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Haloperidol Attenuates Conditioned Place Preferences Produced by Electrical Stimulation of the Medial Prefrontal Cortex

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DUVAUCHELLE, C. L. AND A. ETTENBERG. *Haloperidol attenuates conditioned place preferences produced by electrical stimulation of the medial prefrontal cortex.* PHARMACOL BIOCHEM BEHAV **38**(3) 645–650, 1991.—A Conditioned Place Preference test procedure [Ettenberg and Duvauchelle (13)] was used to investigate the effects of dopamine antagonist challenge on the rewarding properties of medial prefrontal cortex (MPFC) electrical stimulation. Rats exhibited strong preferences for the side of a two-compartment test apparatus in which they experienced sessions of experimenter-administered 0.5-s trains of MPFC sine-wave 60-Hz stimulation. Pretreatment with the neuroleptic dopamine antagonist drug, haloperidol (0.0, 0.15, or 0.3 mg/kg IP), resulted in a dose-dependent reduction in the magnitude of observed place preferences. Preference tests were conducted 24 hours after drug-conditioning trials and, hence, were not subject to motoric or other nonspecific actions of the neuroleptic treatments. In a control experiment, haloperidol did not block the place aversions produced by dorsomedial tegmental stimulation. Animals can, therefore, recall place-associations formed in the presence of haloperidol, a result which challenges "state-dependent learning" explanations of the drug's actions. Together, these results are consistent with the view that dopamine neurotransmission is involved in the rewarding consequences of electrical stimulation in the medial prefrontal cortex.

Prefrontal cortex Self-stimulation Haloperidol Neuroleptics Place conditioning Brain-stimulation reward

STIMULATING electrodes placed in the medial prefrontal cortex (PFC) have been observed to support self-stimulation behavior in the rat (7, 30, 38, 40). The fact that the prefrontal cortex is the only cortical brain region that both supports self-stimulation behaviors (40) and receives mesencephalic dopaminergic afferents (2, 16, 46) clearly suggests that central dopamine substrates may subserve the reinforcing properties of PFC brain stimulation. Consistent with this view is the demonstration that injections of relatively specific dopamine receptor antagonist drugs (such as spiroperidol and pimozide) have also been shown to decrease PFC self-stimulation behaviors (15, 24, 41).

However, many qualitative differences exist between self-stimulation of the prefrontal cortex and self-stimulation of other brain areas suggesting perhaps that the neural basis for PFC reward may be somewhat unique. Higher current intensities and a longer training period are required for sustaining PFC self-stimulation behavior compared to lateral hypothalamic regions (6, 8, 11, 38). The rate-increasing effects typically induced by higher stimulation intensities or by pretreatment with stimulant drugs such as amphetamine, are not readily observed in animals with electrode placements in the prefrontal cortex (17,37). In addition, psychophysical measures of refractory periods, spatial summation, strength-duration characteristics and spatio-temporal integration (42–44), as well as functional 2-DG mapping studies (49), provide convincing evidence for separate neural systems underlying self-stimulation of the prefrontal cortex and lateral hypothalamus.

EXPERIMENT 1

To further investigate the putative role of central dopamine mechanisms in the rewarding properties of PFC stimulation, we have examined the effects of the dopamine antagonist drug, haloperidol, in a Conditioned Place Preference test. This procedure makes use of the fact that rats will readily learn to avoid or approach distinctive environments paired with either aversive or rewarding stimuli, respectively [e.g., see review (3)]. We have recently employed the Conditioned Place Preference paradigm as an index of the reinforcing value of lateral hypothalamic (LH) stimulation (13). In that study, animals developed preferences for

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a distinctive environment paired with sessions of rewarding experimenter-administered LH brain stimulation. Pretreatment with the dopamine receptor blocker, haloperidol, produced a dose-dependent attenuation in the size of these reward-induced place preferences. Using this paradigm, the reward-attenuating properties of neuroleptic drugs can be dissociated from drug-induced motoric or sedative properties since: a) the animals do not have to make any responses while in a drugged state (i.e., the brain stimulation reward is experimenter-delivered) and b) the test data are collected well after the direct pharmacological effects of the drug have subsided. The present study was, therefore, devised to determine whether animals would develop conditioned place preferences for an environment paired with rewarding PFC stimulation and, if so, whether the establishment of such preferences could be prevented by pretreatment with haloperidol.

METHOD

Subjects

The subjects were 33 male albino Sprague-Dawley rats (275–350 g) obtained from Charles River Laboratories. The animals were individually housed in metal wire hanging cages located within a temperature-controlled (22°C), 12-hour light/dark (lights on at 0700) vivarium environment. Food and water were made available on an ad lib basis throughout the course of the experiment.

Surgery

Each rat was stereotaxically implanted with a bipolar stimulating electrode (Plastic Products Co.; diameter = 0.14 mm) under 50 mg/kg IP sodium pentobarbital anesthesia supplemented with an 80 mg/kg IP injection of chloral hydrate. An additional 250 μg/kg atropine sulfate was administered IM (in a volume of 0.2 ml/rat) to alleviate potential respiratory congestion. The stimulating electrodes were aimed at the medial prefrontal cortex using the following stereotaxic coordinates: the toothbar was set at 5.0 mm above the interaural line and the electrodes were implanted 4.5 mm anterior to bregma, 0.7 mm lateral to midline, and 3.5 mm ventral to the skull surface.

Self-Stimulation Apparatus

All ICSS training and testing took place in six identical self-stimulation boxes (26 L × 26 W × 66 H cm) each having a single metal lever located on the rear wall 5.0 cm above the wire-mesh floor. A lever press resulted in the delivery of a 0.5-s train of 60-Hz sine wave intracranial stimulation. The stimulation delivery and parameters, as well as the collection of response and reinforcement data, were controlled by a TRS-80 Model III computer in conjunction with a LaFayette Data Systems interface. The electrode leads were connected to mercury swivel commutators mounted above each chamber to provide freedom of movement during the self-stimulation sessions.

Procedure

Self-stimulation training. One week following surgery the rats were individually trained to lever-press for intracranial stimulation during four to twelve 20-min sessions. Current intensities were manually adjusted to a value for each rat that produced steady responding throughout the course of a training session. Once reliable responding was produced, rats were allowed to lever-press at this current intensity until reinforcement rates over a 20-min session became stable (remained within ± 10%) over three consecutive days. Stimulation parameters for each animal were established by noting current intensity as well as mean reinforcement rate during the three-day period. Animals showed consistent lever-pressing behavior at current intensities ranging from 60–75 μA with reinforcement rates ranging from 200–550/20-min session.

Place preference baseline. Once an animal's stimulation parameters were established, a no-stimulation baseline test was conducted in the place preference apparatus. This apparatus was a large 3-chamber rectangular box (94 L × 43 W × 61 H cm) with each of the three chambers distinct from each other. One side of the box (42 L × 43 W × 61 H cm) was constructed entirely of black Plexiglas (including the floor). The opposite side of the box was of the same dimensions but made entirely of white Plexiglas, except for a wooden floor, which was covered with a thick layer of animal bedding (wood chips). The middle chamber of this box was a "neutral" gray strip (10 L × 45 W × 61 H cm) with a bare wood floor. For the baseline preference test, partitions between each chamber were removed to allow the animal free access to all areas of the box. Animals were individually placed in the neutral area of the apparatus and the time spent in both the black and the white side during the next 10 minutes was recorded by stopwatch. A subject was considered to be occupying an area when both rear paws were observed to be within that area.

Conditioning trials. Conditioning trials took place on a single day approximately 24 hours after the baseline preference test. The partitions were replaced in the preference apparatus so that three separate enclosures were created (black, white and neutral). Each rat was placed in either the black or white environment for five minutes (see "Treatment Conditions" below), followed by a 5-min time-out in a plastic holding cage, and then an additional 5 min in the alternate environment. The animal was then returned to the holding cage for approximately 30 minutes, after which the procedure was repeated with the order of environment exposure reversed. This procedure continued until each animal had been exposed to each side five times (10 trials total). It should be noted that the apparatus was thoroughly cleaned after each 5-min conditioning session.

Drugs. An intraperitoneal injection of either haloperidol (HAL; 0.15 or 0.3 mg/kg prepared in a 0.002 M vehicle solution of lactic acid), or the vehicle (VEH) solution alone was administered 45 min prior to the first conditioning trial. Injection volume was held constant at 1.0 ml/kg of body weight.

Treatment conditions. Animals were assigned to one of five treatment conditions. Group assignments were made such that the mean self-stimulation rates (from training) and the mean amount of time spent on the less preferred side of the preference box during Baseline were approximately equal across all stimulation groups. Three groups received experimenter-administered intracranial stimulation only while in the less preferred of the two sides of the apparatus (as determined during Baseline). No stimulation was delivered when the animals were in the alternate environment. These animals constituted three STIM/NO STIM groups which received stimulation at the same current intensities and rate as during the final three days of self-stimulation training. On the conditioning day, these rats were pretreated with either VEH (n = 7), 0.15 mg/kg HAL (n = 7), or 0.3 mg/kg HAL (n = 7). As in our previous work (13), an additional vehicle-treated control group was administered intracranial stimulation during exposure to both sides of the conditioning apparatus, i.e., a STIM/STIM condition (n = 5) and a final control group (n = 7) was pretreated with VEH and connected to the stimulator but received no intracranial stimulation on either side of the conditioning apparatus (a NO STIM/NO STIM condition).

Place Preference test. Twenty-four hours following the final conditioning trial a single 10-min Place Preference test was con-

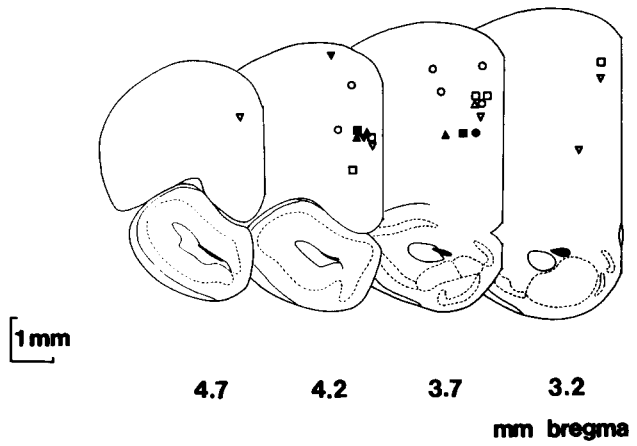

FIG. 1. Histological verification of electrode placements within the medial prefrontal cortex. Hollow symbols depict placements in the contralateral location. Histology was unavailable for one of the animals in the Stimulation/Stimulation (Vehicle) group. Inverted triangles represent the Stimulation/No Stimulation (Vehicle) group; squares represent the Stimulation/No Stimulation (HAL 0.15) group; circles represent the Stimulation/No Stimulation (HAL 0.3) group; triangles represent the Stimulation/Stimulation (Vehicle) group. The numbers at bottom represent millimeters posterior to bregma [from Paxinos and Watson (29)].

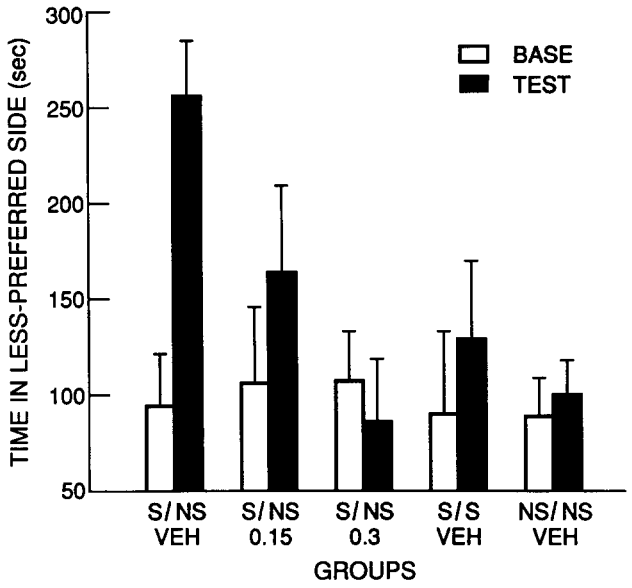

FIG. 2. Mean number of seconds (±S.E.M.) spent in the "less-preferred" environment before (Baseline: open bars) and after (Test: dark bars) conditioning trials for each group. Animals that experienced stimulation in only one side of the preference apparatus (VEH-STIM/NO STIM group) demonstrated strong preferences for that side of the preference box when tested 24 hours after conditioning. No such preferences were observed in subjects that experienced the identical treatments, either MPFC stimulation or No stimulation, while in both sides of the preference box (the STIM/STIM and NO STIM/NO STIM groups, respectively). Haloperidol pretreatment interfered dose-dependently with the MPFC-induced place preferences of STIM/NO STIM animals.

ducted as described above for the Place Preference Baseline.

Histology. Upon completion of the experiment the animals were killed with an overdose of sodium pentobarbital and perfused through the heart with physiological saline followed by a solution of 10% formalin. The brains were removed and stored in 10% formalin until histological analyses could be conducted. Electrode locations within the medial prefrontal cortex were then confirmed from 50 μ cresyl violet stained frozen sections (see Fig. 1).

RESULTS

The results of this experiment are shown in Fig. 2 which depicts the mean time spent in the nonpreferred environment during baseline and preference test. A two-factor (group × trial) Analysis of Variance on the data from Fig. 2 demonstrated that while there were no reliable between-group differences, $F(4,28) = 1.23$, n.s., significant effects were observed over Trials [Baseline vs. Test; $F(1,28) = 12.94$, $p = 0.001$] and for the Group × Trial Interaction, $F(4,28) = 5.02$, $p = 0.004$. The "Trial" effect indicates that there was an overall difference between Baseline and Test performance when averaged across all groups, while the Group × Trial interaction suggests that the magnitude of the Trials effect differed for different groups. One-way ANOVA's confirmed that while all five groups performed comparably during Baseline, $F(4,28) = 0.126$, n.s., group differences did occur during the Test session, $F(4,28) = 3.43$, $p = 0.021$. Subsequent comparisons of each groups' baseline and test performance (two-tailed Student's *t*-tests for correlated samples) confirmed that control animals having experienced either rewarding stimulation or no stimulation in *both* sides of the conditioning apparatus (i.e., the STIM/STIM and NO STIM/NO STIM groups, respectively) demonstrated no reliable change in place preference behavior, $t(4) = -1.25$, n.s.; $t(6) = -0.73$, n.s. In contrast, nondrugged rats that experienced rewarding brain stimulation while in the nonpreferred environment and nothing while in the more preferred environment (i.e., the STIM/NO STIM vehicle-treated group), subsequently demonstrated a shift in preference towards the reward-associated (non-preferred) side of the apparatus, $t(6) = 5.02$, $p = 0.002$. This group averaged a 158% increase in the amount of time spent in the environment paired with rewarding medial prefrontal cortex stimulation compared to a mean increase of 20% in the two control groups. No other group demonstrated any reliable change in place preference from Baseline to Test. Pretreating animals with the dopamine antagonist drug, haloperidol, dose-dependently blocked the establishment of place preferences in the HAL 0.15 and HAL 0.3 STIM-NO STIM groups, $t(6) = 1.38$, n.s.; $t(6) = -0.88$, n.s., respectively. It would seem then, that the statistically reliable effect of Trials and the Group × Trial interaction effect observed in the 2-way ANOVA were essentially a consequence of the performance of one group of animals (i.e., the vehicle STIM/NO STIM group).

Since haloperidol treatments were associated with both sides of the preference box, it was important to determine whether any putative aversive drug effects might have resulted in a shift in preference away from both sides and toward the "neutral" gray region. A two-factor analysis of variance was, therefore, computed on total amount of time spent while subjects were in either side of the conditioning apparatus (excluding the "neutral" region) from Baseline to Test. This analysis revealed no differences between groups, $F(4,28) = 1.64$, n.s., nor over trials, $F(1,28) = 2.87$, n.s., nor for the Group × Trial interaction, $F(4,28) = 0.14$, n.s. Therefore, haloperidol did not reduce the total amount of time spent in either side of the apparatus, i.e., there was no reliable shift in preference away from the two drug-paired environments.

EXPERIMENT II

To aid in the interpretation of our stimulation-place preference

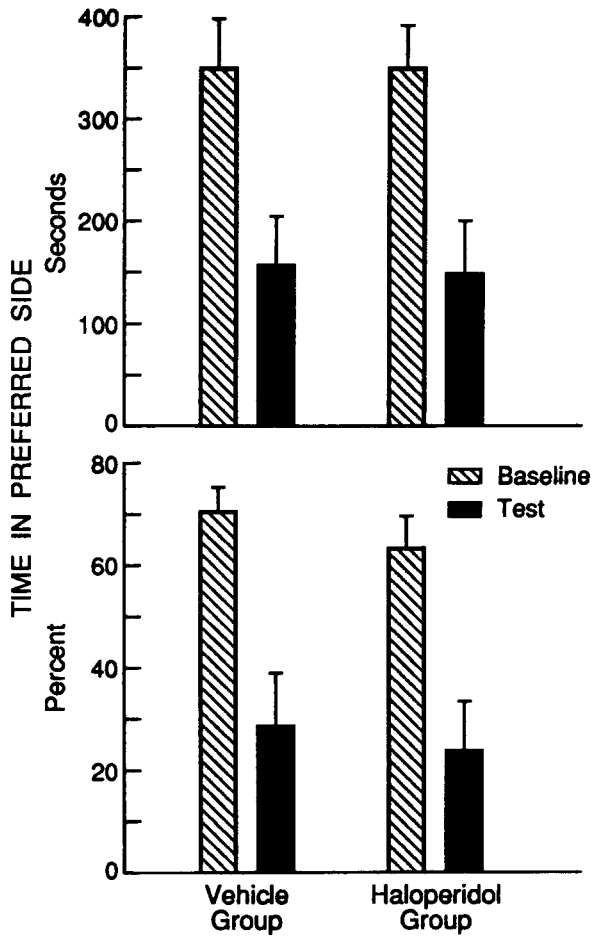

FIG. 3. Mean Place Test performance (±S.E.M.) of two groups of rats (Vehicle Group and Haloperidol Group) on Baseline and Test days. The top panel depicts mean number of seconds spent in the more "preferred" environment before (Baseline) and after (Test) place-stimulation pairings. The bottom panel expresses the same data as a percent of total test time spent in the preferred environment on Baseline and Test days. Note that animals exhibit a profound shift in preference away from the previously preferred side after that side had been paired with dorsomedial tegmental stimulation. The development of this conditioned place aversion was not affected by haloperidol pretreatment.

data, it was of interest to determine a) whether place conditioning procedures would also be sensitive to aversive properties of dorsomedial tegmental stimulation (9,10) and b) whether pretreatment with the dopamine antagonist drug, haloperidol which, in Experiment I prevented the establishment of stimulation-produced place preferences, would similarly interfere with the development of any stimulation-induced aversions.

METHOD

Subjects

The subjects were 21 male albino Sprague-Dawley rats (300–350 g) obtained from Charles River Laboratories and housed as described for Experiment I.

Surgery

Each rat was stereotaxically implanted with a bipolar simulating electrode using the procedures described in Experiment I. The stimulating electrodes were aimed at the dorsomedial tegmentum using the following stereotaxic coordinates: the toothbar was set at 5.0 mm above the interaural line and the electrodes were implanted 3.6 mm posterior to bregma, 1.0 lateral to midline, and 6.0 mm ventral to dura.

Procedure

Stimulation parameters. One week following surgery, stimulation parameters were determined for each rat in a single session. Current intensity was set at 5 μA (60-Hz sine-wave stimulation) at the beginning of the session and increased in 5 μA steps. At each step, 3 trains of 0.5-s experimenter-administered stimulation were automatically delivered by computer. Step increments continued until withdrawal behaviors (e.g., backing up, jumping, etc.) were observed. Testing then stopped and the current intensity at which these behaviors occurred was noted for each animal.

Baseline, conditioning and testing. Animals underwent baseline, conditioning and testing trials exactly as described in Experiment I.

Treatment conditions. Animals were randomly assigned to one of two groups. Both groups received computer-delivered intracranial stimulation while in their most preferred side (as determined during baseline) and no stimulation while in the less preferred of the two conditioning environments. For each rat, the stimulation was delivered at the same current intensities previously determined to produce withdrawal behaviors during the initial stimulation session. Each animal received a total of 25 trains of stimulation (at 12-s intervals) during each 5-min place-stimulation pairing. The two groups differed in their pretreatment condition. One group (n = 11) was pretreated 45 min prior to the first conditioning trial with 0.3 mg/kg IP haloperidol (HAL) prepared in a 0.002 M solution of lactic acid and delivered in a volume of 1.0 ml/kg. The second group (n = 10) was pretreated with an equivalent volume of the vehicle solution alone. Note that the dose of HAL employed here was chosen on the basis of the data from Experiment I which demonstrated that this dose reliably attenuated conditioned place preferences.

Histology. Electrode locations within the dorsomedial tegmentum were easily identified by the aversive reactions of subjects upon delivery of the brain stimulation. Subsequent histological analyses confirmed the presence of the electrodes within this brain region using the same procedures described in Experiment I.

RESULTS

The results of this experiment are depicted in Fig. 3. A two-factor (group × trial) Analysis of Variance computed on the raw data revealed a statistically significant effect for Trials, $F(1,19) = 34.03$, $p<0.001$. However, no reliable between-group difference, $F(1,19) = 0.02$, n.s., nor significant Group × Trial Interaction, $F(1,19) = 0.01$, n.s., were observed. The reliable "Trial" effect clearly resulted from the uniform shift in performance from baseline to test observed in all animals. Vehicle-treated rats learned to avoid the place where they had experienced the dorsomedial tegmental stimulation. These animals spent 43% less time in the stimulation-paired environment than they had during baseline. Haloperidol pretreatment had no effect on this conditioned place aversion. The HAL-group spent 41% less time in the stimulation-paired environment on Test day compared to baseline.

GENERAL DISCUSSION

Although the prefrontal cortex is a site that supports intracranial self-stimulation in the rat, there is controversy regarding the

neurochemical basis of this behavior. Evidence for dopamine involvement in MPFC stimulation includes the findings that rates of MPFC self-stimulation decrease with neuroleptic treatment (15, 25, 41) and with lesions of the dopamine afferents to the MPFC (31). However, unlike lateral hypothalamic sites, MPFC stimulation reward is not enhanced by the indirect dopamine agonist, amphetamine (18, 37, 45). In addition, lesioning of nondopamine efferent cells in the MPFC has been reported to abolish self-stimulation of the area (14,26), indicating a critical involvement of nondopaminergic substrates in MPFC self-stimulation.

The demonstration here that the DA antagonist drug, haloperidol, can dose-dependently attenuate the stimulation-induced conditioned place preferences is certainly consistent with the notion of a dopaminergic involvement in MPFC reinforcement. However, the precise nature of the underlying circuitry for this involvement remains unclear. It may be, for example, that dopamine postsynaptic receptors are located on MPFC efferent neurons whose role in reinforcement is related to synaptic action outside of the frontal cortex. It is known, for example, that projections from the prefrontal cortex innervate the anterior portion of the nucleus accumbens, a structure often implicated in reward processes (1, 4, 32, 33). Furthermore, lesioning and pharmacological manipulations of dopamine elements within the prefrontal cortex have been associated with changes in the activity of dopamine cells within, and behaviors thought to be mediated by, the nucleus accumbens (12, 19, 20, 34). Suffice to say, that the results of the present study, while implicating dopamine transmission in the neurobiology of MPFC reward, do not address the precise location of the rewarding signal (i.e., within or outside of the MPFC) nor the potential exclusivity of dopamine's role.

One might account for the present results (Experiment I) by suggesting that the reductions in place preferences occurred because haloperidol in some way interfered with the encoding of information, thus on test day subjects were unable to effectively recall the previous day's events [e.g., (28)]. However, the results of Experiment II demonstrate that "memory" for place-stimulation events does remain accessible on test day even in animals pretreated with haloperidol on conditioning day. Haloperidol did not block the development or expression of conditioned place aversions produced by electrical stimulation of the dorsomedial tegmentum. Of course, one might intuitively suggest that memories for aversive events are more salient (and hence less easily disrupted) than those for rewarding events. While this certainly remains a possibility, the credibility of such a position is compromised by the fact haloperidol does *not* disrupt place preferences produced by methylphenidate, bupropion or morphine (21, 22, 27). It would seem, therefore, that haloperidol only interferes with the development of place preferences in a selective manner that is not based on simple differences in the affective valence of the incentive stimulus.

The place preferences observed in Experiment I were not due to nonspecific effects of repeated exposure to the preference apparatus, since animals that received either stimulation or no stimulation in both sides of the apparatus did not increase their preference for the less-preferred side. Although the number of animals in the stimulation/stimulation group was relatively small, these identical conditions have been previously tested with hypothalamic electrode sites (13) and similar results were obtained.

This is the first demonstration of conditioned place preferences induced by MPFC stimulation. We are aware that others (36) observed conditioned place preferences for MPFC stimulation only in animals that had received bilateral cuts of the connections between the MPFC and the sulcal prefrontal cortex and not in intact animals. However, there are numerous apparatus and methodological differences between our study and theirs. Since associability factors were of the utmost importance in the Robertson/Laferriere study, differences in place preference apparatus alone may be enough to account for the discrepant results (Robertson, personal communication, November 1988). In any event, it is clear that under the conditions utilized in the present study, robust place preferences were established using experimenter-administered MPFC stimulation.

In conclusion, the most parsimonious explanation for the results of the present MPFC study are that: 1) experimenter-administered stimulation of the medial prefrontal cortex is rewarding and 2) the dopamine receptor antagonist, haloperidol, can decrease the rewarding properties of such stimulation. These observations are therefore consistent with the view that dopamine is involved in the neurobiology of MPFC reward (5, 15, 23–25, 31, 39, 41).

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