tation sites and thereby allow for successful predictions of implantation frequency.

Methods and materials. A total of 46 virgin female rats of the Charles River CD outbred albino strain were mated and divided into 3 groups designated as uninjected controls, saline-injected controls and histamine dihydrochloride-injected animals. The number of individuals within these groups varied with 18, 7 and 21, respectively. Histamine dihydrochloride was administered as 7 dose levels in concentrations ranging from 0.05 mg/cornu to 2.0 mg/cornu. Injections were given between 14.00 and 16.00 h on the 5th day of pregnancy; the injected fluid was maintained at 37 °C, pH 7.4 and 0.05 ml volume. The injections were accomplished by passing a 25-gauge hypodermic needle through the antimesometrial surface into the lumen of the left uterine cornu approximately midway between the tubouterine junction and the cervix. The right uterine cornu remained uninvolved in surgery and thus served as a contralateral control. On the 18th day after copulation, the animals were autopsied and examined for viable implantation sites.

Results. The results of the present study indicate that there is no inherent unilateral bias in the number of implantations per cornu in this strain of laboratory rat ($p < 0.005$). The trauma induced by surgery and injection of the left cornu had no significant effect on the right cornu of the same animal ($p < 0.05$), but significantly reduced the number of implantations in the left cornu of the saline-injected group ($p < 0.05$). The effect of histamine dihydrochloride was observed to be localized in the left cornu and did not significantly affect the contralateral cornu ($p < 0.005$). Reductions in the number of implantations were also observed in the histamine dihydrochloride-injected group at concentrations ranging from 0.05 mg/cornu to 1.2 mg/cornu. Only the 2 highest concentrations of histamine dihydrochloride (1.5 mg/cornu and 2.0 mg/cornu) were observed to significantly increase the number of implantations as compared to the left (surgery-involved) cornu of the saline-injected group ($p < 0.005$).

Discussion. The reductions in the number of implantations observed in the histamine dihydrochloride group (0.05 mg/cornu – 1.2 mg/cornu) are suggested as being caused by the initiation of artificially-induced deciduomas which may have altered the intrauterine environment necessary for normal blastocyst implantation. Vascular constriction due to the proliferation of decidual tissue may have increased competition between blastocysts for nutritive and hormonal support and thereby increased implantation failure. Apparently, the implantation promotive effect at the 2 highest concentrations of histamine (1.5 mg/cornu and 2.0 mg/cornu) was sufficient to surpass the inhibitory effect thought to be caused by the induced deciduomas. A linear regression analysis provided a description of the relationship and was found to be $Y = -0.0126 + 3.393\ X$. The strength of association (r^2) between Y (number of viable implantations) and X (histamine dihydrochloride dose level) was found to equal 0.5315. The results of this study show that pharmacological doses of histamine dihydrochloride injected intraluminally induced deciduomas (all concentrations) and significantly increased implantations (1.5 mg/cornu and 2.0 mg/cornu).

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Evidence for an involvement of acetylcholine in self-stimulation of the prefrontal cortex in the rat

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Summary. The effects of injections of antagonists of muscarinic and nicotinic receptors on self-stimulation of the prefrontal cortex in the rat were studied. The results of this investigation suggest that acetylcholine is involved in self-stimulation of the prefrontal cortex through activation of muscarinic receptors, and also suggest a possible interaction between acetylcholine and dopamine in mediating self-stimulation of this area of the brain.

The neurochemical properties of the prefrontal cortex are currently of great interest because of its functional involvement in a variety of types of behaviour (see references cited by Mora et al.[2,3]). At present, there is considerable evidence for an involvement of dopamine in self-stimulation of the prefrontal cortex (medial and sulcal areas), although, as shown recently, this neurotransmitter does not seem to be the exclusive neurochemical substrate[4,5]. Since noradrenaline, also present in the prefrontal cortex, does not seem to participate in self-stimulation of this area of the brain (Mora et al. unpublished results) it would be possible that other neurotransmitters, different from catecholamines, are also involved[6].

Recently it has been reported that acetylcholine, substance P and dopamine terminals coexist within the same deep layers in the medial prefrontal cortex[7]. This coexistance suggest that acetylcholine and/or substance P may participate in the mediation of self-stimulation in this area of the brain together with dopamine.

In the present series of experiments we have investigated the possible participation of acetylcholine in self-stimulation by studying the effects of subcutaneous injections of muscarinic and nicotinic receptor antagonists.

Material and methods. Monopolar stainless steel electrodes, insulated except for 0.5 mm at the tip, were implanted in the medial prefrontal cortex of male albino rats. After recovery from surgery, the animals were trained for self-stimulation by lever pressing. Stimulus parameters were: 0.3 sec trains; 100 Hz square pulses; 0.3 msec pulse duration; and a current intensity that varied among animals from 0.08 to 0.3 mA. Current intensity was kept constant for all experiments performed on a given animal. Spontaneous motor activity was measured via contacts lining the floor of a $26 \times 29 \times 36$ motility chamber[8,9].

The protocol consisted of measuring spontaneous motor activity for the last 10 min of a 15-min session. This period was followed by a 2nd 15-min session in which self-stimulation was measured for the last 10 min. These sessions were performed daily while drug injections were made every 4 days.

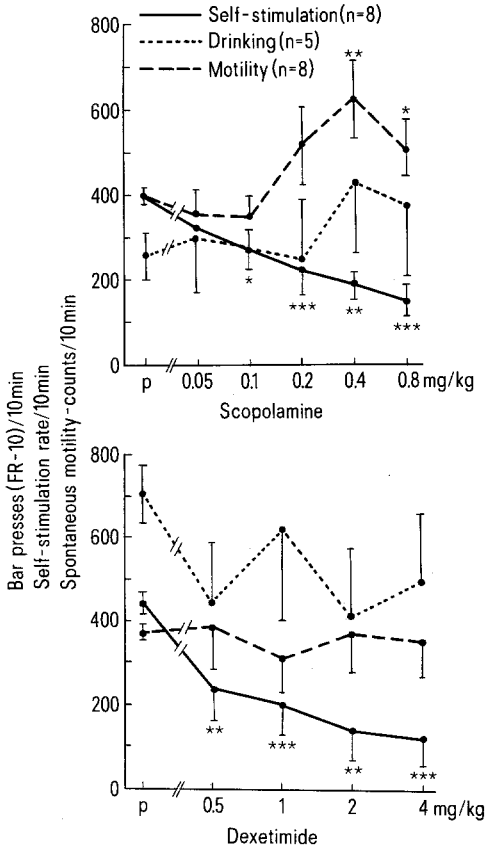

Fig. 1. Effects of 2 different muscarinic antagonists on self-stimulation of the medial prefrontal cortex, spontaneous motor behaviour and drinking behaviour on a FR-10 schedule. The upper figure shows the effects of scopolamine. Scopolamine produces a dose-related decrease of self-stimulation which is statistically different from that with placebo injections (saline), $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Spontaneous motor behaviour was facilitated at the higher 2 doses and drinking behaviour was unaffected. The lower figure shows the effects of dexetimide. As in the upper figure, a dose-related inhibition of self-stimulation was produced, while spontaneous motility and drinking behaviour were unaffected; n = number of animals.

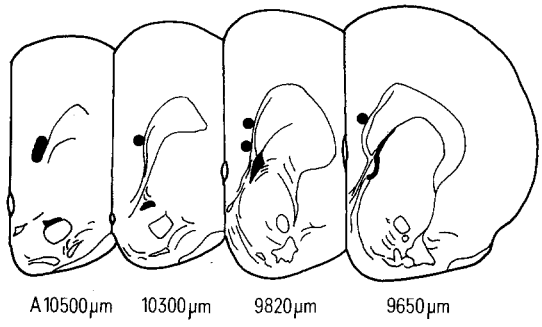

Fig. 2. Sites of electrodes in the medial prefrontal cortex used for self-stimulation in the rat. The outlines were taken from the atlas of König and Klippel.

To provide further control for operant behaviour a different group of rats were put on a 22-h water-deprivation schedule and trained to bar-press for water on a FR-10 schedule. In both groups of rats similar rates of responding were obtained for self-stimulation and for water (figure 1).

The drugs used were scopolamine (0.05, 0.1, 0.2, 0.4 and 0.8 mg/kg) and dexetimide (0.5, 1.0, 2.0 and 4.0 mg/kg) both antagonists of muscarinic receptors and mecamylamine (2.5, 5.0 and 7.5 mg/kg) an antagonist of nicotinic receptors. Concentrations were expressed as the free base. The results were statistically evaluated using Student's t-test.

Restults. Figure 1 shows the effects of scopolamine and dexetimide on self-stimulation of the medial prefrontal cortex, motor activity and drinking behaviour on a FR-10 schedule. Scopolamine produced a significant dose-related attenuation of self-stimulation together with a significant facilitation of the spontaneous motor activity of the same animals. Drinking behaviour, which required a similar operant response to that of self-stimulation, was unaffected. Similar effects were found with dexetimide. The nicotine antagonist, mecamylamine, had no effect on self-stimulation or spontaneous motor behaviour. At the end of the experiments the location of the electrode tips was verified histologically (figure 2).

Discussion. The fact that self-stimulation of the prefrontal cortex is a) attenuated by selective antagonists of muscarinic receptors, but not by nicotinic antagonists and b) that spontaneous motor activity or a similar operant response to that of self-stimulation but for a different reinforcer (drinking) was not affected or even facilitated, strongly suggest that acetylcholine transmission through muscarinic receptors is involved in self-stimulation of the prefrontal cortex. Contrary to these results, other investigators[10,11] have reported a facilitation of self-stimulation of the lateral or posterior hypothalamus using muscarinic antagonists. This would suggest that muscarinic receptors in the prefrontal cortex may play a different role from those in the hypothalamus in mediating self-stimulation behaviour.

These results are the first to suggest a role for acetylcholine in self-stimulation of the prefrontal cortex. Similarly to the case for motor behaviour in basal ganglia[8], it is possible that an interaction between acetylcholine and dopamine could be mediating self-stimulation in the prefrontal cortex. In addition, the results reported here could also be important for the understanding of the neurochemical substrates underlying psychiatric disorders[12,13].

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