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BRIEF COMMUNICATION

Self-Stimulation of the MFB or VTA after Microinjection of Haloperidol into the Prefrontal Cortex of the Rat[1]

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MORA, F., R. D. MYERS AND A. M. SANGUINETTI. *Self-stimulation of the MFB or VTA after microinjection of haloperidol into the prefrontal cortex of the rat.* PHARMAC. BIOCHEM. BEHAV. 6(2) 239–241, 1977. – Haloperidol, a dopamine receptor antagonist, was microinjected in doses of 12 or 24 μg into the prefrontal cortex of the rat. Its effects on self-stimulation of the ventral tegmental area (VTA) or the medial forebrain bundle (MFB) were examined. It was found that these injections failed to attenuate self-stimulation at either structure. However, when haloperidol was injected into the caudate-putamen complex, a decrease in self-stimulation occurred within these structures. These results suggest that dopamine in the medial prefrontal cortex is not necessarily a part of the neurochemical substrate underlying self-stimulation of the ventral tegmental area or medial forebrain bundle.

Prefrontal cortex Dopamine Ventral tegmental area Self-stimulation Haloperidol

A DESCENDING pathway from the prefrontal cortex, with cell bodies of origin in the medial and sulcal area, has been proposed to be involved in self-stimulation of the medial forebrain bundle (MFB) as well as other areas in the diencephalon [14, 15, 17]. Rolls and Cooper [16] reported that self-stimulation in the lateral hypothalamus (LH) or pontine tegmentum is disrupted after procaine anesthetization of the sulcal prefrontal cortex. An attenuation of self-stimulation in the substantia nigra after sulcal prefrontal lesions, and a similar reduction in midbrain tegmental stimulation after ipsilateral MFB lesion further implicate the involvement of descending fibers in intracranial self-stimulation of midbrain structures [2,3].

Both the medial prefrontal as well as the sulcal cortex receive dopaminergic terminals from the A10 area [4, 5, 18]. That self-stimulation within the medial prefrontal cortex could be mediated by dopamine has been suggested [7]. Because of the possibility that dopamine is a putative neurotransmitter linking the ascending mesocortical dopaminergic system with the frontal descending pathway in the medial prefrontal cortex, this study was designed to test the possible participation of descending fibers through that dopaminergic link. Therefore, we determined whether the blockade of dopamine receptors in the prefrontal cortex [9] would attenuate self-stimulation of the ipsilateral medial forebrain bundle, at the level of the lateral hypothalamus, and of the ipsilateral ventral tegmental area (VTA) where cell bodies of the mesocortical pathway are located.

METHOD

Six male Sprague-Dawley rats weighing 250–350 g were anesthetized with 35 mg/kg sodium pentobarbital given intraperitoneally. Using procedures described previously [11], a single 22 ga stainless steel guide tube for microinjections was implanted within the medial prefrontal cortex (AP 10.4; Lat 0.8; Hor 3.0). During the same surgery, a bipolar electrode (Plastic Products) was positioned either in the ipsilateral MFB (AP 5.0; Lat 2.0; Hor 8.2) or VTA (AP 3.0; Lat 2.0; Hor 8.5). Using the apparatus and lever-pressing procedures described elsewhere [13], the animals were trained to self-stimulate for 30 min every day. Once the animals learned to respond reliably, a response-current intensity curve was then plotted so that a current intensity just above threshold could be used for

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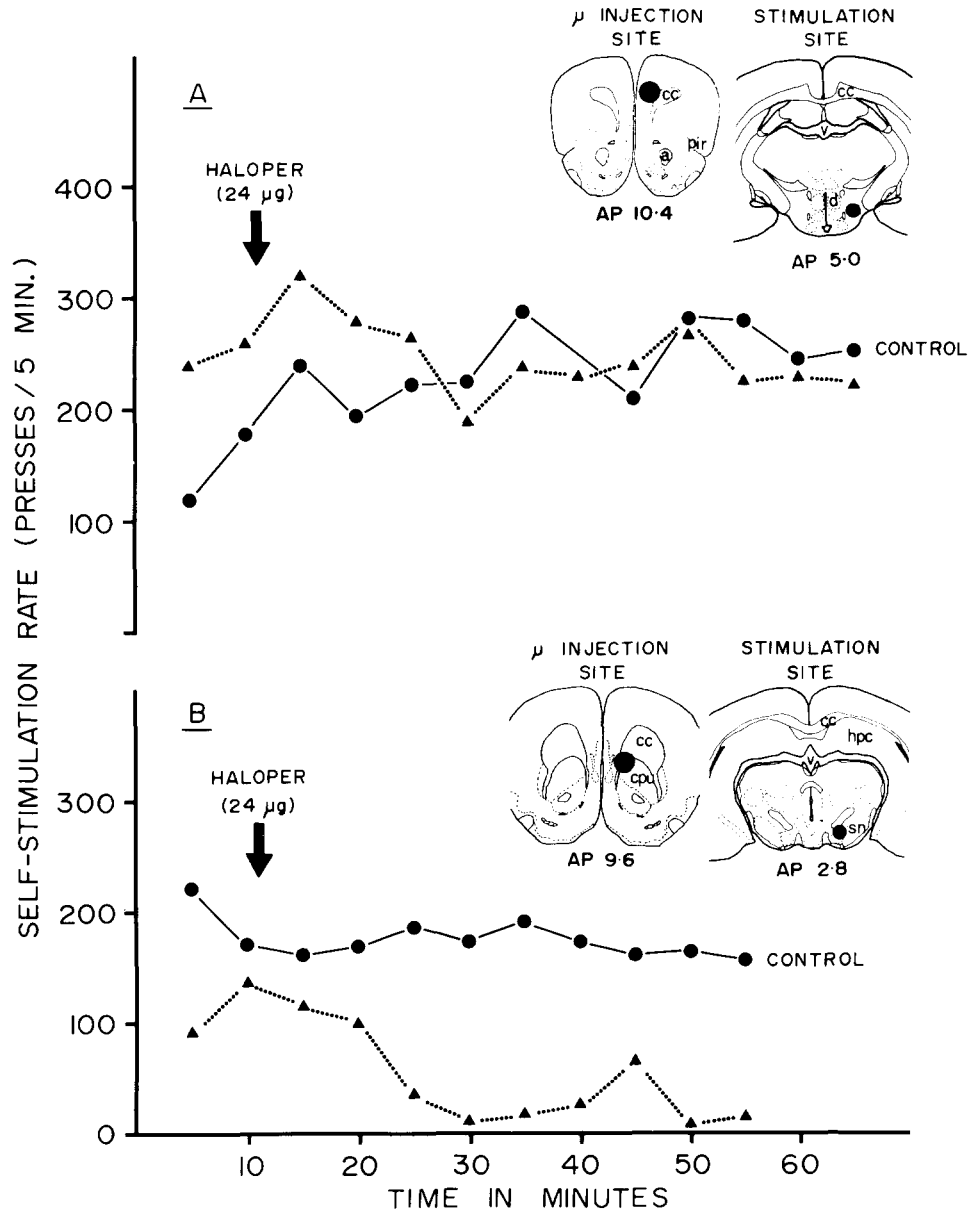

FIG. 1A (TOP) haloperidol (24 μg) injected into the medial prefrontal cortex at AP 10.4 (left inset) during self-stimulation of the medial forebrain bundle at AP 5.0 (right inset). Ordinate represents the rate of self-stimulation. B (BOTTOM) Injection of haloperidol in the same dose into the prefrontal-neostriatum at AP 9.6 (left inset) during self-stimulation of the ventral tegmental area (right inset).

subsequent pharmacological tests. Thereafter, each rat was allowed to self-stimulate for 1 hour every day.

Before each experiment, an inner 28 ga injector cannula was lowered into the guide cannula, and the animal was allowed to self-stimulate. The injector cannula was connected by way of polyethylene tubing (PE 20) to a microliter syringe mounted on an infusion pump [11]. After the self-stimulation behavior had stabilized for 10 min, a 1.0 μl volume of 12–24 μg of haloperidol, dissolved in 0.01 M tartaric acid, was injected over an interval of 30–60 sec into the medial prefrontal cortex of the rat. The lever-pressing rate was recorded for the next 60 min. Doses of haloperidol were selected on the basis of their known efficacy when administered in the brain substance [12].

Each experiment was repeated as follows. The animals were allowed to self-stimulate for 10 min. At the end of this period, each rat was disconnected from the stimulator and removed from its test chamber. A microinjection under similar conditions as before, was delivered to the medial prefrontal cortex and 30 min later the animals were returned to the respective test chamber for an additional 10 min during which self-stimulation was recorded.

At the end of the experiments, each rat was given an overdose of sodium pentobarbital and the thoracic aorta was

perfused retrograde with 0.9% saline followed by a solution of 10% Formalin. The electrode placements and microinjection sites were determined following standard histological procedures [19].

RESULTS AND DISCUSSION

The injections of haloperidol in doses of either 12 or 24 μg did not attenuate self-stimulation of the MFB or VTA in any of the animals with the cannula tips resting within the medial prefrontal cortex. Figure 1A shows the results of a representative animal in which the stimulating electrodes were localized in the MFB. A microinjection of the higher dose of 24 μg of haloperidol into the medial prefrontal cortex (Inset left) did not appreciably alter the rate of self-stimulation as the current was delivered to a site (Inset right) within the MFB.

In two animals, the histological analysis revealed that deeper microinjections of haloperidol dispersed beyond the cortical limit and reached the caudate-putamen complex. In both of these cases, self-stimulation behavior either elicited within the medial forebrain bundle or ventral tegmental area was markedly attenuated. Figure 1B illustrates a representative experiment in which the antagonistic action on one of the rats exerted by haloperidol is clearly evident.

In spite of the fact that anterograde degeneration of the fibers from self-stimulation sites in the medial prefrontal cortex extends into the MFB [16], the present experiments reveal that the blockade of dopamine receptors in the medial prefrontal cortex fails to disrupt self-stimulation behavior. This result strongly suggests, therefore, that dopaminergic synapses in the medial prefrontal cortex may not be an essential part of the neurochemical substrate underlying the self-stimulation of the MFB or VTA. This suggestion is consistent with the finding that self-stimulation of the VTA does not produce an enhanced release of dopamine in the medial prefrontal cortex [13].

The sulcal prefrontal cortex, on the other hand, seems to have descending connections with other reward sites. That is, it has been reported that either localized anesthetization or lesions produce an attenuation of self-stimulation within the MFB, pontine tegmentum or substantia nigra [2, 3, 16]. Therefore, it would be of interest to determine whether dopamine is a crucial link with the descending frontal pathway in this sulcal portion of the prefrontal cortex. In the rhesus monkey, a microinjection of spiroperidol at self-stimulation sites within the orbitofrontal cortex, an area which may correspond anatomically to the sulcal prefrontal cortex in the rat [6], attenuates self-stimulation of the lateral hypothalamus [8]. These results from the monkey thus would suggest such a link in the rat.

The fact that haloperidol injected into the neostriatum, a structure implicated in motor behavior, attenuates self-stimulation of the MFB or VTA, confirms previous reports indicating that the effect produced by the antagonist may be due to an impairment in motor performance rather than to any specific effect on the reward mechanism [1,10].

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