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The dopamine receptor agonist 7-OH-DPAT modulates the acquisition and expression of morphine-induced place preference

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Abstract

The present study investigated the effects of systemic administration of the putative dopamine D_3 receptor agonist 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) on the acquisition and expression of morphine-induced place preference in male Wistar rats. Using a a 3-day schedule of conditioning it was found that 7-OH-DPAT in a broad dose range (0.01, 0.25 and 5.0 mg/kg) did not produce significant place preference. However, the administration of either 0.25 or 5.0 mg/kg of 7-OH-DPAT 15 min prior to the exposure to morphine (1 mg/kg) prevented the acquisition of a morphine place preference, whereas the 0.01 mg/kg dose of the dopamine receptor agonist was uneffective. In addition, when 7-OH-DPAT was acutely administered 15 min prior to the testing session of an already established morphine place preference, the 0.01 mg/kg dose prevented the expression of this conditioned response. This effect was not observed with either 0.25 and 5.0 mg/kg doses of this dopamine D_3 receptor agonist. It was suggested that the different dose related effects of 7-OH-DPAT on the acquisition and expression of morphine place preference might be related to the intrinsic ability of this agonist for interacting with pre- and postsynaptic dopamine D_3 receptors located in limbic projecting areas of the mesencephalic dopamine system, although involvement of dopamine D_2 receptors cannot be excluded. The pattern of effects seen with 7-OH-DPAT suggests that it may be useful for treating opiate dependence and craving.

Keywords: Morphine; 7-OH-DPAT (7-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin); Place preference; Conditioning; Dopamine; Dopamine D_3 receptor; (Rat)

1. Introduction

Drug craving, the desire to experience the effects of a previously experienced psychoactive substance, remains as a keystone problem in the search for therapeutic approaches to drug addiction. Neuropharmacological studies on the effects of most abused drugs have established an important role for ascending dopaminergic projections and their forebrain connections, as a neurobiological basis of the reinforcing properties of abused drugs (Koob, 1992a,b). It is well established that most drugs of abuse unconditionally evoke dopamine release in the terminal fields of ventral tegmental area dopamine neurons (Di Chiara and Imperato, 1988; Koob, 1992a,b). The activation of this neuronal pathway has been particularly implicated in drug-induced incentive learning such as that measured in the conditioned place preference paradigm (Spyraki et al., 1982). This behavioral paradigm has been widely used as a model for studying both the reinforcing properties of drugs of abuse and drug craving (Swerdlow et al., 1989; Hiroi and White, 1991; Markou et al., 1993). Using conditioned place preference tests it has been shown that surgical or pharmacological manipulations which result in the alteration of mesolimbic dopamine activity in the brain, are able to disrupt both the acquisition and expression of amphetamine or opiate-induced place preference (Schwartz and Marchok,

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1974; Mucha et al., 1982; Spyraki et al., 1983; Mackey and Van der Kooy, 1985; Hand et al., 1989).

Neuroleptics, drugs which act as dopamine receptor antagonists, were considered for pharmacotherapy of drug seeking behavior (for review see Koob, 1992b). However most of these drugs are unselective for specific dopaminergic receptor subtypes, and thus have the untoward effects of all dopamine antagonists used clinically. The recent discoveries of up to 5 different dopaminergic receptors in the brain, each one exhibiting a characteristic profile in its anatomical distribution, signal transduction mechanisms, and selectivity for a battery of available dopamine receptor antagonists and agonists (for review see Schwartz et al., 1992), have opened possibilities for the developing of new pharmacological strategies for drug craving. Much interest has been focused on the so-called dopamine D_3 receptor: this receptor is distinguished by a predominant localization in mesolimbic regions of the brain such as accumbens nucleus, islands of Calleja and olfactory tubercle (Sokoloff et al., 1990; Bouthenet et al., 1991), suggesting a role in the mediation of dopamine action on emotional and cognitive functions. This receptor is also present in the cell bodies of dopamine neurons of the substantia nigra and ventral tegmental area, where it presumably acts as an autoreceptor. This neurobiological profile suggests a potentially important target for developing therapeutic strategies for drug abuse. Using this approach it has been recently shown that both 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) and quinpirole, dopamine receptor agonists which exhibit a high affinity for dopamine D_3 receptors, are very effective at decreasing cocaine self-administration in rats (Caine and Koob, 1993). Interestingly both dopamine agonists worked at doses which were not reliably self-administered by the animals. This observation suggests that dopamine agonists with this pharmacologic profile may be a possible source for pharmacotherapy for cocaine abuse. However, there is no further information concerning the effects of these putative dopamine D_3 receptor agonists on other behavioral paradigms of drug craving and other classes of abused drugs, such as opiates or the amphetamines.

Although it is clear that opiates like morphine or heroin, elicit their reinforcing properties through μ-opioid receptors (Van der Kooy et al., 1982; Mucha and Herz, 1985; Hand et al., 1989), and that opiate self-administration persists in the absence of the mesolimbic dopamine system (Pettit et al., 1984), it appears that the integrity of mesolimbic dopamine neurons is necessary for the full expression of its rewarding properties in the place preference model (Mucha and Herz, 1985; Bals-Kubik et al., 1993; Shippenberg et al., 1993). The possible interaction between opioid and dopamine mechanisms on the mediation of the reinforcing properties of abused drugs is further supported by the observation that opioid antagonists block the acquisition of amphetamine-induced place preference (Trujillo et al., 1991). Moreover, cocaine and morphine can elicit a similar profile of neurobiological actions on dopamine neurons of the ventral tegmental area (Kalivas and Duffy, 1988; Beitner-Johnson and Nestler, 1991) suggesting a convergent mechanism of these drugs of abuse on this reward relevant neuronal pathway.

In this work we have evaluated the interaction of the putative dopamine D_3 receptor agonist 7-OH-DPAT with the conditioned place preference produced by morphine 1 mg/kg body weight, a dose which produces a consistent place conditioning, without inducing physical dependence, as indicated by naloxone application. To this end we have examined (i) the effects of 7-OH-DPAT as a reinforcer in the place preference paradigm, and (ii) the effects of this dopamine receptor agonist on the acquisition and expression of morphine-induced place preference. The utilization of the place conditioning procedure allowed us to evaluate other aspects of the psychopharmacological profile of this dopamine agonist such as its intrinsic ability for evoking associative learning and its effects on psychomotor activation.

2. Materials and methods

2.1. Animals

Male Wistar rats (Panlab, Barcelona, Spain) weighing 300–400 g were housed in groups of 4 per cage, in a room with controlled photoperiod (08:00–20:00 h lights on) and temperature (23 ± 1°C). They had free access to standard food (Panlab, Barcelona, Spain) and water.

2.2. Apparatus

The place conditioning apparatus was similar to that described by Hand et al. (1989) and consisted of three interconnected rectangular boxes of 40 × 35 × 35 cm, situated at 120° angles from each other. In the middle there was a triangular area with a smooth glass floor, from which any of the three compartments were accessible. Each compartment was equipped with a set of different sensory stimuli which make them different: compartment A was equipped with a sand floor, plain walls and a small container with a drop of 10% acetic acid. Compartment B contained a removable soft plastic floor, walls painted with white dot circles (7.5 cm) and a small container with a drop of anise extract. Finally the compartment C had a cork floor, alternating white strips (5 cm wide) painted on the walls and no odor (a container with drops of distilled water). The

apparatus was placed in an isolated room dimly illuminated (110 Lux). Each compartment was equipped with eight photocells which allowed us to monitor the position of the animal, and to automatically register the time spent in each compartment and the locomotor activity. After testing each animal, the floors were washed and changed to avoid odor cues.

2.3. Behavioral testing

Experiments were performed between 9:00 and 19:00 h. Each place conditioning experiment consisted of a 5-day schedule, with three phases: preconditioning, conditioning and testing:

Preconditioning

Animals were placed in the middle of the apparatus, and they were allowed to freely explore the three compartments for the next 45 min. The time spent in each compartment was computed and those animals exhibiting strong unconditioned aversions ($< 10\%$ of the session) or preferences ($> 60\%$ of the session) for any compartment were discarded for the conditioning sessions. The two compartments which exhibited the most similar time of preference were chosen for each animal for the conditioning sessions. In one of these compartments, randomly chosen, the animals received morphine, and in the other they were administered with the vehicle (isotonic saline). This selection permitted us to avoid the interference of natural preferences of the animals with the conditioning drugs. Thus, the average time spent during the preconditioning sessions in the afterwards considered saline-paired compartment was 648.4 ± 46.1 s ($n = 50$ animals). This time was not different to that spent in the morphine-paired compartment (610.3 ± 35.9 s, $n = 50$ animals)

Conditioning

This consisted of a 3-day schedule of double conditioning sessions. The first day involved a morning session (9:00–13:00 h) in which animals received a single i.p. dose of the drug to be tested (morphine/7-OH-DPAT) and were immediately placed in one of the compartments chosen as described above for 30 min. This compartment had been isolated from the others using removable panels. In the evening session (16:00–19:00 h) the animals received a single i.p injection of saline, and were placed for 30 min in the other compartment chosen for conditioning experiments. On the second day of conditioning the animals received the saline injections in the morning session and the drug administration in the evening session. The third day of conditioning had the same schedule as the first one. We have chosen this schedule for avoiding circadian variability (morning/evening), based on preliminary studies in our laboratory (data not shown). Photocell counts throughout conditioning sessions were automatically registered and used as an index of locomotor activity. The conditioning sessions were videotaped and used for scoring several motor behaviors such as rearing activity and time spent grooming.

Testing

On the 5th day of the schedule the animals were allowed again to freely explore the three compartments, exactly as in the preconditioning phase. The time spent in each compartment was automatically registered. We defined the *change of preference* as the difference (in seconds) between the time spent in the drug-paired compartment on the testing day, and the time spent in this compartment in the preconditioning session. This variable was chosen as an index of drug-induced place preference, as previously described (Hand et al., 1989). The change of preference in the two non-drug-paired compartments (saline and discarded) was also evaluated for assessing the possible aversive effects of both the injection procedure and the drug being administered (data not shown).

2.4. Drugs

Morphine hydrochloride was supplied by Centro Nacional de Estupefacientes y Psicótropos. Naloxone was obtained from Endo Laboratories (Garden City, NY, USA). 7-Hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT-HBr) was provided by Research Biochemical International as a part of the Chemical Synthesis Program of the US National Institute of Mental Health, contract 278-90-007 (BS). All the drugs were dissolved using isotonic saline as vehicle.

2.5. Experimental designs

In a preliminary experiment (data not shown), we established a dose-response function for morphine place conditioning. Six doses of morphine (62, 125, 250, 500, 1000 and 2000 μg/kg) were tested for their ability to produce place conditioning. The possible development of morphine physical dependence was also evaluated in the morphine-conditioned animals, by studying the appearence of signs of precipitated abstinence after the acute administration of naloxone (1 mg/kg). This study was confirmed to be negative (data not shown). A separate group of animals received saline in two equally preferred compartments in order to confirm that the injection and conditioning schedule were not affecting the time allotment in the apparatus.

Based in these data, the dose of 1000 μg/kg was selected for the different experiments designed in order to evaluate the possible modulatory role of 7-OH-

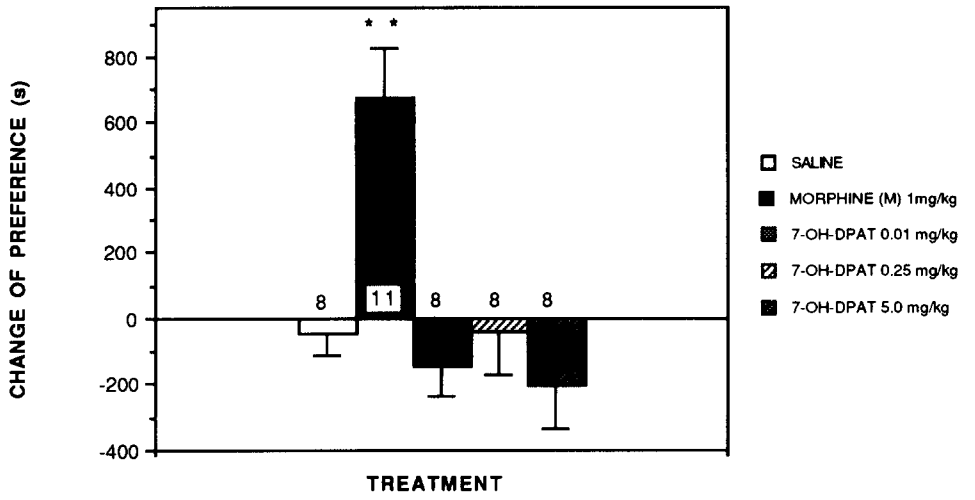

Fig. 1. Place conditioning produced by morphine (1 mg/kg) or 7-OH-DPAT (0.01, 0.25 and 5.0 mg/kg) in a 3-day schedule of conditioning. Ordinates are means ± S.E.M. of the difference between the time spent on the day of testing and the time spent on the day of preconditioning session. Numbers in columns indicate the animals tested per group. * * $P < 0.001$, Newman-Keuls, vs. control (saline) group.

DPAT on the acquisition and expression of morphine place preference conditioning:

Experiment 1. 7-OH-DPAT dose-response analysis

In this experiment we evaluated the ability of 7-OH-DPAT to induce place conditioning when administered under the 3-day schedule described above. Three doses of 7-OH-DPAT (0.01, 0.25 and 5.0 mg/kg) were given s.c. during the three conditioning days. Two additional groups were added: one received morphine 1000 μg/kg i.p., whereas the other group received saline and served as a control. The locomotor activity was automatically evaluated throughout the conditioning sessions. Rearing and grooming activities were also scored by trained observers.

Experiment 2. Effects of 7-OH-DPAT administration on the acquisition and expression of morphine-induced place preference

Effect of 7-OH-DPAT pretreatment on morphine-induced place preference. Five groups of rats were used. The first group was subjected to a conditioning regimen with saline. The other three groups received respectively 0, 0.01, 0.25 or 5.0 mg/kg of 7-OH-DPAT s.c. 15 min prior to the administration of morphine 1 mg/kg during conditioning sessions. Subjects were tested 24 h after the last conditioning session, with no preceding injection.

Effect of 7-OH-DPAT treatment on established morphine-induced place preference. Four groups of animals were conditioned with morphine (1 mg/kg) and tested 24 h later. 15 min before the test session these groups were given saline, 0.01, 0.25 and 5.0 mg/kg of 7-OH-DPAT s.c. in order to establish the effect of this dopaminergic agonist on an established place preference.

2.6. Statistics

Data were assessed by analysis of variance (ANOVA). Following a significant F value, post-hoc analyses (Newman-Keuls) were performed for assessing specific group comparisons. Calculations were performed using the BMDP statistical package.

3. Results

3.1. Experiment 1: 7-OH-DPAT dose-response analysis

The administration of a wide range of doses of the dopaminergic agonist 7-OH-DPAT did not induce con-

Table 1
Effects of acute 7-OH-DPAT administration on locomotor and rearing activities, and time spent grooming measured during conditioning sessions

Treatment (mg/kg)	Crossings	Rears	Time of grooming (s)
Control	127.1 ± 27.7 [a]	37.4 ± 7.5 [a]	48.7 ± 29.1 [a,b]
7-OH-DPAT 0.01	41.7 ± 10.8 [b]	22.5 ± 6.2 [a,b]	84.7 ± 34.2 [b]
7-OH-DPAT 0.25	309.3 ± 54.7 [c]	16.2 ± 4.2 [b]	18.5 ± 14.5 [a,c]
7-OH-DPAT 5.0	328.8 ± 29.6 [c]	7.9 ± 2.2 [c]	6.8 ± 4.3 [c]

Values are means ± S.E.M. of 7–8 animals *per group*, tested over 30 min. Statistical differences among the different groups were assessed by analysis of variance, followed by the Newman-Keuls test for pairwise comparison. Values with a different superscript (a,b,c) are statistically different, $P < 0.05$ vs. controls (Newman-Keuls).

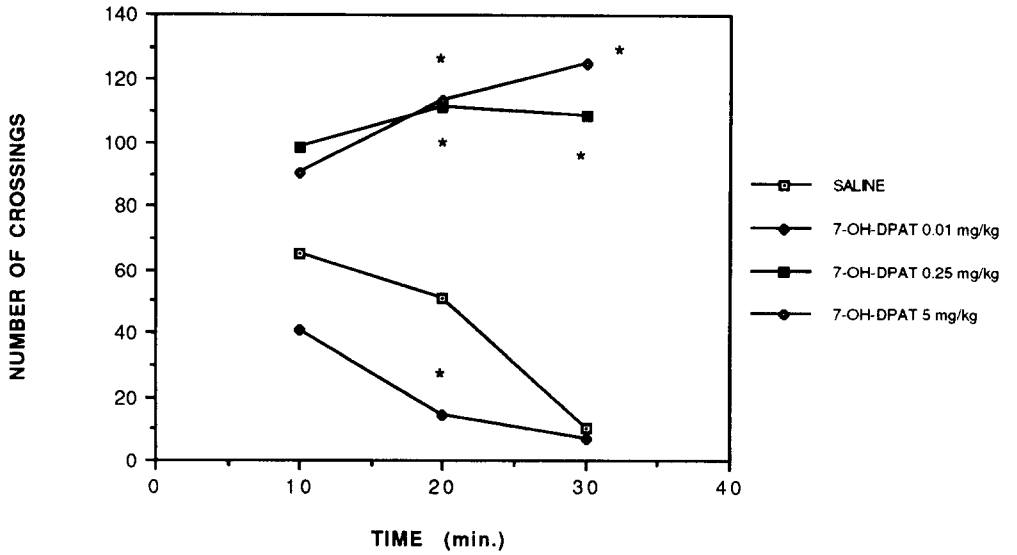

Fig. 2. Time course of the effects of 7-OH-DPAT on locomotor activity. The results are means of the number of beam interruptions recorded during three consecutive periods of 10 min. * $P < 0.01$, Newman-Keuls, vs. control (saline) group.

ditioned place preference (Fig. 1) under the conditioning schedule used in this study ($F(3,34) = 0.54$, $P = 0.66$, n.s.). Moreover, most of the animals exhibited a negative change of preference (7 of the 8 exposed to the 0.01 mg/kg dose, 5/8 of the treated with 0.25 mg/kg, and 6/8 of the animals receiving 5 mg/kg of 7-OH-DPAT), which was very similar to that exhibited by saline-treated animals. However, the administration of the agonist clearly produced changes in motor behavior (Table 1): with locomotor activity, the administration of 7-OH-DPAT produced clear dose-related effects ($F(3,27) = 11.11$, $P < 0.0001$). A detailed analysis showed (Table 1) that the low dose decreased locomotor activity, whereas the intermediate and the high ones increased it ($P < 0.01$, Newman-Keuls). This effect appeared 20 min after the injection of the agonist and it was clearly evident at the end of the 30 min of study ($F(6,54) = 3.74$, $P < 0.05$), as revealed in the time-course study done during conditioning sessions (Fig. 2). 7-OH-DPAT also attenuated other spontaneous motor behaviors related to dopaminergic activity such as time spent grooming and rearing. Both time

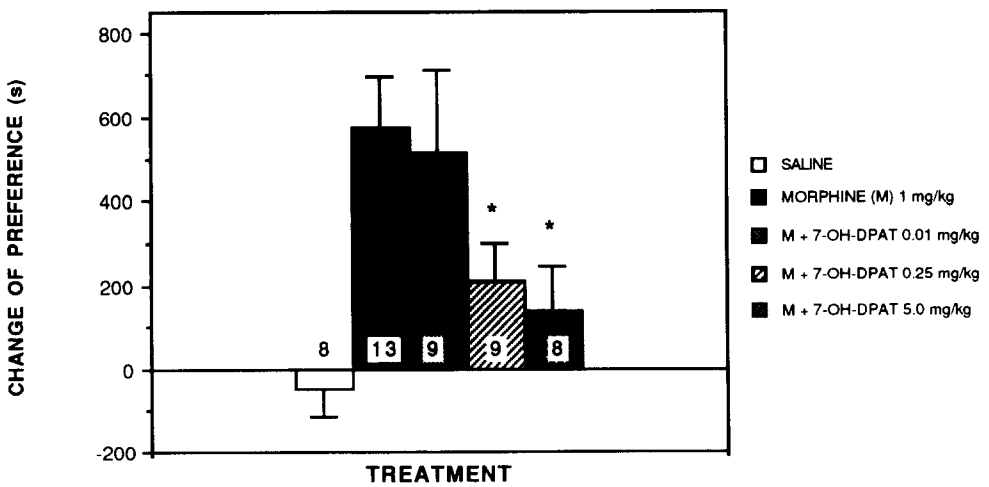

Fig. 3. Effects of 7-OH-DPAT on the acquisition of morphine-induced place preference. Treatment with 0.25 and 5.0 mg/kg of 7-OH-DPAT 15 min prior to the exposure to morphine 1 mg/kg prevents the acquisition of conditioned place preference. Numbers in columns indicate the animals tested per group. * $P < 0.01$, Newman-Keuls, vs. morphine group.

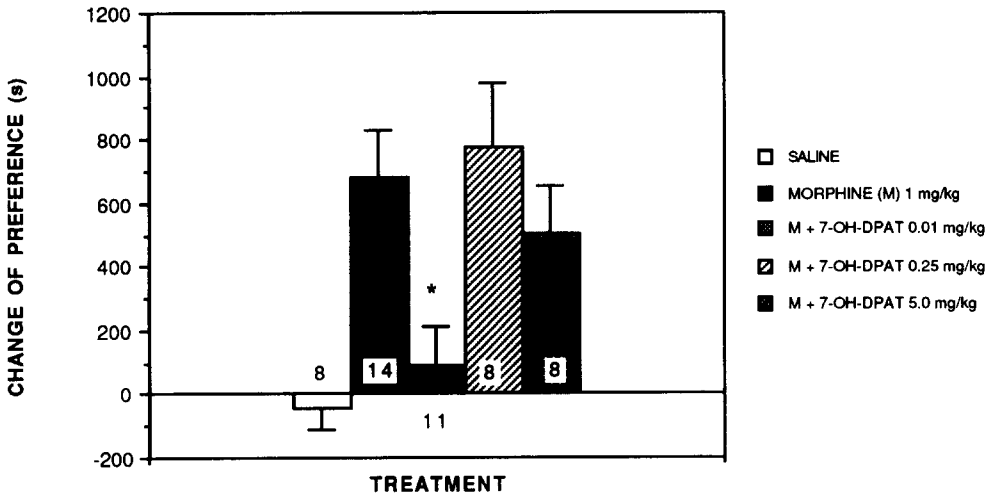

Fig. 4. Effects of 7-OH-DPAT treatment on the expression of morphine- induced place preference. Treatment with 0.01 mg/kg but not 0.25 or 5.0 mg/kg of 7-OH-DPAT 15 min prior to the testing prevents the expression of already established conditioned place preference. Numbers in columns indicate the animals tested per group. * $P < 0.01$, Newman-Keuls, vs. morphine group.

spent grooming ($F(3,26) = 2.86$, $P < 0.05$), and rearing activity ($F(3,26) = 3.82$, $P < 0.05$), were depressed by 7-OH-DPAT in a dose-dependent fashion (Table 1).

3.2. Experiment 2: Effects of 7-OH-DPAT on the acquisition and expression of morphine-induced place preference

Fig. 3 shows that treatment with either 0.25 or 5.0 mg/kg of 7-OH-DPAT 15 min prior to conditioning sessions was sufficient to prevent the acquisition of morphine-induced place preference ($F(4,45) = 5.51$, $P < 0.005$). Animals exposed to 0.01 mg/kg of this agonist displayed the same place preference as those exposed to morphine 1 mg/kg. However, only the low dose (0.01 mg/kg) of 7-OH-DPAT was able to disrupt an established place preference ($F(4,49) = 8.61$, $P < 0.001$) when it was administered 15 min prior to the test session (Fig. 4). Moreover, there was no increase in the preference for the morphine-paired compartment in 5 out of 11 animals tested with this very low dose of the dopamine agonist. The expression of morphine-induced place preference was not affected in any of the animals exposed to the 0.25 and 5.0 mg/kg doses of 7-OH-DPAT. This effect seems not to be produced by

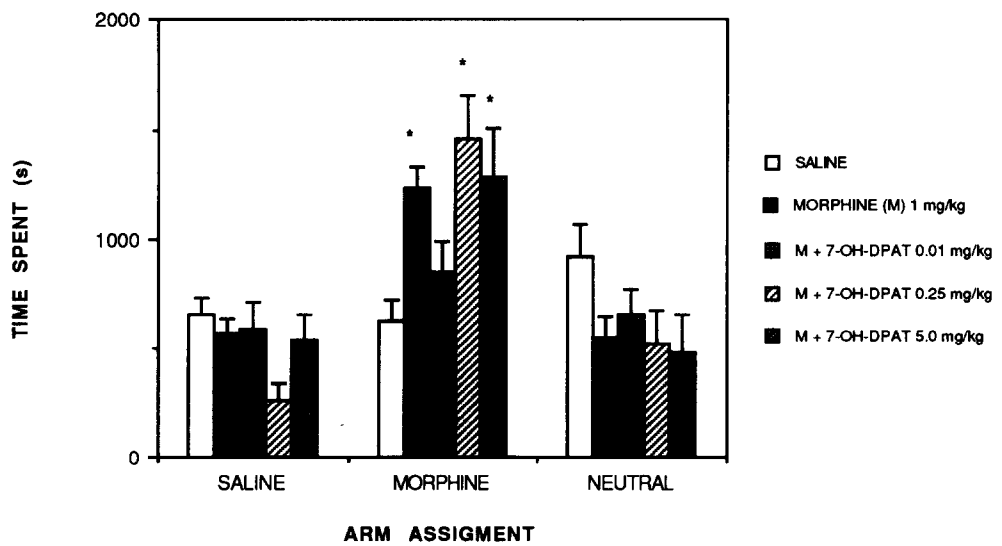

Fig. 5. Effects of 7-OH-DPAT treatment on the time spent in any of the three chambers of the place conditioning apparatus during the expression of morphine-induced place preference. Treatment with 0.01 mg/kg but not 0.25 or 5.0 mg/kg of 7-OH-DPAT 15 min prior to the testing prevents the expression of already established conditioned place preference. * $P < 0.01$, Newman-Keuls, morphine-paired vs. saline-paired chamber.

the depressing effect of the low dose (0.01 mg/kg) of 7-OH-DPAT, since the animals injected with this dose spent a similar time in the three compartments (Fig. 5), without showing the clear preference for the morphine-paired compartment exhibited by the animals exposed to the other doses of this agonist ($F(8,126) = 4.91$, $P < 0.0001$).

4. Discussion

Two major findings arose from this study. The first was the lack of significant induction of place preference after the administration of any of the three doses tested of 7-OH-DPAT. Moreover, 18 out of 24 animals tested actually exhibited an aversion to the dopamine agonist-paired compartment, a proportion that was similar to that exhibited by controls when compared to saline-paired compartments, which might be reflecting an aversive state to the injection procedure. The timing of administration should be adequate for eliciting reinforcing properties since a clear onset of a dose-related pattern of motor behavior alterations during conditioning sessions was observed (Fig. 2). 7-OH-DPAT closely resembles other dopamine agonists such as quinpirole or apomorphine in eliciting alterations on locomotor activity (Waddington, 1989). As reported recently (Daly and Waddington, 1993) the low dose of 7-OH-DPAT induced a decrease in locomotor activity, accompanied by a decrease in exploratory behaviors, whereas higher doses increased it when compared to saline-treated animals. Our observations extend these results since we have observed a dose-dependent reduction in spontaneous rearing activity and grooming activity, a dopamine D_1 receptor-related behavior. These results are consistent with the observation of a lack of reinforcing properties of 7-OH-DPAT via the intravenous route, at a dose (10 μg/injection) that was similar to that decreasing cocaine self-administration (Caine and Koob, 1993).

The second, and more relevant, finding was the intrinsic ability of 7-OH-DPAT for altering both the acquisition and especially the expression of morphine-induced conditioned place preference. The results show that only the higher doses of this dopamine agonist were capable of blocking the acquisition of morphine-induced place preference, whereas the lower dose was effective only at decreasing the expression of an already established place preference. These data seem to be contradictory, but it is important to note that (i) the range of doses used was broad enough to elicit the characteristic biphasic effects of dopamine agonists, reflecting its ability for interacting with pre- and postsynaptic dopamine receptors; and (ii) the mechanisms underlying the acquisition and expression of opiate place preference are different, although they converge in the mesencephalic dopaminercic neurons of the ventral tegmental area (Hand et al., 1989; Kalivas, 1993).

The ability of the low dose of 7-OH-DPAT to block the expression of morphine place preference conditioning seems to be independent of the agonist-induced decrease on locomotor activity: the time spent in the three compartments was very similar (Fig. 5), indicating that the animals explore the three compartments in a way similar to saline-conditioned control animals. Moreover, the three-chamber apparatus minimizes the effects of activity because it is a choice situation. A more likely hypothesis to explain these results is that the effects observed on the expression of morphine place preference were caused by a 7-OH-DPAT-induced disruption of the activity of mesolimbic dopamine neurons. This neuronal pathway is involved in filtering signals coming from other limbic structures and in gating mechanisms that mediate basic biological drives and mediate motivational variables (Koob, 1992b). The attribution of incentive salience to stimuli reliably associated with the administration of a reinforcing drug like morphine presumably involves an associative process that may be mediated by mesolimbic dopamine neurons (Robinson and Berridge, 1993). These neurons are also activated by signals predicting the availability of natural and chemical reinforcers (Robinson and Berridge, 1993; Koob, 1992b). This may be the basis for effects of 7-OH-DPAT on the expression of morphine-induced conditioned place-preference behavior observed here. Both dopamine D_3 and D_2 receptors are located as autoreceptors on ventral tegmental area dopamine neurons (Bouthenet et al. 1991; Kalivas 1993). These autoreceptors may decrease both the firing of these cells and the release of dopamine in the mesolimbic terminal fields (Wolf and Roth, 1987; Santiago et al. 1993), this latter event being associated with rewarding events. The possible mechanisms of 7-OH-DPAT as a dopamine agonist could be either a decrease in the firing of ventral tegmental neurons mediated by somatodendritic autoreceptors, or the blockade of dopamine release in mesolimbic terminals elicited trough terminal autoreceptors. It has been recently demonstrated that quinpirole, a dopamine agonist, which also exhibits a higher affinity for dopamine D_3 rather than dopamine D_2 receptors, is able to block the release of dopamine from mesolimbic terminals of ventral tegmental dopamine neurons (Santiago et al., 1993). Higher doses might also interact with postsynaptic dopamine D_3 receptors or could lose selectivity and interact with dopamine D_2 (or D_1) receptors, activating long-loop feedback mechanisms also involved in the expression of rewarding properties of abused drugs (Koob, 1992a). The fact that only the low dose of 0.01 mg/kg of 7-OH-DPAT was able to block the expression of an already established morphine con-

ditioned place preference may then be related to the intrinsic ability of this very low dose to interact only with dopamine autoreceptors. This interaction might lead to a blockade of the activation of mesolimbic dopaminergic neurons and then to suppress the conditioned 'wanting' response evoked by environmental cues associated with morphine administration. Whether this effect is mediated through dopamine D_3 or D_2 receptors remains to be conclusively determined.

Regarding the blocking effects of 7-OH-DPAT on the acquisition of morphine-induced place preference the mechanism involved seems less clear. The possible interaction within the opiate and dopamine cells may occur both at the level of the ventral tegmental cells and in their terminal fields, where opioid receptors and dopamine terminals are co-localized (Pollard and Llorens, 1977). At the mesencephalic level, opiate administration increases the firing of ventral tegmental dopamine cells by releasing inhibitory γ-amino-butyric acid (GABA)-containing neurons within this mesencephalic structure (Kalivas, 1993). Moreover, the administration of μ-opioid receptor agonists into the ventral tegmental area elicits a conditioned place preference (Bals-Kubik et al., 1993). The administration of a dopamine agonist with a selectivity for dopamine receptors located in mesolimbic dopaminergic cell bodies or projecting areas, like 7-OH-DPAT, might disrupt the opiate-induced activation of these neurons, and thus block the process of incentive salience attribution. Whereas it is well kown that place preference produced by systemically administered opiates is dependent on the activation of μ-opioid receptors, there are contradictory data on the role of mesolimbic dopamine neurons in the acquisition and expression of this behavior. Heroin place preference can be produced after chronic treatment with the dopamine antagonist flupenthixol (Stinus et al., 1989), whereas it has recently been postulated that the onset of morphine-induced place preference is dependent on the activation of mesolimbic dopamine neurons (Bals-Kubik et al., 1993; Shippenberg et al., 1993). It is possible then that the dopamine agonist tested here decreased the ability of morphine to increase the firing of ventral tegmental dopamine cells, and thus prevented the onset of a conditioned place preference. A possible mediation by terminal autoreceptors regulating the release of dopamine may also be considered, as it has been suggested above (Santiago et al., 1993).

However it is important to note that high doses of this agonist elicit a disorganized behavior: it has been reported that 7-OH-DPAT is able to evoke compulsive sniffing (Daly and Waddington, 1993) and to produce stereotypic behavior (Caine and Koob, unpublished) when administered at doses greater than 1 mg/kg. This might disrupt attentional functions necessary for environmental stimuli to become associated with the administration of the opiate, which might prevent the onset of a conditioned response, reflected in the blockade of the acquisition of morphine place preference. Additionally, the possibility of a state-dependent learning contribution to the high dose effects may be considered. It is possible that the stimulus effects of 7-OH-DPAT themselves contribute to the place preference produced by morphine. Further experiments testing animals with 7-OH-DPAT injected prior to the place preference test will be necessary to test this hypothesis.

It may be important for therapeutic reason that the putative dopamine D_3 receptor agonist 7-OH-DPAT blocked the expression of an already established opiate-induced conditioned place preference. Since this pharmacological effect appeared at a dose of 7-OH-DPAT that did not induce a place preference by itself, the data suggest that dopamine receptor agonists with a D_3/D_2 receptor profile may be effective as a treatment for opiate craving. The neurobiological basis of this pharmacological action will be subject of further investigation.

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