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Effects of Acute Nicotine and Ethanol on Medial Prefrontal Cortex Self-Stimulation in Rats

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ARREGUI-AGUIRRE, A., F. CLARO-IZAGUIRRE, M. J. GOÑI-GARRIDO, J. A. ZÁRATE-OLEAGA AND I. MORGADO-BERNAL. *Effects of acute nicotine and ethanol on medial prefrontal cortex self-stimulation in rats.* PHARMACOL BIOCHEM BEHAV **27**(1) 15–20, 1987.—The acute effects of nicotine and ethanol were studied in low and high rates of intracranial self-stimulation (ICSS) of the medial prefrontal cortex (MPFC) in the rat. Nicotine tended to increase low ICSS rates but did not change or even reduced high ICSS rates. Independent of ICSS rate, ethanol tended to decrease ICSS, but only at high doses (1.0 g/kg). It is suggested that the effects of nicotine and ethanol on ICSS may be mediated by their effects on dopamine.

Nicotine Ethanol Intracranial self-stimulation Medial prefrontal cortex

CURRENT knowledge of the effects of nicotine and ethanol on intracranial self-stimulation (ICSS) is largely limited to electrodes in or around hypothalamic component of the medial forebrain bundle (MFB) in rats. The effects of nicotine appear to be dependent on the baseline response rate and on the dose of nicotine. Nicotine, at doses as low as 0.1 mg/kg, increases low ICSS rates. This increase occurs whether the low ICSS rates are associated with low stimulation intensities [4, 22, 31], posterior hypothalamic electrode locations [22] or prolonged training sessions [22].

Nicotine either has no effect on, or inhibits, high ICSS rates [4, 19, 22, 31]. Recently, Shaeffer and Michael [25] showed that nicotine had no effect on continuously reinforced ICSS, whereas it had a biphasic effect on ICSS maintained on a fixed ratio 15 reinforcement schedule. Low doses increased ICSS rates and high doses decreased ICSS rates. Thus, the effects of nicotine on hypothalamic ICSS are both rate and dose dependent. At low rates and low doses, the effects of nicotine on ICSS appear to be mainly excitatory. At high rates and high doses, the effects of nicotine on ICSS appear to be mainly inhibitory. Overall, the effects of nicotine appear to be determined more by response rate than by nicotine dose.

The effects of ethanol on ICSS are somewhat less complex than those of nicotine. The effects of ethanol on ICSS are dose dependent, but there has been no suggestion of any rate dependency. Low doses of ethanol (0.4–0.8 g/kg) increase the rate of ICSS [3, 12, 14, 30], whereas high doses (>1.0 g/kg) either have little effect on, or decrease the rate of ICSS [3, 14, 24]. However, even the effects of ethanol on hypothalamic ICSS may be more complex than is generally appreciated. For example, the effects of ethanol may vary as a function of electrode location within the hypothalamus [28].

There are few data on the effects of either nicotine or ethanol on ICSS at extrahypothalamic locations. Routtenberg [24] reported that even a high dose of ethanol had no effect on ICSS of the dentate gyrus. To clarify the importance of electrode location in determining the effects of both nicotine and ethanol on ICSS, it is of interest to investigate electrode locations quite anatomically and functionally distinct from the lateral hypothalamus. The medial prefrontal cortex (MPFC) is such a site. Besides being remote from the hypothalamus, the fibres stimulated in MPFC appear to be anatomically [5,6] and electrophysiologically [26] distinct.

EXPERIMENT I

In this study, we investigate the effects of several doses of nicotine on ICSS of the MPFC at several different current intensities.

METHOD

Animals and Electrode Implantation

Thirty-one experimentally naive, male Wistar rats with a

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mean age of 152 days (SD=20.90) and a mean weight of 396 grams (SD=14.15) at the time of surgery were used as subjects (Ss). All rats were acclimated to laboratory conditions for 4 days prior to surgery. Each rat was implanted with a bipolar stainless steel electrode (130 μm in diameter) while under Nembutal anesthesia (50 mg/kg, IP). The electrodes were aimed at the left MPFC according to the atlas of Pellegrino, Pellegrino and Cushman [21]. The stereotaxic coordinates according to that atlas were: AP: 5, L: 1 and V: 2.5 with the dura mater as dorsal reference.

Procedure

Six to seven days after surgery the rats were taught to self-stimulate by pressing a lever in an experimental chamber. Electrical brain stimulation consisted of 50 Hz sinusoidal waves with a train duration of 0.3 sec. First, the range of intensities that would support responding in each rat on a continuous reinforcement schedule was explored. An additional criterion was that the stimulation did not produce any convulsive or other abnormal behaviours. Then, rates of lever pressing were recorded for successive increases of current intensities in sessions conducted at the same time during each of several consecutive days. Starting with 10 μA, the current intensity was increased 5 μA every 3 minutes. Sessions finished when the rates of lever pressing did not increase during three consecutive current increases (±3 responses) or when it decreased by 20 percent with respect to the response rate for the preceding current intensity. These tests were finished when, after a minimum of 8 sessions, the optimal intensity (OI), i.e., the current intensity that gave rise to the highest response rate, had the same value (±5 μA) during 3 consecutive sessions. After this, all rats received 6 standard sessions, one per day, of ICSS, each consisting of four successive 5 min periods of self-stimulation at 40, 60, 80 and 100% of OI (the range of OI was 15–250 μA rms). Previously all Ss had been randomly assigned to 4 groups each one to be given a pre-ICSS treatment of 0.2, 0.4, 0.6 or 0.8 mg/kg of IP nicotine (L-1-Methyl-2-(3-pyridyl)-pirrolidine sulfate). For this pretreatment, each of these 4 groups were divided into two equal subgroups which received a counterbalanced treatment of IP saline and respective dose of nicotine as shown below:

Session	Subgroup A (n/2)	Subgroup B (n/2)
1	Saline	Nicotine
2	Nicotine	Saline
3	Saline	Nicotine
4	Nicotine	Saline
5	Saline	Nicotine
6	Nicotine	Saline

To assure the complete absorption of the drug, the injections were always administered 15 min before the test-session. The volume of liquid injected was the same (2.0 ml/400 g of weight) for saline and all of the nicotine doses. To overcome the initial depression of locomotion generally caused by nicotine, non-contingent stimulation was administered when necessary but only at the start of the session. The timing of any test-session was not begun until the rat had made at least three responses within a one min period.

TABLE 1

MEAN SCORES OF ICSS FOR EACH GROUP AND TREATMENT OF NICOTINE

	ICSS (responses/5 minutes)			
	LRI		HRI	
Dose (mg/kg)	Saline	Nicotine	Saline	Nicotine
0.2	81.96	92.58	167.81	167.33
(n=8)	(60.20)	(68.35)	(69.48)	(68.80)
0.4	127.23	158.33	245.42	242.61
(n=7)	(98.34)	(99.14)	(61.36)	(56.86)
0.6	129.20	165.20	232.60	215.97
(n=8)	(88.00)	(84.44)	(63.86)	(71.14)
1.0	120.49	158.20	204.67	191.25
(n=8)	(79.97)	(91.37)	(93.67)	(81.60)

The standard deviations appear in parentheses below each mean.

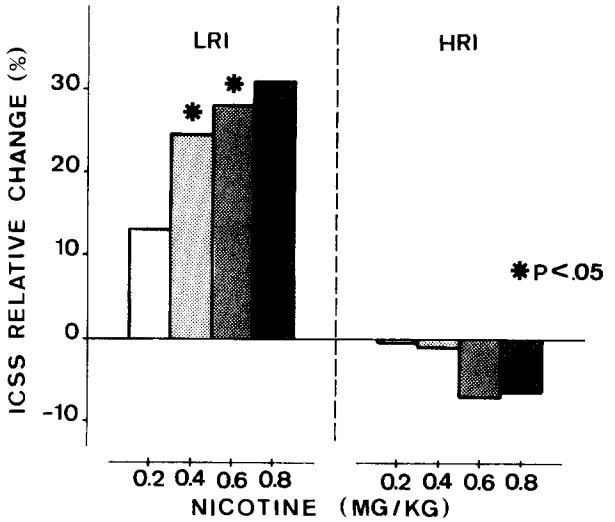

FIG. 1. Effects of the 4 doses of nicotine upon the ICSS saline baseline response rates for each of the two stimulation intensities (LRI and HRI).

Histology

At the conclusion of the experiments, the rats were killed with an overdose of Nembutal. They were then perfused intracardially with saline followed by 10% formalin in distilled water. The brains then were removed, frozen and sectioned at 40 micrometers on a freezing stage microtome. The tissue was stained with cresyl violet and examined under a microscope. Electrode tip locations were reconstructed on plates from the atlas of Pellegrino *et al.* [21].

RESULTS

All Ss showed stable lever pressing throughout the experiment. Further, as a way of knowing the consistency of the obtained ICSS scores, reliability indexes were determined by performing ANOVAS [11] for each experimental condition. The reliability indexes of the individual responses (intensities × sessions) were sufficient (>0.5) in all the cases

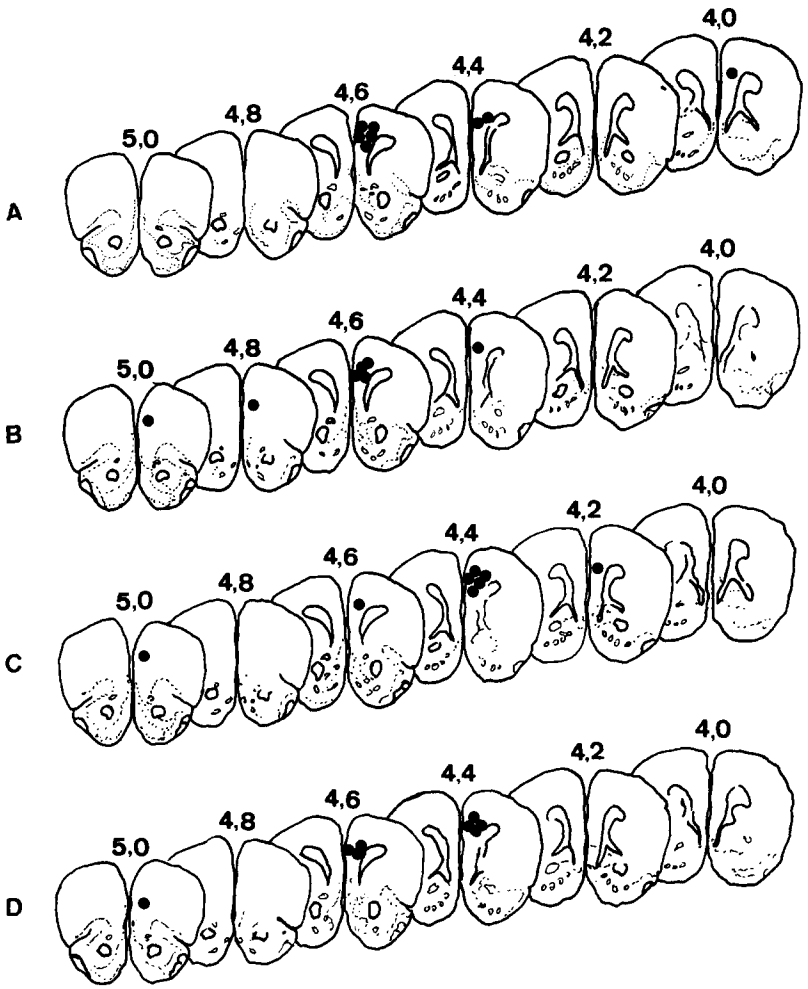

FIG. 2. Locations of the electrodes with reference to the stereotaxic atlas of Pellegrino, Pellegrino and Cushman [21]. A, B, C and D refer to the 0.2, 0.4, 0.6 and 0.8 mg/kg dose groups of nicotine.

except for 2 Ss whose scores then were replaced by the mean of those obtained in the two higher correlated of the 3 ICSS sessions of each case. Reliability of the group responding (Ss × sessions) was obtained in the same way for every treatment situation. Again, the reliability indices were sufficient (>0.5) in all the cases except for the lower intensities (40% of OI) as is common with near threshold performance. This did not affect the overall results because, as is indicated below, none of the lower intensities was used for evaluating the effects of nicotine.

As has been previously reported [23], ICSS of the MPFC is more independent of current intensity than is ICSS of the MFB. Perhaps for this reason, the maximal response rates in the 6 test-sessions of our experiment (see above) were not always coincident with the OI previously calculated. This problem was circumvented by evaluating drug effects against an average maximal baseline response rate for each subject. This average maximal rate was the mean of the maximal ICSS rates obtained in each of the 3 saline sessions (see above) independent of the stimulation intensity. The drug effects on the sub-maximal ICSS rates also were evaluated. The sub-maximal ICSS rate was the mean of the 3 response rates obtained for the 3 current intensities immediately (i.e., 20%) below those giving rise to the maximal ICSS rates. "High rate intensity" (HRI) and "low rate intensity" (LRI) then refer to the theoretical intensities respectively generating these calculated maximal and sub-maximal average rates of ICSS. Mean scores then were obtained for the whole group and compared with the equivalent scores for the same rats after treatment with nicotine. The same procedure was applied to each group at each drug dose.

The mean scores obtained for each group and treatment are shown in Table 1.

The effects of the 4 doses of nicotine relative to the respective ICSS saline baselines for each of the two stimulation intensities (LRI and HRI) are shown in Fig. 1. Nicotine tended to increase the ICSS rates generated by LRI, whereas the same doses tended to decrease the rates generated by HRI. Repeated-measures three factor ANOVAS showed a significant nicotine × intensity (LRI-HRI) interaction, $F(1,6)=16.58$, $p<0.007$, at a dose of 0.6 mg/kg. The same ANOVAS showed a significant intensity factor for 0.2 mg/kg, $F(1,6)=7.53$, $p<0.03$, 0.4 mg/kg, $F(1,5)=5.93$, $p<0.05$, 0.06 mg/kg, $F(1,6)=9.67$, $p<0.02$, and 0.08 mg/kg, $F(1,6)=13.78$, $p<0.01$, doses of nicotine. There was also a not significant ($p<0.05$) counterbalanced treatment order

factor in each of these treatment situations. Paired t-tests for each of the dose-group and intensity conditions showed a significant effect of the 0.4 mg/kg, $t(6)=2.38, p<0.05$, and 0.6 mg/kg, $t(7)=2.55, p<0.03$, doses for LRI. None of the other comparisons approached statistical significance ($p<0.05$).

The histological analysis indicated that the electrode tips were located in the MPFC as shown in Fig. 2.

EXPERIMENT II

This study investigated the effects of several doses of ethanol on ICSS of the MPFC at different stimulation intensities.

METHOD

Animals, Electrode Implantation and General Procedure

Twenty-six naive, male Wistar rats with a mean age of 155 days (SD=21) and a mean weight of 402 g (SD=30.88) at time of surgery were used as Ss. Acclimation to laboratory conditions, electrode implantation, shaping of self-stimulation, OI determination, general procedure and histology were as in Experiment I, except: (a) the drug administered here was ethanol (20% v/v solution prepared from 99.5% ethanol and sterile saline); (b) the rats were randomly assigned to 3 groups to be given a pre-ICSS treatment of 0.2, 0.6 and 1.0 g/kg of IP ethanol; (c) to assure the complete absorption of the drug the injections were always administered 20 min before the test sessions; (d) the volume of liquid injected for the dose of 0.2 g/kg (0.6 ml/500 g), 0.6 g/kg (1.9 ml/500 g) and 1.0 g/kg (3.1 ml/500 g) doses were always the same for the saline and ethanol treatments; and (e) to assure the complete elimination of ethanol before the saline tests, no testing was given to the rats between every two ICSS sessions, as shown below:

Session	Subgroup A (n/2)	Subgroup B (n/2)
1	Saline	Ethanol
2	Rest	Rest
3	Ethanol	Saline
4	Rest	Rest
5	Saline	Ethanol
6	Rest	Rest
7	Ethanol	Saline
8	Rest	Rest
9	Saline	Ethanol
10	Rest	Rest
11	Ethanol	Saline

RESULTS

All rats showed stable ICSS rates throughout the experiment. The individual reliability indices, calculated as in Experiment I, were sufficient (>0.5) except for 2 Ss whose scores were then replaced by the mean of those obtained in the two higher correlated of the 3 ICSS sessions of each case. Another subject with a very low reliability index was excluded from the experiment. The group reliability indices, also calculated as in Experiment I, were sufficient (>0.5) in all cases except for the 60% of OI in the 1.0 g/kg dose group of Ss. A closer examination of the data showed that the low reliability (<0.5) was caused by the irregular scores of only one rat. However, because the individual ICSS scores of this rat were reliable (>0.5) and also because its relative irregularity was equivalent for saline and ethanol treatment, we did not exclude this subject.

TABLE 2

MEAN SCORES OF ICSS FOR EACH GROUP AND TREATMENT OF ETHANOL

	ICSS (responses/5 minutes)			
	LRI		HRI	
Dose (g/kg)	Saline	Ethanol	Saline	Ethanol
0.2	85.31	101.94	115.57	116.99
(n=9)	(47.04)	(79.76)	(38.53)	(52.02)
0.6	81.28	72.66	138.14	137.28
(n=7)	(50.00)	(42.46)	(44.69)	(41.83)
0.8	90.24	73.11	155.66	124.57
(n=9)	(39.00)	(32.64)	(70.04)	(50.09)

The standard deviations appear in parentheses below each mean.

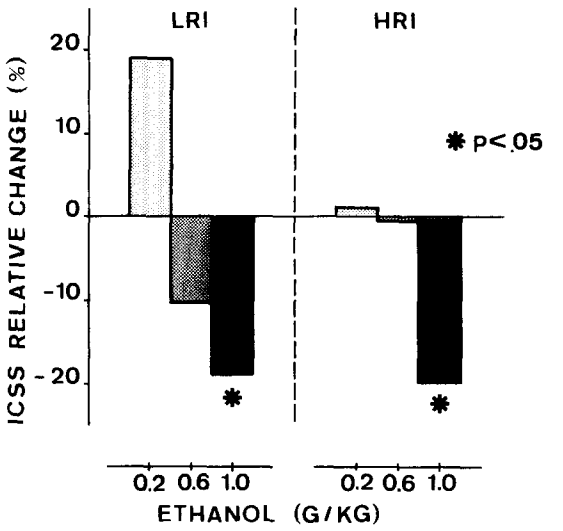

FIG. 3. Effects of the 3 doses of ethanol upon the ICSS saline baseline response rates for each of the two stimulation intensities (LRI and HRI).

As in Experiment I, mean ICSS rates were calculated for LRI and HRI in every group of Ss. Table 2 and Fig. 3 show the results. For LRI, the lower dose (0.2 g/kg) of ethanol tended to increase the ICSS rates and the higher doses (0.6 and 1.0 g/kg) tended to decrease the rates. For HRI, 0.2 and 0.6 g/kg doses of ethanol had little effect, whereas the 1.0 g/kg dose produces a strong depressive effect. Repeated-measure three way ANOVAS showed a significant treatment factor, $F(1,7)=7.42, p<0.03$, at 1.0 g/kg of ethanol. The same ANOVAS showed a significant current intensity factor for 0.6 g/kg, $F(1,5)=10.23, p<0.02$, and 1.0 g/kg, $F(1,7)=9.80, p<0.01$, doses. In the lower dose group (0.2 g/kg), the two levels of intensity (LRI and HRI) had a similar effect on the ICSS rate. Here also, the ANOVAS showed a non signifi-

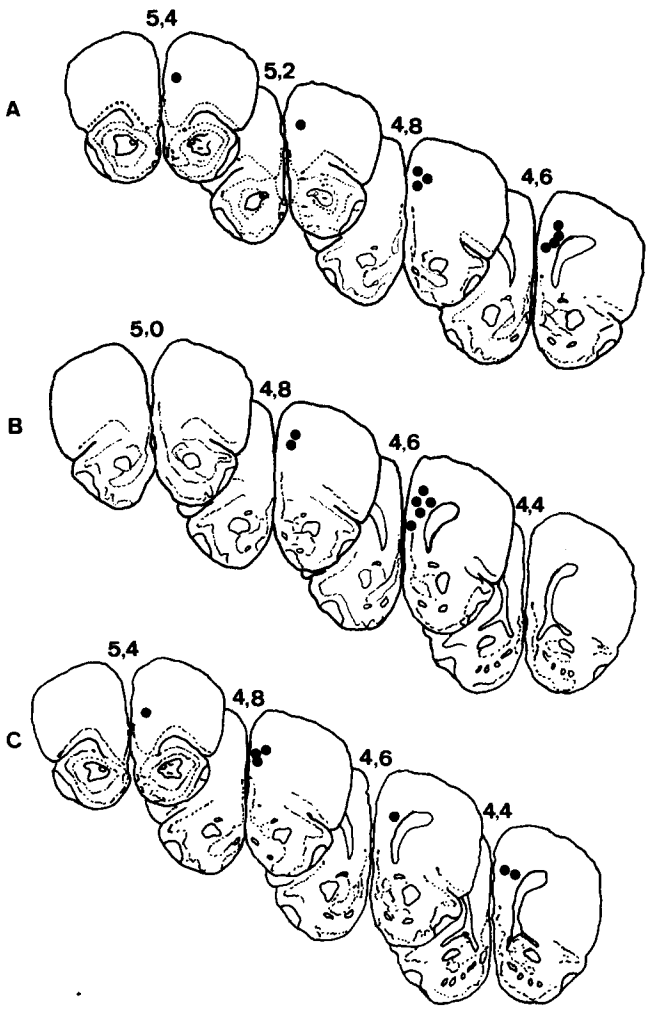

FIG. 4. Location of the electrodes with reference to the stereotaxic atlas of Pellegrino, Pellegrino and Cushman [21]. A, B and C refer to the 0.2, 0.6 and 1.0 g/kg dose groups of ethanol.

cant counterbalanced treatment order factor. That is, as in Experiment I the treatment order (saline-ethanol) did not significantly affect the results.

Histological analysis showed the electrode tips situated in the MPFC as shown in Fig. 4.

GENERAL DISCUSSION

Our results indicate that 0.4 and 0.6 mg/kg of nicotine increase the rate of ICSS for LRI at MPFC. Although not significant, similar tendencies also were observed for Ss treated with 0.2 and 0.8 mg/kg of the drug. Overall, nicotine tended to facilitate low ICSS rates and did not change or even reduced high ICSS rates. These results are similar to, but somewhat smaller in magnitude than those produced by d-amphetamine in a similar paradigm [4, 18, 20, 22, 31]. They are also similar to, but smaller, than those produced by amphetamine on ICSS of the MFB [23].

The effect of nicotine upon ICSS appears to be specific for reinforced responses [22]. Further, it has been observed that doses of nicotine similar to the ones administrated in our experiment not only did not increase but actually decreased spontaneous motor activity in rats [25]. Thus, the observed increase in ICSS rates in the present experiment are not likely due to changes in locomotion produced by nicotine. Nevertheless, peripheal cholinergic locomotor alterations could be the cause of the initial behavioral depression observed in the Ss of our experiment after the injection of the higher nicotine dose (0.8 mg/kg). It is, however, possible that the initial behavioural depression seen at the high dose of nicotine could reflect an inhibition of locomotion produced by peripheral cholinergic blockade [29].

The present results also indicate that 1.0 g/kg of ethanol decreases ICSS rates at MPFC, although not significant increases also were observed in the Ss treated with 0.2 g/kg dose of the drug. Thus, ICSS of the MPFC tends to be increased or decreased by low and high doses of ethanol, respectively, independent of current of intensity. These findings are similar to those observed for the same drug and ICSS at MFB and/or hypothalamic areas [3, 7, 12, 14, 27, 30].

Several considerations suggest that the effects on ICSS observed here are not secondary to changes in motor activity produced by ethanol. Doses less than 1.5 g/kg do not appear to change the ambulation distance, the ambulation time or the ambulation speed in an open field test [9]. Furthermore, doses of ethanol less than 1.2 g/kg do not appear to change the spontaneous locomotor activity in rats [8].

As discussed above, changes in locomotion caused by nicotine or ethanol do not seem to underly changes in rates of ICSS of the MPFC observed in the present experiments. We, therefore, suggest that these changes could be related to the effects of nicotine and ethanol on a brain reward substrate. Nicotine has been shown to be reinforcing in both humans and laboratory animals [10]. This reinforcing effect could be due to the dopaminergic effects of nicotine [1,2]. There is a great deal of evidence which suggest that dopamine may be involved in the brain reward system [27] and particularly in the MPFC [15,16].

Similarly, the effects of ethanol on ICSS rates could be mediated by dopaminergic mechanisms. Ethanol could increase dopamine transmission, by its effect on the adenylate cyclase system, as a consequence of its ability to increase the cell membrane fluidity [13]. How these mechanisms could then increase or decrease the ICSS rates would be a result of the interaction between the stimulation current intensity and the state of the reward system produced by the drug. In the case of nicotine, the increase in ICSS rates for low intensities in our first experiment could be due to increasing the reinforcing properties of the stimulation. The reduction in responding for the high intensities could be due to overexcitation of the reward system. Such an overexcitation could be a consequence of the combined effect of the stimulation and the nicotine. Similarly, the reduction in responding produced by ethanol could be a reduction in the reinforcing properties of the stimulation. These changes could also reflect the particular neurophysiological features of the MPFC. New studies controlling anatomical and physiological variables related to the brain reward system are then necessary to evaluate all these suggestions.

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