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Effect of Fluoxetine on Learning and Memory Involves Multiple 5-HT Systems[1]

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MENESES, A. AND E. HONG. *Effects of fluoxetine on learning and memory involves multiple 5-HT systems.* PHARMACOL BIOCHEM BEHAV **52**(2) 341-346, 1995.—Diverse evidence suggests that 5-HT uptake blockers enhance learning and memory. However, there is no information about the mechanisms of action involved in such effects. The aim of the present work was to investigate the nature of the receptors involved in the effects of fluoxetine on learning. Therefore, a dose-response curve of posttraining injection (intraperitoneal) of fluoxetine was carried out in an associative learning task (autoshaping). Fluoxetine or the vehicle was injected 10 min after 5-HT antagonists: (±)-pindolol, (±)-propanolol, NAN-190, ketanserin, ritanserin, mesulergine, MDL 72222, or SDZ 205-557. Presynaptic activity was eliminated by means of *p*-chloroamphetamine pretreatment. Scopolamine (an anticholinergic) and dizocilpine (a noncompetitive NMDA receptor antagonist) were also used. Results showed that fluoxetine enhanced learning of the conditioned response (CR) in a dose-dependent fashion. All 5-HT antagonists had no effects by themselves but inhibited the effects of fluoxetine at different degrees. Decrement of CR produced by scopolamine was reversed by fluoxetine. Dizocilpine did not affect CR but prevented the effects of fluoxetine. The present findings suggest that the actions of fluoxetine on learning are due to an interaction with multiple receptors of postsynaptic nature.

Serotonin Fluoxetine 5-HT receptors Learning Rats

DIVERSE brain areas have been implicated in learning and memory (57). Taking into account the fact that serotonin (5-hidroxytryptamine; 5-HT) pathways project to many brain areas (25,41,45,52), 5-HT has been suggested to play a role in cognitive processes (51). There is evidence that electrical stimulation of the dorsal raphe or central injection of serotonin increases 5-HT release and its metabolite concentrations in several brain areas (4,13). Both manipulations, stimulation of the dorsal raphe and the central 5-HT injection, impaired learning [see (2,10,31) for reviews], but the increase of 5-HT concentration in the synaptic cleft induced by fluoxetine enhances the cognitive processes (2). The 5-HT uptake blockers improve performance on learning tasks in animals and humans (1,2,14,17,24,31,46,53)—that is, systemic administration of fluoxetine enhanced learning in an avoidance task (1,14,24) and prevented deficit produced by hypoxia (53). Verbal learning is enhanced by fluoxetine but not by amitriptyline; both drugs produce an antidepressant effect, but amitriptyline did not improve learning and produced a significant higher serum anticholinergic activity (46). Fluoxetine is an antidepressant [see (3,17) for reviews] that increases serotonergic neurotransmission by inhibiting 5-HT reuptake. Repeated fluoxetine administration leads to a decrease of spontaneous firing activity of serotonergic neurons (7,11,16,43). Fluoxetine is devoid of affinity for serotonin receptors (3,56), but it acts as an indirect agonist, stimulating multiple 5-HT receptors. Because serotonergic neurotransmission is based on multiple 5-HT receptors types and subtypes, $5\text{-HT}_{1A\text{-}1F}$, $5\text{-HT}_{2A\text{-}2C}$, and $5\text{-HT}_{3\text{-}7}$ (19,20,23,44), the study of the specific blockade of 5-HT receptors could be useful to explain the mechanisms of action of this monoamine on learning and memory.

Cholinergic and glutamatergic neurotransmission systems are involved in learning and memory (49,51). It is well known that central anticholinergic agents such as scopolamine block learning (49). On the other hand, long-term potentiation is a plausible mechanism for the neural substrate of learning and memory (6,8) and is blocked by dizocilpine. Dizocilpine is a noncompetitive antagonist of NMDA receptors, is implicated

[1] The receptor nomenclature used in this article is recommended by the Serotonin Club Nomenclature Committee (Hoyer et al., 1994).

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in functional depression (15), impairs learning (26,50), and induces hyperactivity; the latter effect is enhanced by fluoxetine administration (47). Therefore, the present work was intended to determine the mechanisms of action of fluoxetine and its possible interaction with other neurotransmission systems. The behavioral task used was autoshaping, an associative learning model task (33,35,36). There is no clear consensus regarding reference compounds that enhance or impair learning and memory; however, central anticholinergic are commonly used as blockers and *d*-amphetamine as enhancers (33,40,49).

METHOD

Subjects

Male Wistar rats (12 weeks old) were collectively housed in a temperature- and light-controlled room under a 12 L : 12 D cycle (light on at 0700 h). Water and food were provided ad lib for a week. After that period, the rats' body weights were reduced to 85% by gradually reducing the food intake during seven days.

Apparatus

Operant chambers (25 × 29 × 25 cm) for rats with standard sound-attenuation were used. A retractable lever was mounted 4 cm above the floor and 10 cm from the right and left walls. The lever required a force of 10 g for operation. A food magazine for rat pellets (Bio Serv) was located 5 cm to the right of the lever and 3 cm above the floor. A house light was located in the right top corner. Solid-state programming equipment was used for control and recording (Coulbourn Instruments, Lehigh Valley, PA).

Autoshaping Training

Each rat was placed into an experimental chamber and allowed to habituate to the experimental environment until the animal found and ate 30 food pellets (45 mg/pellet). Immediately thereafter, the program began, consisting of the presentation of an illuminated retractable lever for 8 s [conditioned stimulus (CS)], followed by delivery of a food pellet [unconditioned stimulus (US)] each 60 s. When the animal pressed the CS, the lever was retracted, the light was turned off, a food pellet (US) was delivered immediately, and the response was considered a conditioned one (CR). The increase in percentage of CR was considered to be an enhancement of learning. The first session consisted of 10 trials, and each session thereafter of 20 trials. All compounds were injected immediately after the first autoshaping session and rats were tested 24 h later. The results shown correspond to the second autoshaping session.

Drug Treatment

The drugs used were: fluoxetine HCl (0, 1.25, 2.5, 5, or 10 mg/kg) (Eli Lilly, Indianapolis, IN), (±)-propanolol, HCl (0 or 20 mg/kg), NAN-190 HBr (0 or 0.5 mg/kg), mesulergine HCl (0 or 0.2 mg/kg), ketanserin tartrate (0 or 0.01 mg/kg), ritanserin (0 or 0.1 mg/kg), MDL-72222 (0 or 10.0 mg/kg), *p*-chloroamphetamine (PCA; 0 or 10 mg/kg for 2 consecutive days) 8 and 7 days before the first autoshaping session, dizocilpine maleate (MK-801; 0 or 0.25 mg/kg), and scopolamine (0 or 0.17 mg/kg) (Research Biochemical Inc., Wayland, MA), (±)-Pindolol HCl (0 or 8.0 mg/kg) and SDZ 205-557 (0 or 10 mg/kg) (Sandoz Pharma Ltd., Basel, Switzerland). All drugs were injected intraperitoneally (IP) in a volume of 1 ml/kg. (±)-Propanolol, (±)-pindolol, and MDL-72222 were suspended in methylcellulose. Other drugs were dissolved in physiologic saline.

Measurements and Analysis

Conditioned responses were transformed to a percentage of total trials of the second session. Multiple group comparisons were made using analysis of variance (ANOVA) followed by Dunnett *t*-tests. In all statistical comparisons, $p < 0.05$ was used as criterion for significance. The number per group was eight, and animals were used only once.

EXPERIMENT 1: DOSE-RESPONSE CURVE OF FLUOXETINE AFTER TRAINING

The purpose of this experiment was to determine the dose-response effects of posttraining injection of fluoxetine on consolidation of CR. Animals were injected with vehicle or fluoxetine immediately after the first session, and were placed in their home cage and tested the next day. To exclude an unspecific effect of fluoxetine on learning, we included groups treated with fluoxetine (10 mg/kg) 24 h before the first autoshaping session.

EXPERIMENT 2: ADMINISTRATION OF 5-HT ANTAGONISTS OR PCA AFTER TRAINING

The purpose of this experiment was to determine the effects of diverse 5-HT antagonists to find out whether a 5-HT receptor subtype has a primary influence (18,23,25,37,44) in the learning process. The antagonists used were: (±)-propanolol, (5-$HT_{1B/1A}$ receptors), (±)-pindolol (5-$HT_{1B/1A}$y receptors), ketanserin (5-HT_{2A}y), ritanserin (5-$HT_{2C/2A}$y receptors), mesulergine (5-$HT_{2C/2A}$y receptors), MDL-72222 (5-HT_3 receptors), SDZ 205-557 (5-HT_4 receptors), and PCA (a serotonergic neurotoxin). The partial but selective 5-HT_{1A}y agonist NAN-190 was used.

EXPERIMENT 3: EFFECTS OF VARIOUS 5-HT ANTAGONISTS AND PCA ON THE EFFECTS OF FLUOXETINE

The aim of present experiment was to determine the mechanisms of action of fluoxetine regarding 5-HT receptors. Therefore, fluoxetine or vehicle was administered 10 min after the posttraining injection of 5-HT antagonists.

EXPERIMENT 4: EFFECTS OF SCOPOLAMINE AND DIZOCILPINE ON THE INFLUENCE OF FLUOXETINE ON LEARNING

Scopolamine (a central anticholinergic agent) or dizocilpine [a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist] was injected immediately after the first autoshaping training session, followed 10 min later by the administration of fluoxetine.

RESULTS

Experiment 1

The control group had 13 ± 1% of CR, whereas administration of fluoxetine produced a significant increase in conditioned responses in a dose-related fashion [$F(4, 39) = 6.7$, $p < 0.05$]. A further analysis, with Dunnett *t*-test, showed that fluoxetine significantly increased the number of conditioned responses at 5 and 10 mg/kg (Fig. 1); increments were of 33 ± 4 and 41 ± 3, respectively. The group treated with fluoxetine 24 h before autoshaping showed a significant decrease in

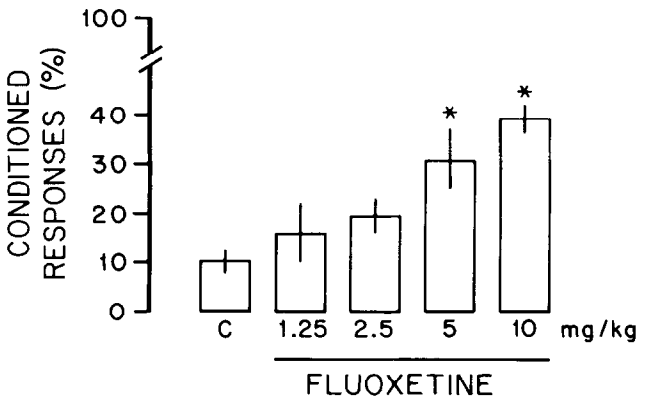

FIG. 1. Dose-response curve of acute posttraining administration (IP) of fluoxetine on autoshaping task in fasting animals. Data are plotted as a percent of control conditioned responses (CR%) All rats received injections immediately after the first training session. Values represent the mean ± SEM of eight different animals. *Dunnett *t*-test < 0.05 vs. vehicle-injected controls.

the CR (3 ± 2); in contrast, animals treated with vehicle showed a score of a 8 ± 2 of CR.

Experiment 2

The 5-HT antagonists doses were selected in terms of the maximal dose of compounds producing no effect by themselves (Table 1). PCA administered at 8 and 7 days before the first autoshaping session did not affect CR.

Experiment 3

Fluoxetine (10 mg/kg, IP) produced an increase of 33 ± 2% in CR, which was clearly and significantly higher than that of the control group (10 ± 2% of CR). The effect was decreased by all 5-HT antagonists tested. Thus, the effect of fluoxetine was decreased by the previous administration of (±)-pindolol to 2 ± 1% of CR [$(F(3, 31) = 61.5, p < 0.05$]

TABLE 1

ADMINISTRATION OF SEROTONERGIC, CHOLINERGIC, AND GLUTAMATERGIC ANTAGONISTS ON AUTOSHAPING TASK

Dose (mg/kg)	*n*	Conditioned Responses (%)
Control	72	10 ± 2
(±)-Propanolol (20)	8	13 ± 3
(±)-Pindolol (8)	8	13 ± 2
NAN-190 (0.5)	8	15 ± 5
Mesulergine (0.5)	8	14 ± 2
Ritanserin (1)	8	15 ± 2
Ketanserin (0.01)	8	16 ± 6
MDL-72222 (10)	8	11 ± 2
SDZ 205-557 (10)	8	11 ± 3
PCA (10 × 2 days)	32	9 ± 2
MK-801 (0.25)	8	7 ± 5
Scopolamine (0.17)	8	4 ± 1*

*$p < 0.05$.

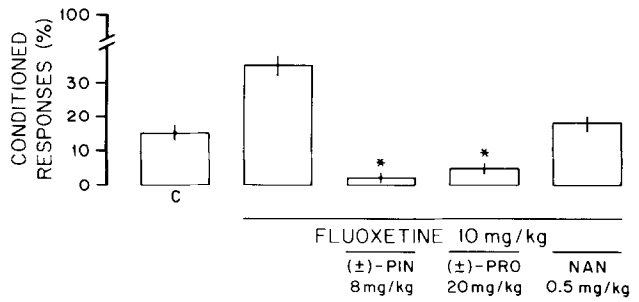

FIG. 2. Effects of 5-HT_1 antagonists (±)-pindolol, (±)-propanolol, and NAN-190 on the enhancement induced by posttraining injection of fluoxetine on CR of autoshaping task in fasting animals. Other conditions are as in Fig. 1.

and (±)-propanolol, to 5 ± 1% of CR [$F(3, 31) = 44.4$, $p < 0.05$]. NAN-190 inhibited the increment in CR produced by fluoxetine (Fig. 2), because this combination produced 13 ± 2% of CR [$F(3, 31) = 18.8$, $p < 0.05$]. The increase in CR induced by fluoxetine was significantly [$F(3, 31) = 12.4$, $p < 0.05$] diminished by previous administration of ketanserin, producing 10 ± 3% of CR; whereas ritanserin and mesulergine also blocked the effect of fluoxetine (Fig. 3), eliciting 9 ± 2% of CR [$F(3, 31) = 37.7$, $p < 0.05$] and 5 ± 2% of CR [$F(3, 31) = 41.6$, $p < 0.05$]. The administration of MDL-72222 decreased the effect of fluoxetine, provoking 8 ± 1% of CR [$F(3, 31) = 19.9$, $p < 0.05$]. The injection of SDZ 205-557 produced a slight decrease (Fig. 4), with 22 ± 8% of CR of the fluoxetine response, which was not significant [$F(3, 31) = 3.6$, $p > 0.05$]. The injection of PCA (Fig. 5) did not alter the effects of fluoxetine, eliciting 38 ± 4% of CR [$F(2, 23) = 1.7$, $p > 0.05$]. However, (±)-pindolol, (±)-propanolol, mesulergine, ritanserin, and MDL-72222 when tested with fluoxetine not only blocked the CR, but decreased it even below control values.

Experiment 4

Scopolamine administration blocked the CR (Fig. 6A), whereas fluoxetine significantly attenuated this effect [$F(3, 31) = 42.3$, $p < 0.05$]. The NMDA receptor antagonist dizocilpine, which was without effect by itself (Fig. 6B), was able to block the effects of fluoxetine [$F(3, 31) = 33.8$, $p < 0.05$].

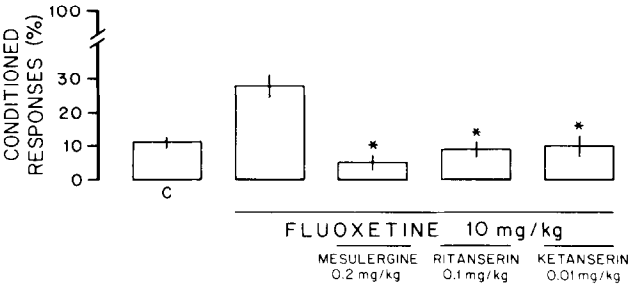

FIG. 3. Effects of 5-$HT_{2A-/2C}$y antagonists ketanserin, ritanserin, and mesulergine on the enhancement induced by posttraining injection of fluoxetine on CR of autoshaping task in fasting animals. Other conditions are as in Fig. 1.

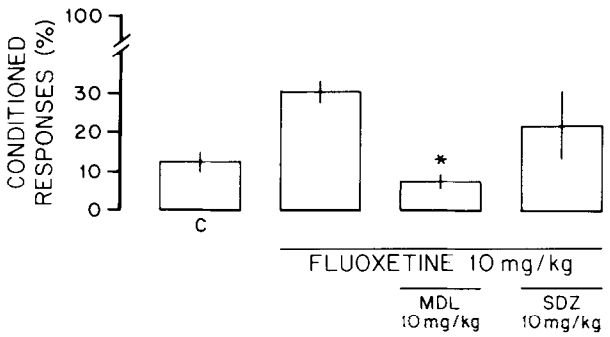

FIG. 4. Effects of MDL-72222 and SDZ 205-557, 5-HT_3, and 5-HT_4 antagonists, respectively, on the enhancement induced by posttraining injection of fluoxetine on CR of autoshaping task in fasting animals. Other conditions are as in Fig. 1.

DISCUSSION

Manipulations leading to an increase in 5-HT release from the raphe nucleus or the hippocampal administration of this monoamine have been reported to impair learning and memory (2,10,31). The present findings indicate that the increase in 5-HT neurotransmission induced by fluoxetine administration improved CR in a dose-dependent fashion. The enhancement of learning elicited by fluoxetine is consistent with reports of Flood and Cherkin (14) and Introni-Collison et al. (23), who showed that systemic administration of fluoxetine enhanced learning and memory. The fact that animals received drugs after training suggests that the present results cannot be attributed to unspecific effects, as may happen when drugs are administered immediately before the training session (32). The posttraining protocol eliminates effects on stress, arousal, and so forth, because animals are tested when the drugs effect has declined (32). In fact, in the present work the administration of 10 mg/kg fluoxetine before training resulted in a decrease of performance in the autoshaping task. Such an effect might be due to its anorexic activity (17).

When we used the β-adrenergic antagonists (±)-pindolol or (±)-propanolol to block 5-HT_{1A} and 5-HT_{1B} receptors (18,37), we observed a blockade of the effects of fluoxetine. In fact, the number of CRs was significantly lower than that of the control group. The selective and partial 5-HT_{1A} agonist

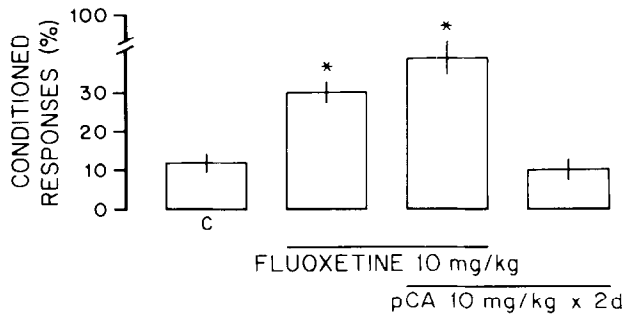

FIG. 5. Effects of PCA (10 mg/kg for 2 consecutive days) on the enhancement induced by posttraining injection of fluoxetine on CR of autoshaping task in fasting animals. Other conditions are as in Fig. 1.

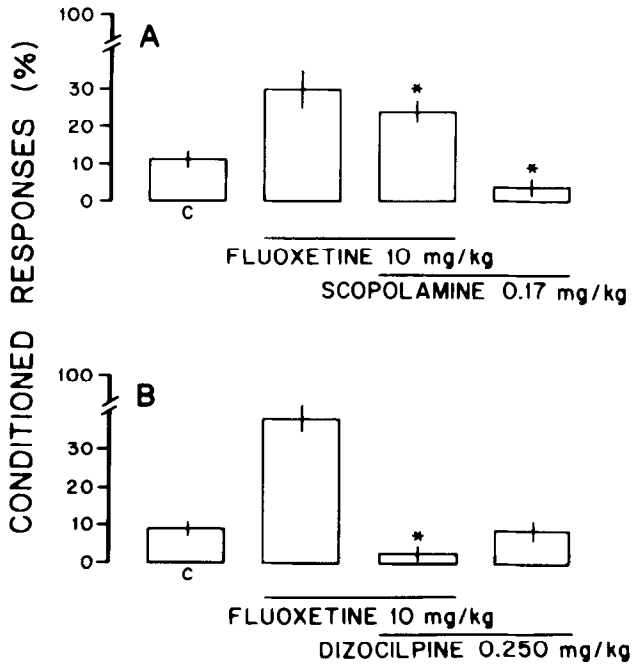

FIG. 6. Effects of scopolamine (6A) or dizocilpine (6B) on the enhancement induced by posttraining injection of fluoxetine on CR of autoshaping task in fasting animals. Other conditions are as in Fig. 1.

NAN-190 produced a partial decrease in the effect of fluoxetine. These findings suggest that both 5-HT_{1A} and 5-HT_{1B}y receptors are involved in the learning process, but 5-HT_{1B}y receptors may have a major role. The present results showed that all 5-HT_2 antagonists blocked the effects of fluoxetine; although mesulergine seemed to produce a greater effect, data were not significantly different from those produced by ketanserin or ritanserin. Mesulergine and ritanserin display higher affinity for 5-HT_{2C}y (formerly called 5-HT_{1C}y) than for 5-HT_{2A}y receptors, whereas ketanserin shows higher affinity for the latter receptors (37). Therefore, the effects of fluoxetine achieved through 5-HT_2 receptors could be attributed mainly to 5-HT_{2C}y receptor subtypes. The evidence for the role of 5-HT receptors in learning and memory processes is fragmentary and limited (2,12,31), however. It has been reported that an agonist effect on 5-HT_{1B}y (34,38,53) and 5-HT_{2C}y receptors impairs (27,34) learning and memory, whereas an antagonistic effect on 5-$HT_{2A/2B}$y or 5-HT_3 receptors enhance these processes (2,12,33). For instance, RU-24969, TFMPP, and mCPP, which display affinity for 5-$HT_{1B/2C}$y and 5-HT_{2A}y receptors (18,37,39,44), impaired learning (27,34,39,55). In fact, we found that the 5-HT_{1B}y agonists TFMPP and mCPP impaired the CR, and such an effect was reversed by fluoxetine and PCA (34). Information related to the effects of 5-HT_3 and 5-HT_4 agonists on learning and memory is scarce, but we also found that 5-HT_3 agonists impaired learning (22), whereas 5-HT_3 antagonists produce the opposite effect (12,22). In the present work, MDL-72222 but not SDZ 205-557 antagonized the increase in learning induced by fluoxetine. These data suggest that 5-HT_3 receptors participate in the fluoxetine-induced increase of learning, but it seems that 5-HT_4 receptors do not.

In experiments using a learning and memory task, the re-

sults obtained with serotonergic agonists and antagonists displaying affinity for one or several 5-HT receptor types or subtypes suggest a complex function of this monoamine (2,12,14,22,31,33–36,38,48,53,55). Apparently, the activation or blockade of serotonergic receptors can increase or decrease learning and memory. Thus, on the one hand, drugs such as fluoxetine activate most 5-HT receptors, but probably in variable degrees. On the other hand, cognitive processes are improved by the selective blockade of either 5-HT_{2A}y, 5-HT_{2C}y, or 5-HT_3 receptors (2,12,33). The report that alaproclate and zimeldine (5-HT uptake inhibitors) enhance learning and memory on an avoidance test (1) provides further support to the idea that this effect on learning may be shared by all 5-HT uptake inhibitors. When 5-HT uptake is blocked extracellular serotonin is increased, but the magnitude of the increase seems to be limited by a compensatory decrease in 5-HT neurone firing and release (16). It has been proposed that fluoxetine elicits antidepressant and hypophagic effects through stimulation of 5-HT_{1A}y and 5-HT_{2C}y receptor, respectively (29). Meanwhile, stimulus properties for drug discrimination (5) and anxiogenic activities of fluoxetine seem to be due to 5-HT_{2A}y and 5-HT_{2C}y receptors stimulation (29). However, in the present case, there seems to be a major participation of several 5-HT receptors, namely: 5-$HT_{1A/1B}$, 5-$HT_{2A/2C}$y and 5-HT_3. Uptake inhibition would be expected to enhance 5-HT input to pre- and postsynaptic neurons in many brain areas to which serotonergic pathways project (25,52). However, in the present work, the elimination of presynaptic activity by PCA pretreatment did not modify the effects of fluoxetine. Therefore, the increase in CR observed after fluoxetine administration in PCA-pretreated rats seems to be due to a simultaneous interaction with multiple 5-HT postsynaptic receptors.

The brain structures implicated in learning and memory processes (21,51,57) contain a large number of 5-HT receptors (9,21,41,45,52) as well as other neurotransmission systems (51). The interaction of fluoxetine with other neural systems was indicated by the results obtained with dizocilpine, a noncompetitive antagonist of NMDA receptors (15,26,50); it was able to prevent the effects of fluoxetine. Furthermore, the interaction between serotonergic and cholinergic systems was also evident, as fluoxetine injection reversed the impairment induced by scopolamine. Therefore, both serotonergic and glutamatergic receptors participate in the enhancement of CR elicited by fluoxetine. It is difficult to establish whether fluoxetine also enhanced the glutamatergic or cholinergic neurotransmission, or whether the observed prevention of the effect induced by scopolamine or dizocilpine injection was the result of a physiologic antagonism. Finally, although the behavioral effects of the stimulation of 5-HT receptors have been extensively studied [see (18,28,54) for reviews], there are only a few publications regarding the effects of this monoamine on learning and memory processes (2,10,12,31). Therefore, further work is required to confirm and extend the present findings.

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