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Effects of 5-HT_4 Receptor Agonists and Antagonists in Learning

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MENESES, A, AND E. HONG. *Effects of 5-HT_4 receptor agonists and antagonists in learning.* PHARMACOL BIOCHEM BEHAV **56**(3) 347–351, 1997.—In the present work, the effects of pre- or post-training (ip) injection of BIMU1 and BIMU8 (5-HT_4 agonists) were figured out in the autoshaping learning task. Furthermore, the post-training effects of these agonists after treatment with SDZ 205-557 and GR 125487D (5-HT_4 antagonists) or *p*-Chloroamphetamine (PCA) were also explored. Animals were individually trained in a lever-press response on the autoshaping task and 24 hours later were tested. The results showed that pre-training injection of BIMU1 (5–20 mg/Kg) or BIMU8 (20 mg/Kg) increased the CR; in contrast, the post-training administration of BIMU1 (10–20 mg/Kg) or BIMU8 (5 and 20 mg/Kg) decreased it. Further experiments revealed that the post-training injections of SDZ 205-557 (1.0–10.0 mg/Kg) or GR 125487D (0.39–1.56 mg/Kg) by themselves did not alter the CR. When BIMU1 or BIMU8 was administered to rats pretreated with SDZ 205-557 (10 mg/Kg) or GR 125487D (0.78 mg/Kg), the decrement induced by 5-HT_4 the agonists was reversed; in contrast, the administration of PCA failed to modify the CR or the agonist-induced responses. The findings showed that the pre-training stimulation of 5-HT_4 receptors enhanced the acquisition of CR, while, post-training activation of 5-HT_4 receptors, impaired the consolidation of learning. The latter effect was not altered by PCA pretreatment. The data show that 5-HT_4 receptors are involved in the acquisition and consolidation of learning. It seems that postsynaptic 5-HT_4 receptors are involved in the latter effect. **Copyright © 1997 Elsevier Science Inc.**

Serotonin 5-HT_4 receptors Learning Rats

SEROTONERGIC neurotransmission involves the action of multiple 5-hydroxytryptamine (5-HT) receptor types and subtypes, i.e. 5-$HT_{1A\text{-}1F}$, 5-$HT_{2A\text{-}2C}$, 5-$HT_{3\text{-}7}$ (12,18), which present heterogeneous distribution (19). Serotonergic pathways project to many brain areas (16), some of them being involved in learning and memory (32). Notwithstanding, there is little and fragmentary information about the role of this monoamine in learning and memory processes (1,13,28). In this concern, it has been reported that 5-$HT_{2A\text{-}2C}$ and 5-HT_3 receptor antagonists improved in learning (1,6,13,15). The experimental evidence concerning the effects of 5-HT_{1A} agonists on learning and memory tasks is controversial (13,15,20–24,27,28). Thus, there are reports suggesting that 5-HT_{1A} agonists impair, improve or have no effects on these processes (1,13,21,22,27,28). In addition, it was recently reported that the pre-training administration of 5-HT_4 receptor agonists improve social learning and prevented amnesia (9–11). Unfortunately, the use of this administration scheme does not exclude possible nonspecific effects (20–23). Therefore, in order to further investigate the role of 5-HT_4 receptors in the consolidation of the conditioned response (CR), we studied the individual and combined effects of some selective 5-HT_4 receptor agonists and antagonists. Furthermore, the effects of the 5-HT depleter, *p*-Chloroamphetamine, were evaluated to find out whether pre- or postsynaptic receptors are involved in the consolidation of CR. Likewise as in the works of Ghelardini et al BIMU1 and BIMU8 were pre-training injected (9–11), we also explored their effects using such scheme of administration. It should be highlighted that the autoshaping task has proved useful to detect enhancing or impairing effects of both aging and drugs on learning (16,17,21–24).

MATERIALS AND METHODS

Subjects

Male Wistar rats (12 wk old) were collectively housed in a temperature and light-controlled room under a 12:12 h

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The receptor nomenclature used in this paper is that recommended by the Serotonin Receptor Nomenclature Committee (Hoyer et al., 1994). Supported by CONACYT grant 4367-M9406.

light:dark cycle (light on at 7:00 A.M.). Water and food were provided ad lib for a week. After that period, their body weights were reduced to 85% by gradually reducing the food intake during seven days.

Apparatus

Operant chambers for rats with standard sound-attenuation were used. Chambers were 25 cm wide, 29 cm long, and 25 cm high. 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, Frenchtown, NJ) 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, USA).

Autoshaping Training

Each rat was placed into an experimental chamber and allowed to habituate to the experimental environment until the animal found and ate 45 food pellets (45 mg each). Immediately thereafter that, the program began. This consisted in 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 sec. When the animal pressed the CS, the lever was retracted, the light was turned off, and a US was delivered immediately; this action was considered a conditioned response (CR). The increase or decrease in percentage of CR in treated groups compared with vehicle animals was considered as an enhancement or impairment retention of the CR, respectively. The first (training) session consisted of 10 trials and the second (test) session of 20. All compounds were injected immediately before or after the first autoshaping session and rats were tested 24 h later. The results correspond to the first and the second autoshaping sessions.

Drug Treatment

The drugs used were: *p*-Chloroamphetamine (PCA $\times$ 2 consecutive days), on days 8 and 7 before the first autoshaping session (Research Biochemical Inc., Wayland, MA); 3-ethyl-2, 3 dihydro- 2-oxobenzimidazol- 1-(3a-tropyl) carboxamide HCl (BIMU1); 3-isopropyl-2, 3-dihydro-2-oxo-1h-benzimidazole-1- 1-(3atropyl) carboxamide HCl (BIMU8) (Boehringer Ingelheim, Milan, Italy); 2-methoxy-4-amino-5-chloro-benzoic acid 2-(diethylamino ester) (SDZ 205-557) (Sandoz Pharma Ltd., Basel, Switzerland); (GR 125487D) (Glaxo, Greeford, Middlesex, UK). All drugs were dissolved in saline and injected (ip) in a volume of 1 ml/Kg.

Measurements and Analysis

The number of CR was transformed to a percentage of total trials of the second session. Since these data represent a continuous variable they were computerized using parametric statistics (8). Multiple group comparisons were made using ANOVA followed by the Dunnet's *t*-test (e.g., vehicle vs several dose treatments, or PCA vs agonist, antagonists or the combination of the neurotoxin plus other drugs). In all statistical comparisons, $p < 0.05$ was used as criterion for significance. The n per group was 8 and animals were used only once.

TABLE 1

GROUPS PRE- OR POST-TRAINING TREATED WITH BIMU1 OR BIMU8 ON THE AUTOSHAPING LEARNING TASK (CR%) IN RATS

First Session	Pre-training	Post-training
Treatment (mg/Kg)		
Control	7.5 ± 2	7.5 ± 1
BIMU1		
5	5.7 ± 1	6.5 ± 2
10	5.0 ± 1	6.2 ± 2
20	6.0 ± 1	6.2 ± 1
Control	5.0 ± 1	6.2 ± 1
BIMU8		
5	5.5 ± 2	5.0 ± 2
20	7.2 ± 1	6.2 ± 3

*Dunnet's t-test < 0.05 vs. vehicle-injected controls.

EXPERIMENT 1

Effects of 5-HT_4 Receptor Agonists and Antagonists in Learning

The purpose of these experiments was to find out the effects of pre- or post-training injection of BIMU1 or BIMU8 on the conditioned response (CR). Animals were injected immediately before or after the first training session with vehicle, BIMU1 or BIMU8 (10-30 mg/Kg). Rats were placed in their home cages and tested the next day.

EXPERIMENT 2

Effects of 5-HT_4 Receptor Agonists and Antagonists or PCA in Learning

The aim of the present experiments was to find out whether post-training injection of 5-HT_4 agonists could be altered by 5-HT_4 antagonists and to investigate the pre- or postsynaptic location of the receptors with which they interact. Therefore, groups of rats were treated with SDZ 205-557 or GR 125487D immediately after the first autoshaping session and 10 min later received BIMU1 or BIMU8. Other animals were pretreated consecutively with PCA (10 mg/Kg) the days 8 and 7 before the autoshaping test and this group was compared with a control group receiving only the vehicle. Other PCA pretreated groups were injected with BIMU1 or BIMU8 immediately after the first autoshaping session and tested 24 h later.

RESULTS

Experiment 1: Effects of 5-HT_4 Receptor Agonists and Antagonists in Learning

During the training session no significant differences between pre- or post-training control and treated animals were found (Table 1); however, in the session test the results show that the pre-training administration of BIMU1 and BIMU8 significantly increased the percent of CR (Fig. 1), [$F(3, 31) = 4.2$, and $p < 0.05$] and [$F(2, 23) = 3.4$, and $p < 0.05$], respectively. In contrast, a significant decrease in CR was observed with post-training injection of BIMU1 [$F(3, 31) = 7.2$, and $p < 0.05$] but not with BIMU8 [$F(2, 23) = 3.9$, and $p < 0.05$] administration (Fig. 1). A further analysis with Dunnett's *t*-test revealed that, at the doses of 5-10 mg/Kg, BIMU1 increased significantly the rate of CR and decreased it, at doses of 10

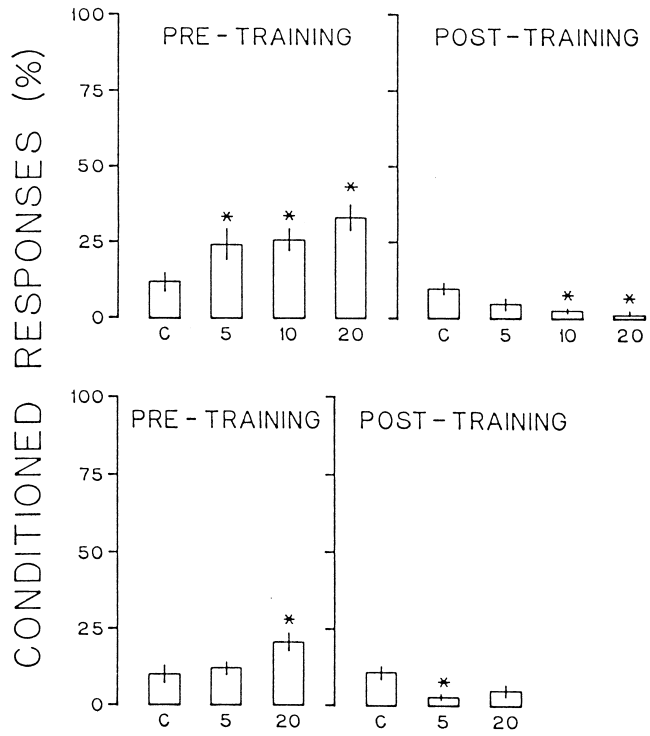

FIG. 1. Effect of acute pre- or post-training administration (ip) of BIMU1 (upper) and BIMU8 (bottom) on the autoshaping task in fasted animals. Data are plotted according to percent of control conditioned responses (CR%) All rats received injection immediately before or after the first training session. Values represent the mean ± S.E.M. of 8 different animals *Dunnet's t-test < 0.05 vs vehicle-injected controls.

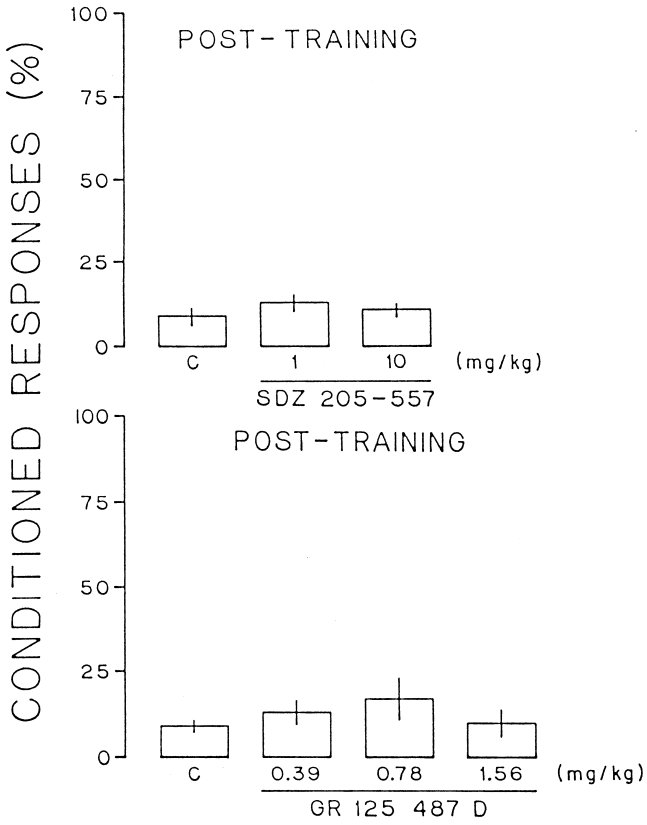

FIG. 2. Effect of acute post-training administration (ip) of SDZ 205-557 or GR 125487D on the autoshaping task in fasted animals. Data are plotted according to percent of control conditioned responses (CR%) All rats received injection immediately after the first training session. Values represent the mean ± S.E.M. of 8 different animals *Dunnet's t-test < 0.05 vs vehicle-injected controls.

and 20 mg/Kg; while BIMU8 increased the CR at a dose of 20 mg/Kg and decreased it at a dose of 5 mg/Kg (Fig. 1).

Experiment 2: Effects of 5-HT$_4$ Receptor Agonists and Antagonists or PCA

SDZ 205-557 or GR 125487D did not alter the number of the CR (Fig. 2). The data from vehicle and PCA-treated animals showed no significant differences [$F(1, 31) = 0.03$ and, $p > 0.05$). Fig. 3 shows that SDZ 205-557 [$F(3,31) = 16.2$, and $p < 0.05$) and GR 125487D [$F(3, 31) = 12.2$, and $p < 0.05$] significantly blocked the decrement in the CR induced by BIMU1 or BIMU8 post-training injection. Post hoc analysis revealed that SDZ 205-557 (10 mg/Kg) or GR 125487D (0.78 mg/Kg) antagonized significantly the BIMU1 and BIMU8 induced impairment. Neither did the PCA injection affect the CR by itself, nor the effect provoked by BIMU1 and BIMU8 (Fig. 3), producing a nearly 6 ± 3% [$F(3, 32) = 1.4$, and $p > 0.05$] and 5 ± 2% of CR [$F(3, 32) = 1.8$, and $p > 0.05$], before and after PCA administration, respectively.

DISCUSSION

The Autoshaping Task as a Model to Test the Effects of Drugs on Learning

The autoshaping procedure has been previously used to assess learning (16,17,21–25). Slight modifications to this procedure may result in variable data. e.g. the training session itself results in significant increases of the CR when comparing the trained group (10 ± 2%) with the untrained group (0.6 ± .6%) (unpublished observations). It was recently shown that when animals are trained without the food-magazine, they displayed a lower percentage of the CRs (3 ± 2%) with respect to the control group trained with the food magazine (8 ± 2% of CR) in the corresponding autoshaping session (22). A similar score was obtained in the present work in PCA-treated animals and their respective controls. It is noteworthy that, during the autoshaping training, animals learn to perform an active behavior (e.g. lever-press responses) as a result of the association between CS and US. Significantly, this association can be modified by drugs and training which implies that the conditions of the test are adequate to detect if a drug modifies learning (16,17,21–25). For instance, the post-training injection of scopolamine produces a significant decrease of the CR (4 ± 1%) (23), while *d*-amphetamine induces a large increment (28 ± 6%) (25). In addition, we have noticed that the use of 10 instead 5 or 20 trials, detects better the drug-induced changes in CR (unpublished results). Furthermore, deteriorated animals (aged or hypertensive) compared to healthy young or normotensive rats clearly display decreased learning (24).

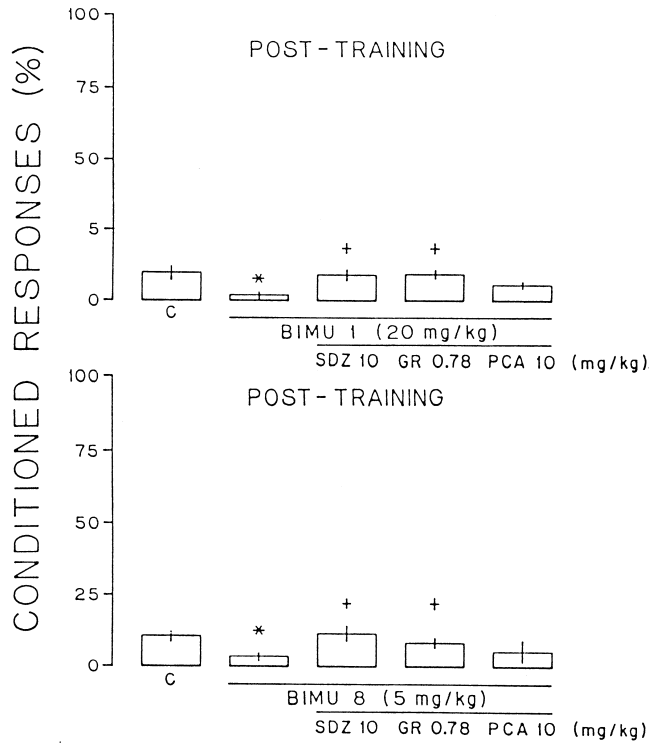

FIG. 3. Effects of post-training injection of SDZ 205-557, GR 125487D or PCA on the impairment induced by post-training injection of BIMU1 (upper) or BIMU8 (bottom) on CR of autoshaping task in fasted animals. Dunnet's t-test < 0.05 * vehicle-injected controls; + PCA vs 5-HT_4 drugs.

Effects of 5-HT_4 Receptor Agonists and Antagonists in Learning

The major finding of the present work was that pre-training injection of 5-HT_4 agonists enhanced the acquisition of learning, while the post-training administration impairs the consolidation. These data clearly suggest that the stimulation of 5-HT_4 receptors is involved in different aspects of cognitive processes (see below). Furthermore, the post-training administration of 5-HT_4 receptor antagonists did not affect learning by itself. These findings suggest that the stimulation of the 5-HT_4 receptors improves the acquisition of learning but impairs its consolidation. The latter effect was reversed by 5-HT_4 receptor antagonists but not by PCA pretreatment thereby suggesting the participation of postsynaptic 5-HT_4 receptors.

Contrasting findings, as those presented here, have been reported by us and Altman and Normile (see 1,13 for reviews, 2,21–23), e.g., pre-training injection of 8-OH-DPAT (a 5-HT_{1A} agonist) or ketanserin, mianserin and pirenperone (5-HT_2 antagonists) impaired the acquisition of the conditioned response or the inhibitory avoidance response, respectively, whereas their post-training administration enhanced the consolidation and retention (1,13,21,22). These effects were interpreted as a decrease in the acquisition of learning (pre-training injection) and as an increase in the consolidation or retention (post-training injection), respectively. It is noteworthy that the manipulation of the 5-HT receptors produces multiple behavioral alterations (6,7,12,18,19). Therefore, on the one hand, the effects observed with the pretraining injections cannot be interpreted exclusively in terms of changes in cognitive processes (13,20–25,27,28). On the other hand, inasmuch as the other animals received the drugs after the first training session, our results most probably reflect a specific effect in the consolidation of learning (20–22). It should be noted that, all saline and drugs treated animals consumed the 50 free pellets, thus suggesting that food intake was not altered. In addition, the comparison between the rate of CR attained by control and treated groups during the first session revealed no significant difference (Table 1); consequently, the differences observed during the second session cannot be attributed nonspecific effects. Therefore, the differences registered during the second session test cannot be attributed to factors as taste aversion, locomotor activity, etc. Notwithstanding, the present interpretations must be taken with caution since the stimulation of 5-HT_4 receptors produces long-lasting effects (7).

BIMU1 and BIMU8 display affinity for 5-HT_4 and 5-HT_3 receptors, while SDZ 205-557 and GR 125487D are considered very potent and selective drugs at 5-HT_4 receptors (see 7,18 for review), GR 125487D being more stable by in vivo studies (4,5). Concerning the doses of 5-HT_4 agonists and antagonists used here, these are similar than those reported by others (4,7,9–11,18). In fact, Ghelardini et al noted that higher doses than those described produced side-effects (9–11). There is evidence that PCA treatment (under the same schedule used here) reduced significantly the 5-HT levels in some cerebral areas (1,13,19). Admittedly, such treatment does not alter all serotonergic innervation, since some neurotoxic amphetamines such as PCA, cause extensive degeneration of fine 5-HT axons in forebrain, while some groups of beaded 5-HT axons and serotonergic cell bodies in the brainstem are unaffected (13,19). This could help to explain why in the present and previous works vehicle and PCA treated animals did not show significant differences in the CR. Furthermore, it has been reported that p-chlorophenylalanine (PCPA) administration alone does not alter learning (13,16,17,21–23,28); indeed, several authors have found that 5-HT depletion induced by PCA, PCPA or 5,7-DHT impaired, improved or had not effect on learning (1,2,13,28). Such discrepancies may be attributed to differences in the behavioral tasks, doses of drugs, pharmacologic treatments and environmental manipulations employed in such studies (1,13).

Autoradiographic studies have revealed that 5-HT_4 receptors are localized in the habenula, hippocampus, amygdala (4,18,19) and present findings suggest that such 5-HT_4 receptors could be involved in the impairing effects of BIMU1 or BIMU8. Ghelardini et al have reported that 5-HT_4 agonists improved learning (9–11). For instance, pre-training stimulation of 5-HT_4 receptors improves social learning, prevents amnesia and reverses defects in learning and memory following exposition to hypercapnia and hypoxia (9–11). In addition, electrophysiological studies have shown that 5-HT_4 receptors mediate a slow but long lasting excitatory response in the hippocampus (3,5,14,19,26,30,31). Such structure is markedly involved in learning and memory processes (29,32). There is also evidence that the 5-HT_3 blockade or 5-HT_4 receptor stimulation enhances the long-term potentiation (LTP) (14,29,31), a form of synaptic plasticity apparently related to learning and memory (29).

The role of 5-HT receptors in learning and memory is far to be established. However, previous data and the present work indicate that 5-HT_{1A} (21,22), 5-HT_{1B} (17) and 5-HT_3 presynaptic receptors (16) and postsynaptic 5-HT_4 (this work) are involved. Thus, for instance, it was reported that the stimulation of 5-HT_{1B} or 5-HT_3 presynaptic receptors impaired retention of the CR (1,16,17), while the activation of 5-HT_{1A}

autoreceptors enhanced it (21,22). Likewise, it is possible that an inverse relationship between learning and 5-HT activity involving such receptors exists. This possibility is consistent with the findings that the electrical stimulation of the dorsal raphe or intrahippocampal injection of serotonin impaired learning on avoidance and Y-maze tasks (see 1,13,15,28 for reviews). However, there is evidence that an increase in 5-HT levels provoking the activation of multiple 5-HT postsynaptic receptors, as occurred with fluoxetine administration, enhanced learning (23). The present work, also strongly suggests that central 5-HT_4 receptors probably, located in postsynaptic neurons, participate in the consolidation of learning though further work using 5-HT_4 agonists plus antagonists in PCA pretreated animals will be required to confirm this suggestion.

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