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Prefrontal Cortex and Neostriatum Self-Stimulation In the Rat: Differential Effects Produced by Apomorphine

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MORA, F., A. G. PHILLIPS, J. M. KOOLHAAS AND E. T. ROLLS. *Prefrontal cortex and neostriatum self-stimulation in the rat: differential effects produced by apomorphine*. BRAIN RES. BULL. 1(5) 421–424, 1976. — In a dose-response experiment, the effects of intraperitoneal injections of the dopamine receptor agonist, apomorphine (0.075, 0.15, 0.3, 0.6 and 1.2 mg/kg) were studied on self-stimulation elicited from electrodes implanted in the medial and sulcal prefrontal cortex and caudate-putamen in the rat. From the medial and sulcal prefrontal cortex electrodes, apomorphine produced a dose-related decrease of self-stimulation rate which was consistent across animals. From the caudate-putamen electrodes, on the contrary, apomorphine produced a facilitatory effect in the majority of the animals at one or more doses, however, at other doses a decreased self-stimulation rate was observed. The clear and consistent effects of apomorphine on self-stimulation of the prefrontal cortex, together with other experimental evidence in the same line, suggest that dopamine is mediating self-stimulation of this cortical area.

Prefrontal cortex	Dopamine	Neostriatum	Self-stimulation	Apomorphine
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IT has recently been shown that there is a mesocortical dopamine system in the rat which arises from dopamine-containing cell bodies in the ventral mesencephalon and terminates in the prefrontal cortex [2, 4, 8, 21, 22]. It is also well established that the caudate-putamen in the rat contains dopamine terminals from the nigro-striatal pathway [9,23].

In mapping studies for neural areas supporting brain stimulation reward, it has been found that self-stimulation can be obtained when electrodes are in the prefrontal cortex and also in the caudate-putamen [14, 16, 17]. Electrophysiological experiments have shown that neurones in the prefrontal cortex are activated during self-stimulation at a number of different brain sites [18,19] and more recently it has also been found that the dopamine receptor agonist, apomorphine, decreases the activity of prefrontal neurones but not of neurones in other cortical areas [13].

Previous neuropharmacological studies of self-stimulation in different areas have investigated the effects of apomorphine, but have reported ambiguous results [3, 7 24]. In view of the recent emphasis on self-stimulation from dopamine terminal areas, it was of interest to study the effects of apomorphine on self-stimulation in the prefrontal cortex and neostriatum.

METHOD

Twelve male Sprague-Dawley rats, weighing 250–350 g at the time of operation were used in this experiment.

Monopolar electrodes aimed at the medial prefrontal cortex, sulcal prefrontal cortex and caudate-putamen were stereotaxically implanted in every animal under sodium pentobarbital anesthesia (50 mg/kg IP). The electrodes were made of 00 gauge stainless steel insect pins, bare only at the cross section of the tip. The coordinates derived from the atlas of König and Klippel and using the bregma as a referent point were the following: caudate-putamen 1.5 mm anterior to bregma, 3.0 mm lateral to the midline and 4.5 mm beneath the dura; medial prefrontal cortex (2.5, 0.8, 2.0); and sulcal prefrontal cortex (2.5, 3.0, 4.0).

The animals were tested for self-stimulation in boxes that were 26 cm × 16 cm × 38 cm. The reinforcer for every lever-press was a 0.1 sec train of capacitively coupled 0.1 msec cathodal constant current stimulus pulses with a frequency of 100 Hz. Current return was via screws implanted in the skull. The animals were trained for self-stimulation 30 min every day for every site until spontaneous self-stimulation was observed. At the end of this training period, seven animals which pressed on all three electrodes were selected.

Current intensity (ranged between 0.05–0.2 mA) was adjusted individually for each animal and for each structure, until reliable self-stimulation was obtained without interference by seizures. After this, the animals were tested as follows: (1) the animals had a self-stimulation session every day until the end of the experiment; (2) the drug was injected every 3 days with 2 days control between every injection; (3) on the control days, the animals were tested

FIG. 1. Anatomical representation of the self-stimulation sites. The outlines were taken from the atlas of König and Klippel. Caudate-Putamen • Sulcal prefrontal cortex ▲ Medial prefrontal cortex. ■

for 10 min at each structure with 2 min intervals between each site to allow stabilization; (4) on the day of drug injection apomorphine or saline was injected 10 min before the self-stimulation session started (all doses of apomorphine and saline control were injected in random order); (5) the structures were always tested in the same order: caudate-putamen, sulcal prefrontal cortex and medial prefrontal cortex.

Apomorphine was used at the doses of 0.075, 0.15, 0.3, 0.6 and 1.2 mg/kg expressed as the hydrochloride. The apomorphine was dissolved in 0.9% saline with 0.5 mg/ml ascorbic acid, 15-20 min prior to each injection given subcutaneously.

At the end of the experiments all the animals were sacrificed and the brains were fixed in 10% formaldehyde solution. Histological analyses were then performed. Electrode placements were determined in 25 μ sections stained with cresyl violet, and located by comparison with the atlas of König and Klippel [5] (see Fig. 1).

RESULTS

Anatomical Analyses

Figure 1 shows the coronal sections of the rat brain indicating the electrode tip placements. As it can be seen in this figure all the electrodes were placed as intended except two of the electrodes aimed at the sulcal prefrontal cortex which were dorsal to the rhinal sulcus. The self-stimulation behavior of these animals, however, did not differ from the rest of the animals with electrodes in the sulcal prefrontal area.

Self-Stimulation

Apomorphine produced a dose-related decrease of self-stimulation rates in animals with electrodes implanted in the medial prefrontal cortex and of the sulcal prefrontal cortex (see Fig. 2). This dose-related effect was observed

FIG. 2. Dose-related decrease of self-stimulation produced by apomorphine in the medial and sulcal prefrontal cortex. The self-stimulation rate is expressed by the total number of presses in 10 min. The vertical bars represent the standard error and n = number of animals used in that experiment.

for individual animals as well as for the group represented in Fig. 2. Different effects of apomorphine were found on self-stimulation rates for rats implanted in the caudate-putamen. In three rats with electrodes in the caudate-putamen, apomorphine increased or had little effect on self-stimulation rates (see Fig. 3). In three other animals the apomorphine, depending on the dose, produced either an increase or a decrease of self-stimulation rate (see Fig. 3).

DISCUSSION

The main finding described here is that apomorphine produces a clear dose-dependent decrease of self-stimulation rates for animals with electrodes in the medial and the sulcal prefrontal cortex, which is consistent across animals,

FIG. 3. Representation for individual animals of the effects of different doses of apomorphine on caudate-putamen self-stimulation. The self-stimulation rate is expressed by the total number of presses in 10 min.

whereas the same treatment failed to produce a clear effect on self-stimulation in the caudate-putamen in the same animals. In the majority of cases, apomorphine at one or more doses increased self-stimulation in the caudate-putamen, but decreased self-stimulation at other doses. These observations confirm previous reports of ambivalent effects of apomorphine on self-stimulation at sites outside the prefrontal cortex. For example, both facilitation and inhibition of self-stimulation has been reported from electrode placements in the lateral hypothalamus, nucleus accumbens, ventral tegmentum and locus coeruleus [3, 7, 24].

The observation that self-stimulation could still occur with electrodes in the caudate-putamen when self-stimulation of the prefrontal cortex had been inhibited in the same animals and in the same testing period provides a convincing control for nonspecific performance effects. This control strengthens the argument that attenuation of prefrontal cortex self-stimulation is due to specific effects of the drug on the neurochemical substrate of brain stimulation reward in this region of the brain.

It is important to note that the differential effects of apomorphine described here, on prefrontal cortex and caudate-putamen self-stimulation, were found at dose levels which do not produce stereotypy (i.e. with doses of, or less than, 0.6 mg/kg). Further, the increase in self-stimulation rate of electrodes in the caudate-putamen is not due to stereotypy since prefrontal self-stimulation was decreased by the same doses of apomorphine in the same testing period (increased motor activity associated with stereotypy may be expected to produce a nonspecific increase in self-stimulation rate at all the sites) and since it was possible to demonstrate extinction of caudate-putamen self-stimulation in at least the rats in which all doses of apomorphine increased the self-stimulation.

Apomorphine is a dopamine receptor agonist, and therefore the dose-related inhibition of self-stimulation in the prefrontal cortex would appear to implicate dopamine in brain-stimulation reward in this particular region of the brain. Further evidence for this hypothesis comes from experiments on the effects of dopamine-receptor blocking agents on self-stimulation. In the monkey, there is some evidence that self-stimulation of the orbitofrontal cortex (an area which may be homologous to the sulcal prefrontal cortex in the rat, [6]) is particularly sensitive to the effects of the dopamine-receptor blocker spiroperidol [7], when administered in low doses via a peripheral route [10, 12, 15]. The fact remains that neuroleptics such as spiroperidol may attenuate self-stimulation by impairing motor performance [20]. However, spiroperidol has been shown to produce a dissociation between brain stimulation reward and motor behavior when injected intracranially in different areas of the brain [11]. Thus, data obtained with dopamine receptor blockers also suggest that dopamine could be involved in self-stimulation of the prefrontal cortex.

The significance of the present data can best be considered in relation to the available evidence on the function of dopamine in the prefrontal cortex. First, it has been demonstrated that there is a mesocortical dopamine pathway with terminals in the medial and the sulcal prefrontal cortex [2, 4, 8, 21, 22]. Second, it has also been demonstrated that there are dopaminergic receptors in the medial prefrontal cortex of the rat [13] and third it has been reported that self-stimulation in the prefrontal cortex of the monkey is particularly sensitive to the blockade of dopamine receptors [12, 15]. These points must now be considered in relation to the finding described here that apomorphine attenuates self-stimulation rate in the prefrontal cortex in a dose-related manner. Taken together,

these points are consistent with the hypothesis that the release of dopamine could mediate self-stimulation of the prefrontal cortex. Therefore, according with that hypothesis the effects of apomorphine in attenuating the self-stimulation could be due to the continuous activation of dopamine receptors by the apomorphine, so that the release of dopamine contingent on the animal's self-stimulation behavior would no longer be reinforcing. It is of interest that in the rhesus monkey, apomorphine attenuates self-stimulation of the orbitofrontal cortex but enhances self-stimulation of the caudate nucleus [5] so that the release of dopamine may also mediate self-stimulation in this comparable region of the primate brain. The fact that the systemic administration of apomorphine or of drugs

which enhance the release of endogenous dopamine (amphetamine and L-dopa) decreases the firing rate of neurones in the medial prefrontal cortex of the rat [13] suggests further that dopamine could mediate self-stimulation of this cortical area through the inhibition of inhibitory neurones.

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