and variable during the treatment. When a larger dose of ritanserin was given into the VTA, the reduction in ethanol intake was accompanied by marked hypodipsia, probably related to behavioral impairment or malaise. These findings suggest that the VTA and the MPC might play only a minor role, if any, in the inhibitory effect of ritanserin on ethanol intake.

The evidence that the NAC is a site of action will surely concentrate on this nucleus future studies aimed at determining the mechanism by which ritanserin reduces ethanol intake. In this regard, it is documented that acute ritanserin administration to rats affects both dopamine and 5-HT release in the NAC (4,5), and that the release of dopamine might be consequent to activation of A10 dopaminergic neurons (35,37) or to the action on 5-HT receptors located on dopaminergic nerve endings in the nucleus accumbens (13–15). Moreover, recent papers have shown that 5-HT_2 receptors can modulate tyrosine hydroxylase activity in the NAC (25,32,34), the 5-HT_2 antagonists lowering the activity of the enzyme. This modulation might play an important role in subchronic or chronic treatments, in conditions in which dopamine release is stimulated by ethanol.

In conclusion, the present results indicate that the NAC is a site of action for the inhibitory effect of ritanserin on alcohol intake. Since the NAC is a major target of the mesolimbic dopaminergic system, this finding suggests, as a working hypothesis, that the effect of ritanserin might be due to interference with the dopaminergic system.

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