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Clonidine produces a conditioned place preference in rats

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Abstract. The possibility that the α-adrenergic agonist clonidine can act as a reinforcing agent was investigated using the conditioned place preference paradigm. Using two different variants of this method we were able to demonstrate reinforcing properties of clonidine at doses of 200 and 400 μg/kg. These results are consistent with those obtained by other investigators using the self-administration technique, and support the view that adrenergic mechanisms may be involved in reinforcement.

Key words: Clonidine – Reinforcement – Conditioned place preference – Reward – Norepinephrine

Within the past 20 years a great deal of attention has focused on defining the neurochemical substrates of reinforcement. Early theories concentrated largely on the role of norepinephrine (NE) as reviewed by Stein (1969), but more recent works have tended to stress a role for dopaminergic mechanisms (Fibiger 1978; Wise 1978). Although there is considerable evidence that a number of dopamine agonists are reinforcing in that they are self-administered by both laboratory animals and humans, much less attention has been paid to the possibility that drugs acting on adrenergic receptors may have reinforcing properties. Davis and Smith (1977) reported that rats will self-administer the α-adrenergic agonist clonidine but their study was criticized on methodological grounds by Wise (1978). There have since been two other reports of clonidine self-administration, one in rats and the other in monkeys (Shearman et al. 1981; Woolverton et al. 1982), and these results raise interesting questions about a role for adrenergic mechanisms in reinforcement.

In an effort to investigate further the controversial area of NE and reinforcement, we sought to determine whether or not clonidine reinforcement could be demonstrated using the conditioned place preference paradigm (CPP). This method of investigating the reinforcement properties of drugs has a number of advantages over the self-administration technique. In the CPP paradigm, known drug dosages may be administered, allowing for a more precise determination of drug reinforcement efficacy. Additionally, this paradigm provides a relatively rate-free measure of reinforcement as it does not require that the animal perform an operant response to obtain the drug. Furthermore, the drug's actions do not interfere with the testing procedure since the animals are not drugged at that time. Our results provide evidence for clonidine reinforcement and suggest the involvement of adrenergic mechanisms in reward.

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Experiment I

Materials and methods

Experimentally naive, male Sprague-Dawley derived rats from a colony maintained by the University of Illinois served as subjects. Rats weighed 400–460 g and were housed six to a cage with food and water freely available. Animals were maintained on an approximate 12-h light-dark cycle and were handled daily for 3 days before the start of the experiment.

Apparatus and procedure. Place preference conditioning was conducted in six similar wooden shuttle boxes, each 75 × 25 cm (length × width) and 36 cm high. Each box contained one small center "choice" section, 11 cm in length, which could be separated from the two larger end chambers by metal guillotine doors. One end chamber was painted gray; the other was painted with vertical black and white stripes, 3 cm in width. The center section was unpainted. Boxes could tilt slightly about a center fulcrum and a microswitch mounted on one end of each box was connected to digital circuitry located in another room. Counters recorded the amount of time each animal spent in the gray compartment of the shuttle box.

During the first phase of the experiment, each animal was placed into a shuttle box with the guillotine doors removed, and was allowed to explore it for 15 min a day for 3 days. The amount of time spent in each compartment was recorded over this period of time and the animals' side preference (gray versus striped) was based on the 3rd days' reading. On the 3rd day any animal that spent more than 85% of the time on one side, or that showed a change in preference compared to the first 2 days, was eliminated from further study since pilot studies had revealed that such animals show large changes in side preference on the test day regardless of drug treatment. Animals remaining in the study were then assigned to one of five drug-treatment groups (see below), matched both for side of preference and preference times. In the second phase of the experiment, started the following day, the conditioning procedure was begun. On days 1, 3, 5, 7, and 9, animals were injected with 0 (n = 14), 50 (n = 10), 100 (n = 14), 200 (n = 18), or 400 (n = 15) μg/kg clonidine (IP) 5–8 min before being

placed into their previously less preferred side of the apparatus. Each rat was confined to that compartment by a metal guillotine door for 30 min and was then returned to its home cage. On days 2, 4, 6, 8, and 10 the procedure was the same except that all animals were injected with the distilled water vehicle before being placed into their previously preferred side for 30 min. All injections were given in a volume of 1 ml/kg.

During the third phase of the experiment, tests for conditioned place preference were conducted. On the day following the last vehicle injection, each rat was placed into the choice compartment of the apparatus (guillotine doors removed) and was allowed to move freely throughout the shuttle box for 15 min. The amount of time spent in the two end compartments was recorded. We then calculated the difference in time spent in the originally less preferred side (as determined in the first phase of the experiment) before and after drug conditioning. A larger positive change in side preference time in drug-treated rats compared to controls would indicate that the previously less preferred compartment had acquired secondary reinforcing properties through its association with the drug.

Results

Differences in mean amounts of time spent in the less preferred compartment before and after drug conditioning are indicated in Fig. 1A, where larger values reflect a greater change in preference. It may be seen that clonidine produced a dose-dependent increase in preference change times and that animals receiving 200 and 400 μg/kg clonidine showed significantly greater changes than those shown by control animals (t (30) = 2.15; $P < 0.05$ for 200 μg/kg and: t (27) = 2.50; $P < 0.02$, for 400 μg/kg, two-tailed). The group receiving 100 μg/kg clonidine failed to differ significantly from controls ($P > 0.1$), who spent an average of 439 ± 22s (SEM) on the "drug"-paired side on the test day.

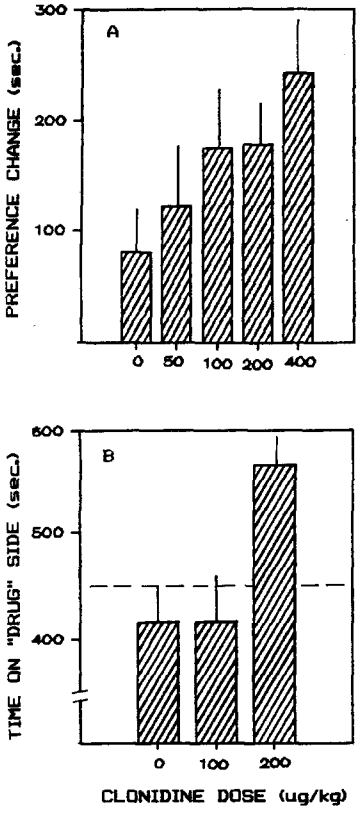

Fig. 1. A Mean change (± SEM) in time spent in the less preferred side before and after conditioning with clonidine. **B** Mean (± SEM) time spent on the drug-paried side after conditioning. Controls were injected with vehicle on both sides of the apparatus. Rats were tested for 900 s, and the *dotted line* represents chance performance

Experiment II

Materials and methods

In an attempt to test for the generality of these findings, additional rats were tested for a clonidine CPP using somewhat different methods. The principal difference between this and the method described above is that rats received the drug treatment in an arbitrarily assigned side of the shuttle box and received vehicle in the other (i.e., rats were not exposed to the apparatus prior to receiving the conditioning trials). In this experiment 35 rats, similar to those described previously, were arbitrarily divided into three groups. Half of the animals in each group received the drug (0, 100, or 200 μg/kg clonidine, IP) in the gray compartment and vehicle in the striped, and the other half of each group received the drug in the striped compartment and the vehicle in the gray. The conditions of injection were as in the previous experiment.

Results

Following the 10 drug/vehicle pairings, animals were tested as described previously. Mean absolute times spent in the drug-paired compartment are shown in Fig. 1B. As indicated, the group receiving the higher dose of clonidine showed a significant preference for the drug-paired side compared to controls [t (21) = 3.820; $P < 0.01$] and the lower-dose clonidine group [t (22) = 3.393; $P < 0.01$].

Discussion

The results of the present study indicate that the reinforcing effects of clonidine can be demonstrated using two different CPP paradigms. Our results support those of the self-administration literature and indicate that clonidine does have reinforcing properties. Other studies using rats have reported that a dose of 15 μg/kg (IV) will support self-administration and the results of the current study suggest that it is at the higher dose ranges that clonidine becomes reinforcing. The preference for relatively high drug doses by rats self-administering clonidine is consonant with reports that those animals showed signs of hyperexcitability and piloerection and that animals would even self-administer a lethal overdose (Davis and Smith 1977; Shearman et al. 1981). Sympathomimetic signs and hyperreactivity were also seen in rats in the present study receiving the 400-μg/kg dose and, to a lesser extent, the 200-μg/kg dose. Monkeys allowed access to clonidine will self-administer from 1,000 to 3,400 μg/kg during a 2-h session (Woolverton et al. 1982). Thus, the available evidence is consistent with our findings that high doses of clonidine, which affect both α1 and α2 receptors (Anden et al. 1976), are reinforcing.

It may be premature to assign a particular neurochemical substrate for these effects of clonidine, Opiate-like behavioral effects of clonidine have been reported, although clonidine self-administration is not blocked by naloxone (Shearman et al. 1981) but is blocked by phenoxybenzamine (Davis and Smith 1977). Although it is possible that dopaminergic mechanisms may be involved in clonidine reinforcement, haloperidol in a dose of 5 mg/kg (IP) has little effect on clonidine self-administration but will suppress it if administered in a dose of 64 μg/kg (IV) simultaneous with clonidine (Shearman et al. 1981). It has also been shown that clonidine can act as an agonist at epinephrine receptors (Blome et al. 1974; U'Prichard 1981) and this effect may possibly underlie the reinforcing properties of clonidine.

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