Pharmacology Biochemistry and Behavior, Vol. 62, No. 1, pp. 159–164, 1999

0091-3057/99 $–see front matter

PII S0091-3057(98)00139-7

The Effects of Diazepam and Zolpidem on Cocaine- and Amphetamine-Induced Place Preference

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Received 19 March 1998; Revised 18 June 1998; Accepted 18 June 1998

MERIRINNE, E., A. KANKAANPÄÄ, P. LILLSUNDE AND T. SEPPÄLÄ. *The effects of diazepam and zolpidem on cocaine- and amphetamine-induced place preference.* PHARMACOL BIOCHEM BEHAV **62**(1) 159–164, 1999.—Drugs such as benzodiazepines, which enhance the effects of inhibitory neurotransmitter gamma-amino butyric acid (GABA), are known to modulate the mesocorticolimbic dopaminergic system, which is considered to mediate the rewarding effects of psychostimulants. The effects of diazepam, a benzodiazepine that binds unspecifically to omega l- (ω1-) and ω2-receptors, and zolpidem, a nonbenzodiazepine drug that binds preferentially to ω1-receptors, on cocaine- and amphetamine-induced place preference were evaluated in Wistar rats. In tests using the counterbalanced method, neither diazepam (0.2, 1, and 5 mg/kg) nor zolpidem (2.5, 5, and 10 mg/kg) alone induced place preference or place aversion. Diazepam pretreatment prevented both cocaine- and amphetamine-induced (15 and 9 mg/kg, respectively) place preference; however, at doses that were earlier shown to cause sedation and amnesia, zolpidem failed to prevent either cocaine- or amphetamine-induced place preference. These results suggest that diazepam interferes with the rewarding properties of the psychostimulants, whereas zolpidem is less effective in this respect, possibly due to differential distribution of ω1- and ω2-receptors in the brain. © 1998 Elsevier Science Inc.

Amphetamine Benzodiazepine Cocaine Conditioned place preference Diazepam Rat Reward Zolpidem

PSYCHOSTIMULANTS, such as cocaine and amphetamine, are known to stimulate dopaminergic neurons. There are several lines of evidence suggesting that dopaminergic stimulation in the mesocorticolimbic system, particularly in the nucleus accumbens, is involved in the rewarding properties of cocaine and amphetamine. For example, the destruction of dopaminergic neurons in the nucleus accumbens with catecholaminergic neurotoxin 6-hydroxydopamine disrupted the reinforcing effects of cocaine and amphetamine as measured in rats using the self-administration method (6,23). Similar results were also obtained in rats pretreated with various dopamine-receptor blockers (17,40).

Many investigators have suggested that mesocorticolimbic dopamine neurons might be under the control of inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Systemic injections of diazepam and midazolam, benzodiazepines that act by enhancing the effects of GABA, reduced the release of dopamine in the nucleus accumbens as measured by microdialysis (16,20). When microinjected into the nucleus accumbens, benzodiazepine flurazepam also attenuated dopamine transmission (41). Moreover, in a recent study it has been shown that both benzodiazepine lorazepam and gamma-vinyl GABA, an irreversible inhibitor of GABA-transaminase, attenuated the cocaine-induced increase of extracellular dopamine levels in the striatum (10). Similar results were also observed in the nucleus accumbens with gamma-vinyl GABA (27).

Conditioned place preference is a behavioral test for measuring the rewarding properties of drugs in animals (7). In several studies cocaine and amphetamine have induced positive place preference, which may indicate their rewarding

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properties and abuse potential. The results obtained with GABAergic drugs, however, are much more dissimilar. Diazepam and other benzodiazepines sometimes have and sometimes do not have induced positive place preference (11,15, 30,36). The discrepancy in the results might be due to different testing conditions. Nevertheless, it has been suggested that GABAergic drugs are only marginally effective as reinforcers in rats, as mentioned in a review by Wood et al. (39). The effect of zolpidem, a nonbenzodiazepine GABAergic drug, in the place preference method is not known.

The aim of this study was to evaluate whether diazepam and zolpidem can prevent cocaine- and amphetamine-induced place preferences in rats. Diazepam enhances GABAergic transmission by binding to both omega1- (ω1-) and ω2-subtypes of $GABA_A$ receptors, whereas zolpidem is considered to bind preferentially to ω1-subtypes (33). The doses used were 0.2, 1, and 5 mg/kg for diazepam, and 2.5, 5, and 10 mg/kg for zolpidem. At these doses both drugs have, for example, depressed locomotor activity or impaired learning and memory (8,13,14,25).

METHOD

Animals

Adult male Wistar rats obtained from the Laboratory Animal Centre, University of Helsinki, Finland, were used. They weighed 180–320 g at the beginning of the experiment and were housed two per cage in a 12 L: 12 D cycle (09/00 on; 21/00 off) in a temperature controlled room (23 ± 2 °C). All behavioral tests were run during the light phase between 16/00 and 21/00 h. Food and tap water were available ad lib. The experimental setup was approved by the Committee for Animal Experiments of the National Public Health Institute.

Drugs and Treatments

Cocaine hydrochloride (Sigma, C 5776, St. Louis, MO), (±)amphetamine sulphate (Sigma, A 1263), and zolpidem hemitartrate (donated by Leiras-Synthelabo, Finland) were dissolved in saline (0.9% NaC1). Diazepam (donated by Orion, Finland) was suspended in a vehicle (0.1% (v/w) Tween 80 in saline). Drug doses were calculated as free base, and all the drugs were injected intraperitoneally at a volume of 1 ml/kg.

The rats were assigned to the following treatment groups: (a) saline in the drug-paired compartment; saline in the opposite compartment ($n = 9$); (b) saline and cocaine (15 mg/kg) in the drug-paired compartment; vehicle and saline in the opposite compartment ($n = 11$); (c) saline and amphetamine (9 mg/kg) in the drug-paired compartment; saline and saline in the opposite compartment ($n = 12$); (d) diazepam (0.2, 1, and 5 mg/kg) and saline in the drug-paired compartment; vehicle and saline in the opposite compartment (n = 8, $n = 9$, $n = 8$, respectively); (e) zolpidem (2.5, 5, and 10 mg/kg) and saline in the drug-paired compartment; saline and saline in the opposite compartment ($n = 9$, $n = 8$, $n = 9$, respectively); (f) diazepam (0.2, 1, and 5 mg/kg) and cocaine (15 mg/kg) in the drug-paired compartment; vehicle and saline in the opposite compartment ($n = 8$, $n = 9$, $n = 8$, respectively); (g) diazepam (0.2, 1, and 5 mg/kg) and amphetamine (9 mg/kg) in the drug-paired compartment; vehicle and saline in the opposite compartment ($n = 9$, $n = 8$, $n = 8$, respectively); (h) zolpidem (2.5, 5, and 10 mg/kg) and cocaine (15 mg/kg) in the drug-paired compartment; saline and saline in the opposite compartment ($n = 8$, $n = 8$, $n = 9$, respectively); and (i) zolpidem (2.5, 5, and 10 mg/kg) and amphetamine (9 mg/kg) in the drug-paired compartment; saline and saline in the opposite compartment ($n = 8$, $n = 11$, $n = 9$, respectively).

Apparatus

The test was conducted in a rectangular box (60 × 30 × 45 cm) made of PVC plastic. The test box was divided into two compartments of equal size by a separating wall with a guillotine door (8 × 6 cm). Both compartments were covered with loose-fitting transparent plastic lids. One compartment was black with two small drops of approximately 9% acetic acid in the back corners, and the other was white with wire mesh on the floor, i.e., the compartments differed in three modalities: visual, tactile, and olfactory. The test was conducted in a room with dim light and constant noise provided by ventilation.

Place Conditioning Procedure

Before any conditioning the rats were allowed to adjust to the laboratory for 1 week and they were handled at least twice for approximately 1 min. In the place preference test a counterbalanced method was employed (7). Each treatment was performed over 10 days and consisted of three phases.

Preconditioning. During the preconditioning phase on the first day the rats were given access to both compartments for 15 min (900 s) and the time spent in each compartment was recorded. The rat was considered to be in a compartment when over the half of its body length (tail excluded) was inside. If the preconditioning time for a rat in either compartment was longer than 600 s the rat was excluded from further testing. The number of rats in each treatment group was counterbalanced between the compartments, i.e., half of the rats were assigned to the black compartment as the drug-paired compartment, whereas the other half was assigned to the white compartment as the drug-paired compartment. Care was taken that the average preconditioning time for each treatment group in the drug-paired compartment was between 435 s and 465 s.

Conditioning. The conditioning phase lasted from the second day to the ninth day, for a total of 8 days of conditioning. All injections were given during this phase. On even-numbered days the rats received saline, diazepam, or zolpidem as pretreatment. After an interval—50 min for groups receiving diazepam and 10 min for groups receiving zolpidem or saline—the rats received saline, cocaine, or amphetamine as a second injection. The shorter interval for zolpidem administration was chosen for two reasons. First, zolpidem is rather short acting, for example, the locomotor depressant effect induced by zolpidem at a dose of 3 mg/kg had disappeared by 75 min after injection (9). Second, zolpidem has been shown to interfere with learning and memory at least within a time range of 10–30 min (see Discussion). Learning and memory are essential for conditioning. As diazepam is known to impair memory; in this way we wanted to also ensure memory impairment by zolpidem, although it may have caused some bias between diazepam and zolpidem groups due to the different exposure times to familiar home cage cues after the first injections. After the second injections the rats were immediately confined to a drug-paired compartment for 50 min. On odd-numbered days the rats were first administered vehicle or saline. After a corresponding interval the rats were given saline, followed immediately by confinement in the saline-paired compartment for 50 min. No pretreatment was administered to the control rats receiving only saline.

Postconditioning. During the postconditioning phase the guillotine door was opened again and the time the rats spent in each compartment was recorded for a total of 15 min. If the

time spent in the drug-paired compartment was longer than the time spent in the saline-paired compartment this was considered a positive place preference.

Statistics

The absolute time in the drug-paired compartment after the treatments (postconditioning time) was taken as a measure of place preference. Statistical analysis of the results was performed using one-way ANOVA followed by Dunnet's two-tailed *t*-test for paired comparisons. Two-sample and paired *t*-tests were used where appropriate. All data are expressed as mean ± standard error.

RESULTS

The rats given saline in both compartments showed no preference for either side (Fig. 1). Diazepam alone at doses of 0.2, 1, and 5 mg/kg and zolpidem alone at doses of 2.5, 5, and 10 mg/kg induced neither place preference nor place aversion (Fig. 1). Instead, both cocaine, at a dose of 15 mg/kg, and amphetamine, at a dose of 9 mg/kg, induced positive place preference (Figs. 2 and 3). The postconditioning time of the cocaine group differed significantly both from the corresponding preconditioning time, $t(10) = 3.921$, $p = 0.003$, paired *t*-test, and from the postconditioning time of the saline-group, $t(18) = 2.573$, $p = 0.019$, two-sample *t*-test. Similarly, the postconditioning time of the amphetamine group differed significantly both from the corresponding preconditioning time, $t(11) = 9.029$, $p < 0.001$, paired *t*-test, and from the postconditioning time of the saline-group, $t(16.6) = 3.153$, $p = 0.006$, two-sample *t*-test.

Pretreatment with diazepam prevented cocaine-induced place preference (Fig. 2a). There was significant difference between the postconditioning times of the treatment groups, $F(3, 32) = 3.135$, $p = 0.039$, one-way ANOVA. Paired comparisons revealed significant difference at a dose of 5 mg/kg of diazepam ($p = 0.021$, Dunnet's two-tailed *t*-test) compared with the saline+cocaine-group. Diazepam pretreatment also prevented amphetamine-induced place preference (Fig. 2b). There was significant difference between the postconditioning times of the treatment groups, $F(3, 33) = 5.183$, $p = 0.005$, one-way ANOVA. Paired comparisons revealed significant differences at doses of 1 mg/kg ($p = 0.031$, Dunnet's two-tailed *t*-test) and 5 mg/kg ($p = 0.008$, Dunnet's two-tailed *t*-test) compared with the saline+amphetamine group. However, zolpidem at doses of 2.5, 5, and 10 mg/kg failed to prevent significantly either cocaine- or amphetamine-induced place preference (Fig. 3).

DISCUSSION

In our study the saline injections did not induce either place preference or place aversion. This indicates that the rats had not either intrinsic preference for or aversion to either compartment of the test box, i.e., that our method is truly "unbiased". Both cocaine at a dose of 15 mg/kg and amphetamine at a dose of 9 mg/kg induced preference for the compartment the rats were conditioned in, which reflects the rewarding properties of the psychostimulants. In particular, the dose of amphetamine needed was relatively high. This can be at least partly explained by the use of racemic amphetamine sulphate, in which the (−)amphetamine is behaviorally rather ineffective. Using our method, amphetamine at doses of 1 and 3 mg/kg failed to induce statistically significant place preference (data not shown).

Neither diazepam (0.2, 1, and 5 mg/kg) nor zolpidem (2.5, 5, and 10 mg/kg) induced place preference or place aversion in our method. In earlier studies quite contradictory results have been obtained. Various benzodiazepines sometimes have and sometimes do not have induced place preference (2,11,15,30,36,37). Moreover, in a recent study conditioned place aversion was also observed (29). The reason for these discrepancies remains unclear. In our study the rather long interval between diazepam injection and confinement in a compartment (50 min) may have attenuated the ability of diazepam to induce place preference. Nevertheless, the inability of diazepam and zolpidem to induce place preference or place aversion indicates that they did not cause any unspecific bias in the results.

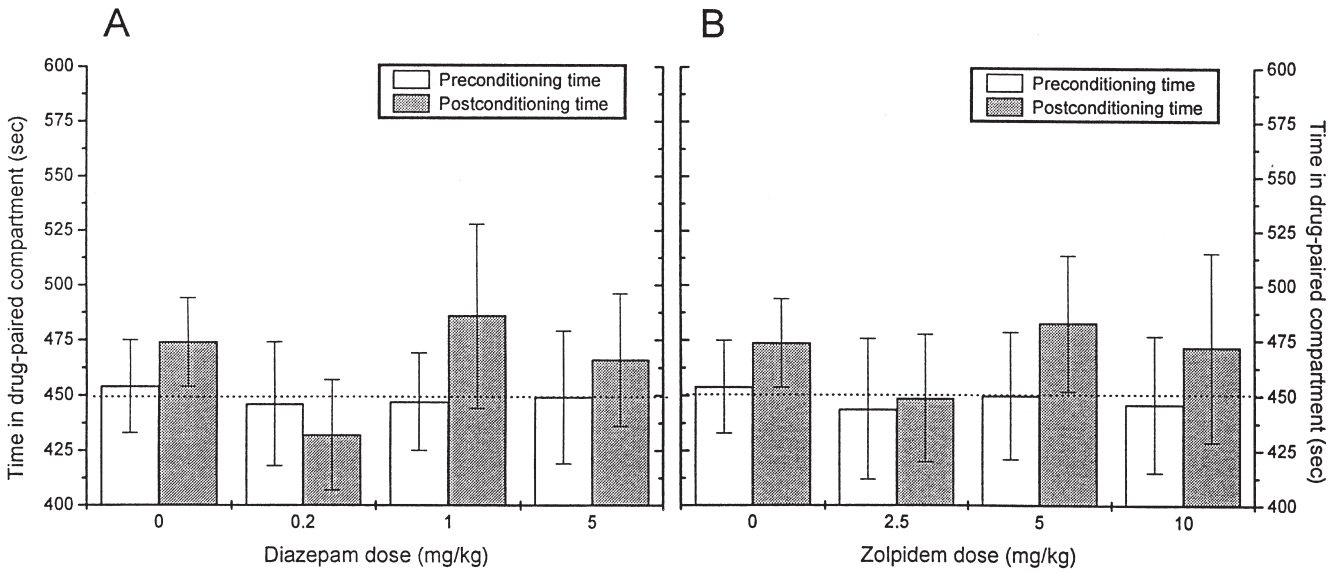

FIG. 1. (A) The effect of diazepam using the place preference method. (B) The effect of zolpidem using the place preference method.

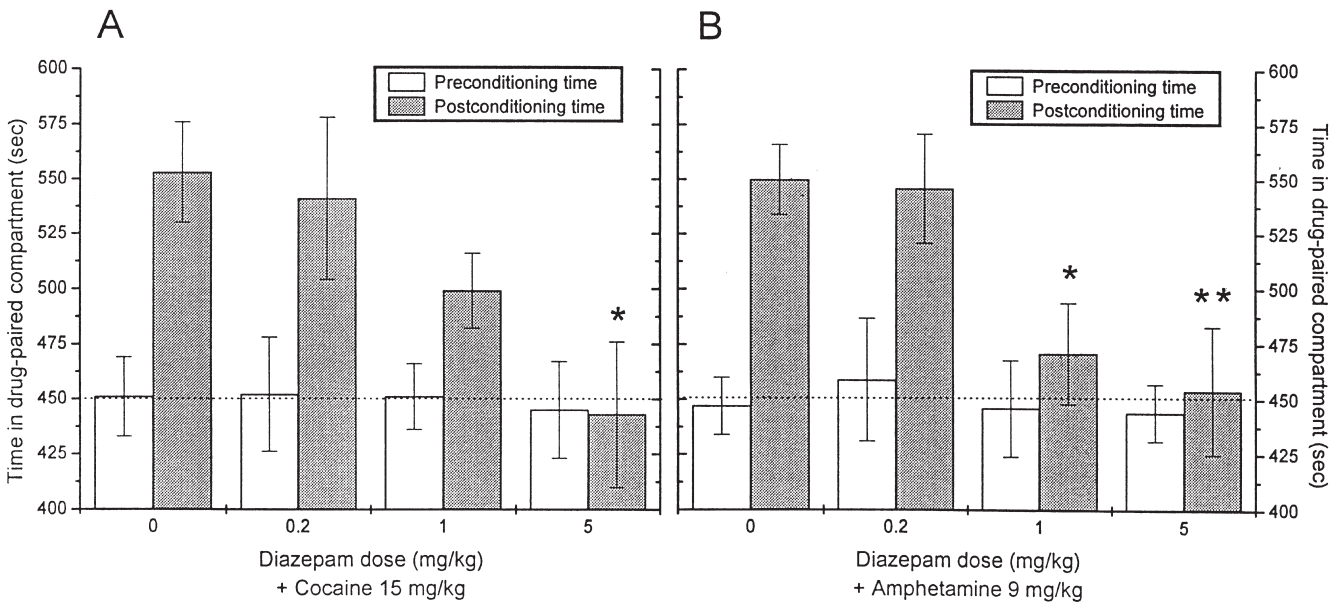

FIG. 2. (A) The effect of diazepam on cocaine-induced place preference. *$p < 0.05$ (Dunnet's two-tailed t-test) as compared with the saline+cocaine group. (B) The effect of diazepam on amphetamine-induced place preference. *$p < 0.05$, **$p < 0.01$ (Dunnet's two-tailed t-test) as compared with the saline+amphetamine group.

Pretreatment with diazepam prevented place preference induced by cocaine, suggesting that diazepam interferes with the rewarding properties of cocaine. This finding is in agreement with self-administration studies in which other benzodiazepines, chlordiazepoxide, and alprazolam, have prevented the reinforcing effects of cocaine (18,19). Baclofen, a $GABA_B$ receptor agonist, has also attenuated cocaine self-administration (31). Furthermore, in intracranial self-stimulation test the cocaine-induced lowering of brain stimulation reward threshold was attenuated by gamma-vinyl GABA, an irreversible inhibitor of GABA transaminase (22). As it did with cocaine, diazepam also prevented place preference induced by amphetamine in our study. It was previously shown that benzodiazepine triazolam attenuates amphetamine-induced place preference (30); this effect can be extended to diazepam. Considered together, it seems that benzodiazepines have some antagonizing effect on the rewarding properties of the psychostimulants. In our study, we could not locate the brain nuclei responsible for this effect, but taking into account earlier results concerning the nucleus accumbens, in which GABAergic

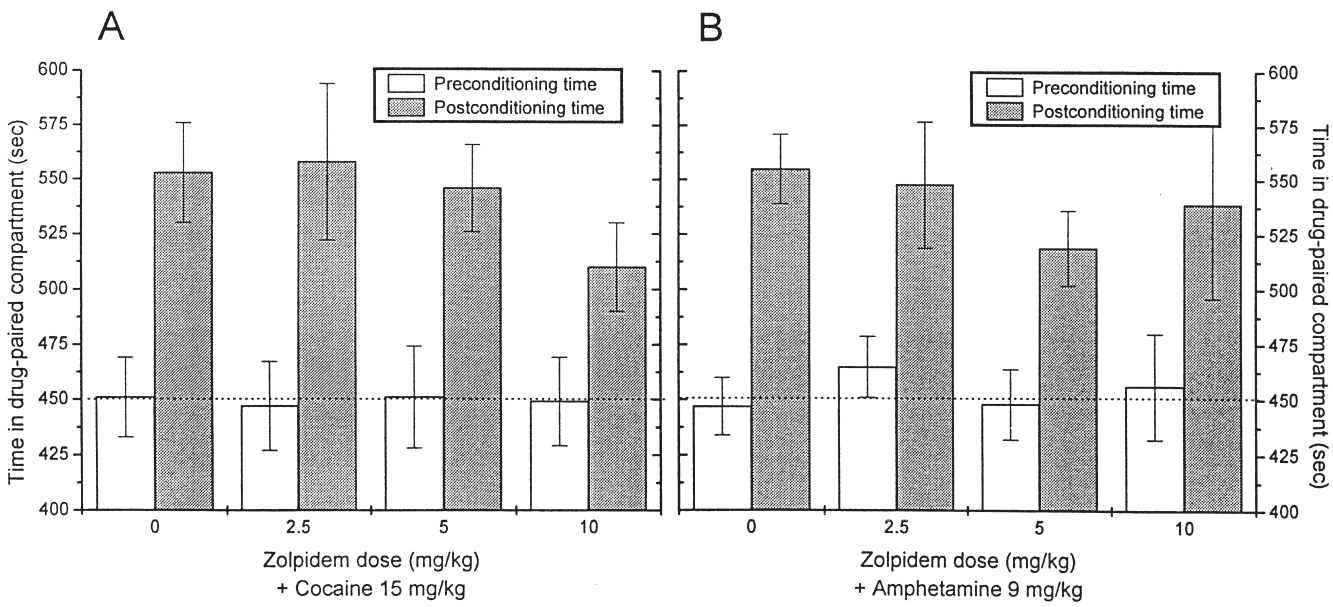

FIG. 3. (A) The effect of zolpidem on cocaine-induced place preference. (B) The effect of zolpidem on amphetamine-induced place preference.

drugs either locally reduced basal levels of dopamine or systemically reduced cocaine-induced elevation of extracellular dopamine (27,41), one might suggest the involvement of this brain nucleus.

Locomotor stimulating effects of psychostimulants are sometimes proposed to be linked to the rewarding properties of these drugs. High doses of benzodiazepines, which depress locomotor activity themselves, have inhibited the stimulating effects of psychostimulants (1,5,10). However, diazepam and chlordiazepoxide at low doses, and sometimes even at higher depressant doses, are reported to enhance the locomotor stimulation induced by cocaine and amphetamine (12,21,34, 35). In our study, no enhancement of the rewarding properties of the psychostimulants was seen at any diazepam dose tested. Our results, combined with the studies mentioned above, imply that the locomotor stimulation does not fully reflect the rewarding properties of the psychostimulants.

Zolpidem pretreatment at doses up to 10 mg/kg failed to prevent both cocaine- and amphetamine-induced place preference. This indicates that zolpidem at the dosage used does not interfere with the rewarding properties of the psychostimulants. Zolpidem, however, seemed to show a tendency, although not a statistically significant one, to attenuate psychostimulant-induced place preference, implying that higher doses could be effective in this respect. The discrepancy between the effects of diazepam, an unspecific ω1/ω2-receptor agonist, and zolpidem, a preferential ω1-agonist, might be due to differential distribution of ω1- and ω2-receptors in the brain. ω1-Receptors constitute the major population of $GABA_A$ receptors in most brain structures, but in some areas such as in the limbic system, in the striatum, and in the spinal cord, which are considered to almost exclusively contain ω2-receptors, the ω1-receptors are presented to a much lesser degree. In the study by Niddam et al. (28) the authors found low levels (<500 fmol/mg of protein) of specific [^{3}H]zolpidem binding in the nucleus accumbens, as well in certain hypothalamic and thalamic nuclei, in certain parts of the hippocampus, in the caudate-putamen, in septal nuclei, etc. In the same study the binding of [^{3}H]zolpidem in the nucleus accumbens was five times lower than that of [^{3}H]flunitrazepam. Also, when the ability of zolpidem to displace unspecific benzodiazepine antagonist [^{3}H]flumazenil was studied, receptors with a high affinity for zolpidem representing ω1-receptors constituted only 32% of [^{3}H]flumazenil binding in the nucleus accumbens (3). Less is known about the effects of zolpidem in other parts of the mesocorticolimbic system, such as the ventral tegmental area and the medial prefrontal cortex. In the study by Benavides et al. (3) the authors presented the finding that 42% of the [^{3}H]flumazenil binding in the frontal cortex showed a high affinity for zolpidem (ω1-receptors), but this area does not fully correspond to the medial prefrontal cortex. Nevertheless, it might be suggested that the rewarding effects of the psychostimulants could be more sensitive to diazepam than to zolpidem as a result of the differential distribution between ω1-receptors and ω2-receptors, although it must be noted that ω1/ω2-receptor classification probably represents an oversimplification.

Diazepam is known to possess amnestic properties, and it can be argued that these are responsible for the preventative effect of diazepam on cocaine- and amphetamine-induced place preference. Drugs selective to ω1-receptors are proposed to have less effect on learning and memory, as the population of this receptor subtype is relatively low in certain parts of the hippocampus. In behavioral tests, however, zolpidem has been found to have disruptive effects on learning and memory. In mice, 2 mg/kg of zolpidem attenuated the acquisition of conditioned fear (32). Also, in passive avoidance tests in mice 1–10 mg/kg of zolpidem caused amnestic effects (13,38). When tested in Wistar rats, zolpidem attenuated the conditioned avoidance response even at a dose of 1.5 mg/kg (8). Another preferential ω1-receptor agonist, CL 218,872, has also impaired learning, as measured in a Morris water maze test (26). Moreover, there are reports indicating that zolpidem causes amnesia in humans (4,24). Altogether, it seems that zolpidem has some attenuating effect on learning and memory, although the mechanism behind it is unclear (33). Because, in our study zolpidem did not clearly prevent cocaine- or amphetamine-induced place preference at doses up to 10 mg/kg, it seems unlikely that the effect of diazepam could be explained solely as memory impairment.

In conclusion, we report that in our study diazepam prevented cocaine- and amphetamine-induced place preference, indicating that diazepam has attenuating effects on the rewarding properties of the psychostimulants. On the other hand, at the doses tested zolpidem failed to prevent either cocaine- or amphetamine-induced place preference. It seems that diazepam is more effective than zolpidem in attenuating the psychostimulant reward, possibly due to differing distribution of ω1- and ω2-receptors.

ACKNOWLEDGEMENTS

Mrs. Riitta Tirkkonen-Vesikko is most gratefully acknowledged for her technical assistance.

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