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Intracranial Self-Stimulation in Orbitofrontal Cortex and Caudate Nucleus of Rhesus Monkey: Effects of Apomorphine, Pimozide, and Spiroperidol

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Abstract. Rhesus monkeys were prepared with stimulating electrodes implanted into the orbitofrontal cortex and head of the caudate nucleus under stereotaxic control. These regions of the brain contain high levels of dopamine, and intracranial self-stimulation was readily elicited from these loci in all animals tested using licking behavior as the operant response.Self-stimulation at both sites was significantly attenuated following peripheral injections of the dopamine receptor blocker spiroperidol (0.02 mg/kg). Similarly, pimozide (0.15 and 0.20 mg/kg) significantly reduced self-stimulation in the orbitofrontal cortex, but the suppression observed at caudate placements did not reach statistical significance. Licking for a reward of blackcurrant juice was unaffected by either drug. Apomorphine (0.2, 0.4 mg/kg) had a differential effect on self-stimulation. This drug significantly attenuated self-stimulation in the orbitofrontal cortex, while the same treatment tended to facilitate self-stimulation in the caudate. Apomorphine did not significantly affect responding for the fruit juice reward. The parallels between the effects of dopamine agonists and antagonists on self-stimulation in the monkey and rat suggest that dopamine influences self-stimulation of some sites in both the primate and the rat.

Key words: Intracranial self-stimulation – Primate – Dopamine – Apomorphine – Spiroperidol Pimozide – Orbitofrontal cortex – Caudate nucleus

Research into the neurochemical substrates of brain-stimulation reward in the rat brain has suggested a role for dopamine (DA). Intraperitoneal injections of the DA receptor blockers pimozide, haloperidol, and spiroperidol attenuated self-stimulation in a dose-related manner (Phillips et al., 1975; Rolls et al., 1974; Wauquier and Niemegeers, 1972). Furthermore, intracranial microinjections of spiroperidol into nucleus accumbens suppressed self-stimulation independently of motor impairment (Mora et al., 1975). Treatment with the DA receptor agonist apomorphine has produced ambiguous results, which may reflect an interaction between the drug and the site of brain-stimulation (Broekkamp and van Rossum, 1974; Herberg et al., 1976; Liebman and Butcher, 1973; St. Laurent et al., 1973; Wauquier and Niemegeers, 1973). For example, apomorphine produced a dose-related suppression of self-stimulation in DA terminal areas of medial and sulcal prefrontal cortex, whereas similar treatment caused both a suppression and facilitation of self-stimulation in the caudate nucleus (Mora et al., 1976).

It is of interest that self-stimulation can be elicited from the prefrontal cortex in the rat (Routtenberg and Sloan, 1972) and the orbitofrontal cortex in the primate (Rolls, 1975), as these areas are thought to be homologous in the two species (Leonard, 1969). As with the prefrontal cortex in the rat (Berger et al., 1976), the orbitofrontal cortex in the primate has also been shown to have a high concentration of DA (MacBrown and Goldman, 1977). Self-stimulation of the primate orbitofrontal cortex is sensitive to the suppressant effect of spiroperidol (Mora et al., 1976). It was therefore of interest to look for further parallels between self-stimulation in these two species, by studying the effect of apomorphine, pimozide, and spiroperidol on self-stimulation at sites in the orbitofrontal cortex and caudate nucleus of the rhesus monkey brain.

Materials and Methods

Subjects. Four rhesus monkeys (*Macaca mulatta*) weighing 2.8–3.2 kg were anaesthetized with pentobarbitol, and insulated stainless-steel monopolar electrodes were implanted bilaterally into the orbitofrontal cortex and the head of the caudate nucleus under stereotaxic control using the atlas of Snider and Lee (1961). The

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animals were housed individually in a climatically controlled colony room, and the feeding regimen consisted of one daily meal of mash supplemented with fresh fruit.

Apparatus. All testing was conducted in a quiet room, with the monkey sitting in a primate chair. A brass drinking spout was positioned in front of the animal's mouth, close enough to permit licking without the tube being touched by random movements of the face or mouth. Licking the tube activated a relay circuit which caused the delivery of either brain stimulation or (by a hydraulic pump) fruit juice reward. The brain stimulation consisted of a 0.5-s train of 0.5-ms capacitatively coupled negative square-wave pulses at a frequency of 100 Hz. The licking rate was recorded on a counter.

Procedure. Two weeks after electrode implantation, the animals were screened for self-stimulation at each electrode site using licking as the operant response. When self-stimulation performance had stabilized, a response/current intensity curve was determined for each electrode placement. This procedure yielded an ogive-shaped curve on which threshold and optimal intensities could be identified, and an intensity which supported half-maximal self-stimulation rates was used for subsequent pharmacologic tests. This intensity was employed to ensure a stable background rate against which any suppressant or facilitatory effects of the drug treatments could be clearly observed. After establishing the appropriate current intensities, test sessions began.

In a test session, the animal was allowed to self-stimulate through the caudate and orbitofrontal cortex electrodes for 10 min at each placement followed by a 10-min test rewarded by drops of blackcurrant juice (Ribena brand, diluted 1:4). The order in which the electrodes were tested was randomized each day throughout the experiment. Any locus-specific effects of the drug treatment on self-stimulation would provide an important control for performance effects. Similarly, the licking response for blackcurrant juice was also incorporated as a control for general disruption of the operant response.

Pimozide and Spiroperidol. Both compounds (generously supplied by Janssen Pharmaceutica, Beerse, Belgium) were dissolved in a heated solution containing 0.01-M tartaric acid. The doses employed were pimozide 0.15 and 0.20 mg/kg, and spiroperidol 0.015 and 0.020 mg/kg. Three control days preceded each injection of a given dose of either pimozide or spiroperidol. The order of injection was randomized with respect to concentration and type of drug. Sterile i.p. injections of spiroperidol were given 1 h before the test session, and pimozide was given 2 h before the test session.

Apomorphine. Apomorphine was used in doses of 0.1, 0.2, and 0.4 mg/kg, expressed as the hydrochloride. The drug was dissolved in a solution of 0.9% saline and 0.5 mg/ml ascorbic acid, 15–20 min before each injection. Two control days preceded each apomorphine test. Sterile solutions of apomorphine were injected s.c. and the test session began 5 min later.

Histology. At the conclusion of the experiments, each electrode site was verfied histologically. The animals were given an overdose of pentobarbital and were perfused with isotonic saline followed by 10% formal saline. The brains were frozen and sections cut at 50 µ were stained with thionin.

Results

Histology. The tips of the self-stimulation electrodes for all 4 monkeys are shown in Fig. 1. In all of the animals, the electrodes were located correctly in the caudal part of the orbitofrontal cortex (area 13). The caudate electrodes were located in either the dorsal (3 electrodes) or the ventral (1 electrode) aspects of the head of the caudate nucleus.

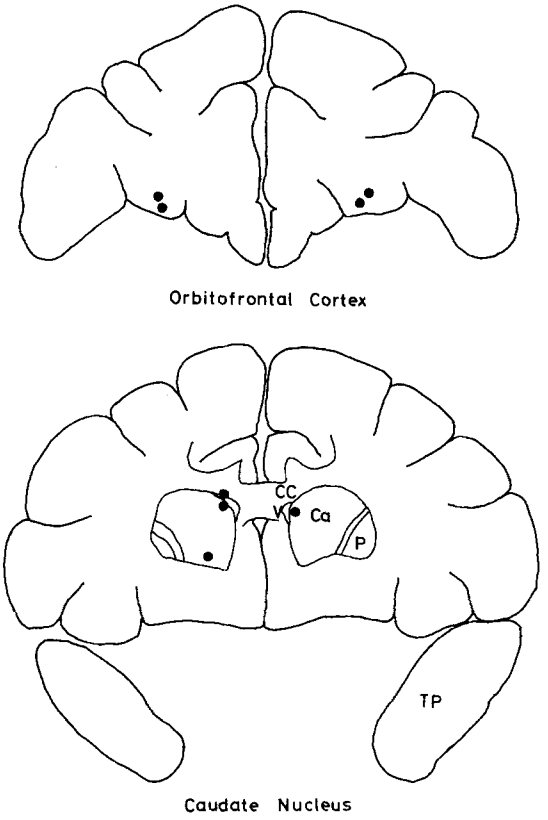

Fig. 1. Electrode placements in the orbitofrontal cortex (section 25 mm anterior to stereotaxic zero) and caudate nucleus (section 20 mm anterior to stereotaxic zero)

Pimozide and Spiroperidol. The raw data for each reward condition were analysed by a one-way analysis of variance and Duncan's multiple range test. The mean scores ($N = 4$) for each reward at each drug dose are shown in Table 1. Pimozide produced a significant reduction in self-stimulation rate in the orbitofrontal cortex at both doses tested ($F = 4.67$; $df = 2,9$; $P < 0.05$). However, the drug produced variable effects in responding for caudate stimulation, and the reduction observed did not reach statistical significance ($F = 1.71$; $df = 2,9$; $P < 0.05$).

The high dose of spiroperidol (0.02 mg/kg) significantly attenuated self-stimulation at both orbitofrontal cortex ($F = 4.29$; $df = 2,9$; $P < 0.05$) and caudate placements ($F = 7.50$; $df = 2,9$; $P < 0.05$). No significant effect was observed on responding for fruit juice reward.

Apomorphine. The effects of apomorphine were studied on 3 monkeys. The baseline control self-stimulation

Table 1. Effects of pimozide and spiroperidol on licking response for brain-stimulation reward in orbitofrontal cortex, and caudate nucleus, or for blackcurrant juice reward[a]

Drug	Reward		
	Brain stimulation		Blackcurrant juice
	Orbitofrontal cortex	Caudate nucleus	
Control	870 ± 32	636 ± 116	1117 ± 50
Pimozide (0.15 mg/kg)	483 ± 77	460 ± 162	739 ± 202
Pimozide (0.20 mg/kg)	424 ± 163	281 ± 114	960 ± 105
Control	862 ± 44	627 ± 92	1171 ± 50
Spiroperidol (0.015 mg/kg)	717 ± 88	566 ± 91	1083 ± 105
Spiroperidol (0.020 mg/kg)	388 ± 173	242 ± 18	889 ± 220

[a] Data expressed as mean ± SEM of responses in each 10-min test period

Table 2. Effects of apomorphine on licking response for brain-stimulation reward in orbitofrontal cortex, and caudate nucleus, or for blackcurrant juice reward[a]

Drug	Reward		
	Brain stimulation		Blackcurrant juice
	Orbitofrontal cortex	Caudate nucleus	
Control	558 ± 20	286 ± 38	790 ± 11
Apomorphine (0.1 mg/kg)	450 ± 40	477 ± 60	774 ± 34
Apomorphine (0.2 mg/kg)	396 ± 31	508 ± 44	760 ± 30
Apomorphine (0.4 mg/kg)	220 ± 79	410 ± 130	770 ± 29

[a] Data are expressed as mean ± SEM in each 10-min test period

rates were lower in this set of 3 monkeys, which were tested several months after the experiment described above. The mean control rates were 558/10 min at orbitofrontal sites and 286/10 min at caudate placements. Baseline scores in the blackcurrant juice tests averaged 790/10 min. The effects of the various doses of apomorphine on responding for the three types of reinforcement are summarized in Table 2. Data were again analyzed by a one-way analyses of variance, and by Duncan's multiple range test. Differential effects were observed in each subject, with apomorphine producing a decrease in responding for stimulation of the orbitofrontal cortex and an increase at caudate placements. The statistical analysis revealed a significant effect on self-stimulation of the orbitofrontal cortex at 0.2 and 0.4 mg/kg ($F = 6.45$; $df = 8,3$; $P < 0.05$). This effect was a decrease in self-stimulation rate. The facilitatory effect of apomorphine on caudate self-stimulation did not reach statistical significance ($F = 1.21$; $df = 8.3$; $P < 0.05$). No significant changes were observed in responding for blackcurrant juice ($F = 0.16$; $df = 8.3$; $P < 0.05$).

Discussion

In the present experiment, self-stimulation of the orbitofrontal cortex and caudate nucleus was significantly attenuated following pretreatment with the DA receptor blocker spiroperidol. These findings confirm earlier observations in the primate of a reduction in self-stimulation of orbitofrontal cortex by spiroperidol (Mora et al., 1976) and extend them to the caudate nucleus, a region which also has a high concentration of DA. Pimozide also attenuated self-stimulation in the orbitofrontal cortex and a trend towards a reduction in self-stimulation of the caudate nucleus was observed.

Perhaps the most important finding in this series of experiments is the effect of apomorphine on self-stimulation in the primate brain. Self-stimulation of the orbitofrontal cortex was significantly attenuated by apomorphine, while the same treatment tended to facilitate self-stimulation in the caudate. Locus-specific effects of apomorphine on self-stimulation have also been reported in the rat. A significant and consistent reduction in self-stimulation was observed at sites in the medial and sulcal prefrontal cortex, but not in the neostriatum (Mora et al., 1976). Herberg et al. (1976) have reported a reduction in self-stimulation at dopaminergic sites in the lateral hypothalamus and ventral tegmentum and facilitation of self-stimulation at sites adjacent to noradrenergic neurons. In addition to the differential locus-specific effects of apomorphine, Herberg and his colleagues (1976) also reported an initial depression of self-stimulation regardless of electrode placement. This effect lasted for approximately 10 min, after which the facilitatory or suppressant effects were observed. Responding for brain stimulation at both electrode sites in the present experiment was measured in two 10-min sessions, and it seems unlikely that an initial depressant effect could account for the present data, as the sequence was randomized across subjects and test days. Further, regardless of the order of testing, apomorphine always attenuated self-stimulation of the orbitofrontal cortex in a dose-related manner, whereas responding on the caudate electrodes never fell below baseline scores even when tested first.

These differential effects of apomorphine on self-stimulation, along with the lack of effect on licking for fruit juice reward, also make it unlikely that the attenuation at orbitofrontal sites was due to motor impairment.

The present results thus provide further evidence that self-stimulation in both the rat and primate can be affected in a similar manner by DA receptor agonists and antagonists. A possible interpretation of these data is that dopamine can influence brain-stimulation reward at some sites in the primate as well as in the rat (see Rolls, 1978; Phillips and Fibiger, 1978).

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