Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 3, pp. 805–807, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0028-G

BRIEF COMMUNICATION

The 5-HT_{1A} Agonist Tandospirone Disrupts Retention But Not Acquisition of Active Avoidance Learning

DAVID QUARTERMAIN,*[1] JONATHAN CLEMENTE* AND ANNE SHEMER†

*Department of Neurology, New York University Medical Center, New York, NY
†Pfizer Inc., New York, NY

Received 30 April 1993

QUARTERMAIN, D., J. CLEMENTE AND A. SHEMER. *The 5-HT_{1A} agonist tandospirone disrupts retention but not acquisition of active avoidance learning.* PHARMACOL BIOCHEM BEHAV **48**(3) 805–807, 1994.—To determine the effects of the 5-HT_{1A} partial agonist tandospirone on acquisition and retention, mice were trained on a one-way active avoidance task and tested for retention 24 h later. Groups of mice were injected with either saline or 1, 5, or 10 mg/kg tandospirone 30 min before acquisition. Training was complete when animals achieved a criterion of five avoidances in a block of six trials. Results showed that tandospirone did not alter the rate of acquisition of the avoidance response, but retention was significantly disrupted by the 1- and 5-mg/kg doses. These findings confirm previous suggestions that 5-HT_{1A} agonists can cause anterograde amnesia.

5-HT_{1A} agonists Active avoidance Anterograde amnesia Tandospirone

RECENT studies of the effects of 5-HT_{1A} agonists such as buspirone and tandospirone on learning and memory in animal subjects have consistently shown that acute administration of these drugs disrupts performance (1,2,3,5,7). However, it is unclear whether the impairment is the result of weakened learning or disturbed retention because deficits occur only when the agents are administered before the training phase. A recent study from this laboratory (7) suggests that the deficit is probably the result of disruption of memory processes because retention was unimpaired if performance was tested 1 rather than 24 h after learning.

The purpose of the present experiment was to obtain more direct evidence of the effects of 5-HT_{1A} agonists on learning and memory by examining performance in a multitrial active avoidance task where alterations in the rate of acquisition can be used as a measure of the extent to which the drug influences learning. Retention of this learning, tested in the absence of the drug, provides a measure of the effects of the agent on memory processes.

METHOD

Subjects were male Swiss Webster mice (Harlan Hsd: ND4), 6 weeks old and weighing 25–30 g.

The apparatus was a two-compartment chamber consisting of an aluminum V trough and a black Plexiglas goal box with a hinged door at the end. The compartments were separated by a guillotine door. The dimensions of the V trough and the goal box were 12.7 × 12.7 × 10.2 cm. The goal box was covered with a black Plexiglas lid and the V trough with a clear acrylic sheet painted white except for a 5-cm^2 area over the door, which was left clear for observation. A 5-W miniature lamp was mounted in the center of the lid. Each of the walls of the V trough was connected to one pole of a Grason

[1] Requests for reprints should be addressed to David Quartermain, Laboratory of Behavioral Neurology, Department of Neurology, New York University Medical Center, 550 1st Avenue, New York, NY 10016.

Stadler constant current shocker (model 700) that was activated by control circuitry to deliver 0.5-mA AC shocks.

Training

A trial was initiated by placing a mouse in the V trough facing away from the door. After 5 s the light and latency timer were activated and the door was raised. After 10 s the shock was automatically initiated. When the mouse crossed into the goal box, the latency timer was stopped and the light and shock were terminated. Mice were removed via the rear door and transferred to a holding cage for the 30-s intertrial interval (ITI). Training trials were continued until the animal achieved a criterion of five avoidances in a block of six trials.

Testing

Retention was tested by employing the procedures used in training except that no shock was administered. Mice failing to cross into the goal compartment within 60 s were given that latency as a test score. The test session consisted of five trials separated by a 30-s ITI.

Drug Treatment

Tandospirone (Pfizer Inc.) was dissolved in distilled water and administered SC in a volume of 10 ml/kg b.wt. Mice were injected with either physiological saline (N = 13), tandospirone 1 mg/kg (N = 12), tandospirone 5 mg/kg (N = 13), or tandospirone 10 mg/kg (N = 11) 30 min prior to the training session. Retention was tested 24 h after training. No drugs were administered before testing.

RESULTS AND DISCUSSION

Training

These data are shown in Table 1. A one-way ANOVA indicated a significant difference among the four treatment groups, $F(3, 45) = 3.45$, $p = 0.024$. Bonferroni t-tests revealed that this difference was mainly the result of faster learning by the tandospirone 1 mg/kg group. The data in Table 1 give no indication that tandospirone disrupts learning processes; in fact, there is a suggestion that low doses of the agonist may actually facilitate acquisition of active avoidance.

Testing

Mean five-trial test latencies for the four groups are shown in Fig. 1. A two-way ANOVA carried out on these data revealed a significant main effect for treatment groups, $F(3, 45) = 3.16$, $p = 0.036$, but no significant effect of test trials (F = 2.1) and no significant interaction between the two variables (F = 0.3). Because test trials were not a significant source of variance, mean five-trial test latency was used to examine the differences among the four treatment groups. The results of Bonferroni t-tests revealed that both the 1- and 5-mg/kg dose significantly ($p < 0.05$) impaired retention when compared to the saline latencies (t = 4.03 and 4.44, respectively). The latencies of both 1- and 5-mg/kg groups were also significantly different from those of the 10-mg/kg group (t = 3.73 and 4.11, respectively). These results indicate that retention of active avoidance was impaired by 1- and 5-mg/kg tandospirone but not by the 10-mg/kg dose. The absence of disruption in the 10-mg/kg group is noteworthy but not unexpected. We have previously shown that 10-mg/kg tandospirone produced less impairment of classical fear conditioning than either 2- or 5-mg/kg doses (7). The reasons for this reversal in the dose–effect curve are unclear.

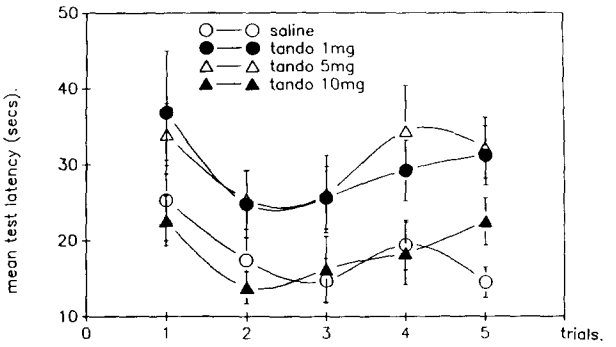

FIG. 1. Tandospirone effects on active avoidance in mice. Test latencies for the four treatment groups 24 h following training. No drugs were administered before testing.

Although the mechanism underlying the disruption of retention cannot be determined from these results, it is likely that the effects of tandospirone are mediated by 5-HT_{1A} receptors. In a previous study (5), we showed that tandospirone-induced disruption of passive avoidance retention could be blocked by the 5-HTA_1 receptor antagonist BMY7378 {8-[2-[4-92-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspirol-[4]-decane-7,9-dione} and mimicked by the 5-HT_{1A} receptor agonist 8-OH-DPAT (8-hydroxy-dipropylaminotetralin HBr). In addition, radioligand binding studies have shown that tandospirone binds with high affinity to a homogeneous population of 5-HT_{1A} binding sites in the brain (4,6). These finding suggest that tandospirone selectively stimulates 5-HTA_1 receptors and that this is most likely the molecular mechanism mediating the disruptive effects on memory retention.

The results of this experiment add to the accumulating evidence that pharmacological activation of the 5-HT_{1A} receptor subtype can cause behavioral disruption in animals. Previous experiments have not adequately assessed the effects of the drugs on acquisition processes so that it was possible that some of the deficit may have been due to weaker learning. The present experiment eliminates this source of ambiguity by showing that rates of acquisition are not retarded by tandospirone. These findings suggest that learning and short-term retention are unaffected by 5-HT_{1A} receptor stimulation and that the locus of the deficit is in processes involved in the formation of durable, long-term memory.

TABLE 1

MEAN TRIALS TO A CRITERION OF FIVE AVOIDANCES IN A BLOCK OF SIX TRIALS FOR MICE TREATED WITH TANDOSPIRONE OR SALINE PRIOR TO TRAINING

Group	N	Mean	SEM
1. Saline	13	12.7	1.98
2. Tandospirone (1 mg/kg)	12	9.1	0.68
3. Tandospirone (5 mg/kg)	13	16.3	1.61
4. Tandosiprone (10 mg/kg)	11	13.1	1.74

One-way ANOVA, $F(3,45) = 3.45$, $p = 0.024$.

Bonferroni pair wise comparisons: group 2 vs. group 3, t = 3.213, $p < 0.05$.

REFERENCES

1. Bass, E. W.; Means, A.; McMillen, B. Buspirone impairs performance of a three-choice working memory water escape task in rats. Brain Res. Bull. 28:455–461; 1992.
2. Carli, M.; Samanin, R. 8-Hydroxy-2-(di-n-propylamino) tetralin, impairs spatial learning in a water maze: Role of postsynaptic 5-HT_{1A} receptors. Br. J. Pharmacol. 105:720–726; 1992.
3. Carli, M.; Tranchina, S.; Samanin, R. 8-Hydroxy-2-(di-n-propylamino) tetralin, a 5-HT_{1A} receptor agonist, impairs performance in a passive avoidance task. Eur. J. Pharmacol. 211:227–234; 1992.
4. Hamik, A.; Oksenberg, D.; Fischette, C.; Peroutka, S. Analysis of tandospirone (SM-3997) interactions with neurotransmitter receptor binding sites. Biol. Psychiatry 28:99–109; 1990.
5. Mendelson, S. D.; Quartermain, D.; Francisco, T.; Shemer, A. 5-HT_{1A} agonists induce anterograde amnesia in mice through a postsynaptic mechanism. Eur. J. Pharmacol. 236:177–182; 1993.
6. Miller, L.; Thompson, M.; Byrnes, J.; Greenblatt, D.; Shemer, A. Kinetics, brain uptake and receptor binding of tandospirone and its metabolite 1-(2-pyrimidinyl)-piperazine. J. Clin. Psychopharmacol. 12:341–345; 1992.
7. Quartermain, D.; Clemente, J.; Shemer, A. 5-HT_{1A} agonists disrupt memory of fear conditioning in mice. Biol Psychiatry 33:247–254; 1993.