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Inhibition-Mediating Dopamine Receptors and the Control of Intracranial Reward

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Abstract. A receptor selective agonist and antagonist of inhibition-mediating dopamine receptors (type II receptors) produced significant and dose-related alterations in bar-pressing for intracranial reward. Receptor inhibition by piribedil increased responding for reward while receptor activation by 3,4-dihydroxyphenylamino-2-imidazoline reduced responding. Inhibition-mediating receptors may therefore play a role opposite to classic excitation-mediating receptors in controlling reward.

Key words: Brain stimulation – DPI – Dopamine – ET-495 – Intracranial reward – Piribedil

Two pharmacologically, anatomically, and electrophysiologically distinctive classes of dopamine (DA) receptor have been identified in the central nervous system (Costall and Naylor, 1975, 1976; Costentin et al., 1975; Cools and Van Rossum, 1976). These receptors have been classified as type 1 and 2 by Costall and Naylor, who described different patterns of behavioral activation and stereotypy depending upon the relative degree of occupation of these receptor classes. Cools and Van Rossum (1976), using a variety of criteria, including neurophysiological responses and behavioral differences, proposed that these receptors are excitation or inhibition mediating.

Type 1, or excitation-mediating (EM) receptors, are activated by apomorphine and inhibited by haloperidol and other butyrophenones. These have been more widely investigated psychopharmacologically than type 2, or inhibition-mediating (IM) receptors. They are activated by (3,4-dihydroxyphenylamino)-2-(imidazoline) (DPI) and blocked by piribedil (ET-495; 1-(2-pyrimidil)-4-piperonyl piperazine).

A role for EM-DA (i.e., type 1) receptors in the control of reward has been clearly established. The EM-DA stimulant apomorphine is readily self administered (Baxter et al., 1974). Additional support for an EM-DA reward hypothesis comes from numerous pharmacologic manipulations of self-stimulation, in which EM-DA agonists and antagonists respectively increase or decrease rates of responding for reward (Wauquier and Niemegeers, 1972; Leibman and Butcher, 1973; St. Laurent et al., 1973; Broekkamp and Van Rossum, 1974; Herberg et al., 1976; Phillips et al., 1976).

Since the specific contributions of IM-DA receptors in reward motivation have not been fully or systematically investigated, we have examined the effects of an IM selective receptor agonist and antagonist upon responding for rewarding brain stimulation. Our findings support a role that is converse to the role of EM-DA receptors.

Materials and Methods

Subjects. Twelve adult male Sprague Dawley rats (Charles River, Portage, MI, U.S.A.) – 300–450 g each – were maintained with food and water continuously available and automatically programmed lighting cycles of 12 h light/12 h darkness.

Surgery. Subjects were anesthetized with 35 mg/kg sodium pentobarbital (Nembutal) administered i.p. Each subject received a stereotaxic implant with a single bipolar stainless steel electrode made of 0.005-mm diameter wire insulated to the tip (Yissum Co., Haifa, Israel). All electrodes were aimed at the substantia nigra and subjects were allowed 1 week to recover prior to any testing.

Apparatus. Subjects were tested in 20 × 25 × 30 cm wooden chambers with plexiglass tops. A single 8.9-cm wide lever was located 6.7 cm from the chamber floor, and operated a microswitch with an operating requirement of 25.0 g. A constant level of approximately 30 dB background noise was provided by a ventilating fan.

Drugs. DPI was injected in doses of 0, 1.25, 2.5, and 5.0 mg/kg and piribedil was injected in doses of 0, 25, 50, and 100 mg/kg. All injections were administered i.p., 1 ml/kg in 0.9% sodium chloride vehicle, between minutes 25 and 30 of a self-stimulation session.

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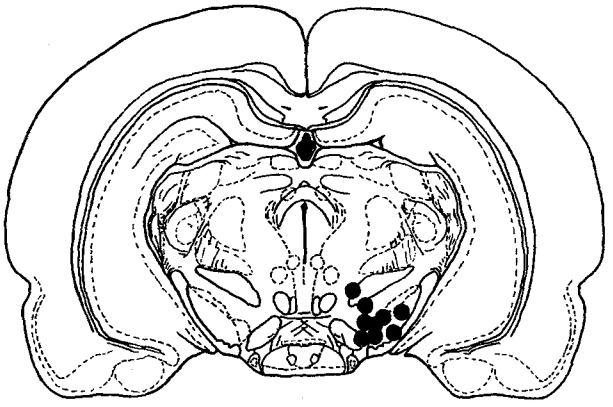

Fig. 1. Composite histology for self-stimulating animals ($n = 9$). Definitive visualization of two sites was impossible, one site is approximately 1 mm caudal to the plane (plane is redrawn after Fig. 44b of Konig and Klippel, 1964) = 2580 μ from ear bar zero

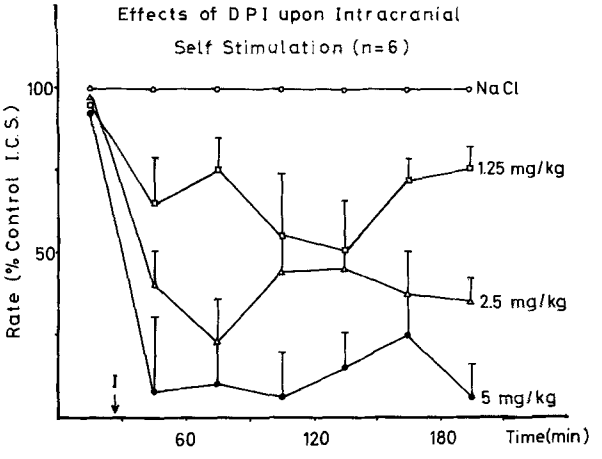

Fig. 2. Dose-response relationship for DPI upon self-stimulation at substantia nigra. All data are presented as % mean plus % standard error. Drug is administered at I (min 25–30)

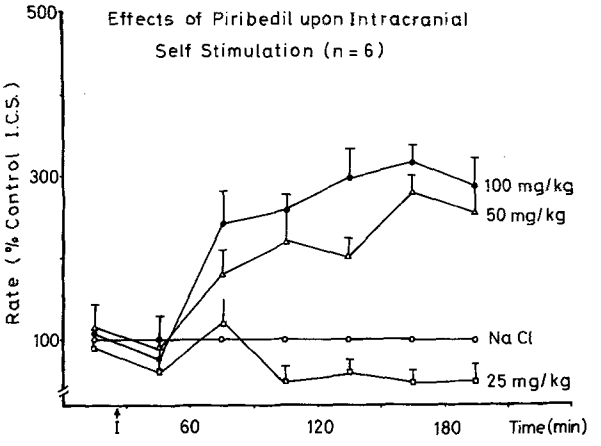

Fig. 3. Dose-response relationship for piribedil upon self-stimulation at substantia nigra. All data are presented as % mean plus % standard error. Drug is administered at I (min 25–30)

Dosages were based both upon previously published reports and pilot studies in our own laboratory (Garattini et al., 1974; Poignant et al., 1974; Thornburg and Moore, 1974).

Behavioral procedure. Subjects were initially trained to bar press for a reinforcement of intracranial reward. Each reinforcement consisted of a 0.2-s train of 60 cycle/s sinusoidal current delivered through a 50 Ω resistor and across a zero-crossing relay to maintain approximately constant current conditions. Current was continually monitored through a 100-Ω resistor in series with the subject upon a 130-B Hewlett-Packard oscilloscope.

All subjects were given five 220-min training sessions spaced 48 h apart. During this initial period current was adjusted so that each subject responded at a high, stable rate (1,000–3,500 responses/per hour). Final current values ranged from 50–150 μA. Subjects were divided into two groups, each of which received four treatments of either DPI or piribedil. Responses were recorded continuously for all sessions, and were analyzed as 30-min blocks.

Statistics. Drug effects upon performance were initially transformed to individual percentage of vehicle (0 mg/kg) performance so as not to weight unduly the high or low responders. Statistical analysis was by Friedmans two-way ANOVA (Siegel, 1956).

Histology. At the close of testing, all subjects were injected with an overdose of sodium pentobarbital, and perfused initially with normal saline and subsequently with formalin-alcohol-acetic acid fixing solution (Luna, 1960). The brains were removed, sliced in 40-μ sections and stained with cresyl violet. Microscopic examination revealed that all sites were located close to or within the substantia nigra (Fig. 1).

Results

The two drugs both had significant effects upon bar-pressing for reward. DPI reduced rates of responding in a graded, dose-related manner (Fig. 2) ($x^2 r = 10.5$, $df = 3$, $P < 0.02$). Piribedil also produced a significant effect ($x^2 r = 12.2$, $df = 3$, $P < 0.01$), which in general represented an increase in rates, although inspection of Fig. 3 indicates that some suppression of responding occurred at the lowest dose of drug. Individual response records were reanalyzed after the histology was completed. Particular attention was paid to the three most dorsal sites, all of which appeared to be external to the substantia nigra. Response rates for these sites were below the median value (1,000–1,250 responses per hour), however, in all cases DPI inhibited responding while piribedil facilitated it. Informal observations of piribedil-treated animals indicated a significant increase in stereotyped sniffing immediately after injection. No other changes in behavior were noted.

Discussion

Previous studies, employing several psychopharmacologic techniques, have suggested that EM-DA receptors are involved in reward. Apomorphine, a relatively pure EM-DA agonist (Cools and Van Rossum 1976) is readily self administered. It may be concluded from this

finding that contingent occupation of EM-DA receptors is sufficient for the maintenance of a reinforcement contingency. Other studies indicate that apomorphine facilitates intracranial reward. For example, Broekkamp and Van Rossum (1974), St. Laurent et al. (1973), and Herberg et al. (1976) all report increased response rates after a wide range of apomorphine doses. This response facilitation is site specific, involving a number of areas outside of established DA-containing cells and fibers, in addition to DA-containing systems. On the other hand, EM-DA receptor antagonists, e.g., phenothiazine and butyrophenone neuroleptics, reduce intracranial reward, and again both dopamine-containing regions of the central nervous system and extradopaminergic sites may be involved (e.g., Wauquier and Niemegeers, 1972). Again, this is consistent with the EM-DA hypothesis. Finally, careful examination of striatal DA sensitive sites that support self-stimulation indicates a high coincidence between contraversive turning and reward. Contraversive turning to stimulation is also EM-DA mediated (Cools and Van Rossum, 1976).

The present study examined a second distinctive class of DA receptors for their possible role in intracranial reinforcement. Our results show that IM-DA receptor blockade by piribedil increased ICS while IM-DA receptor activation by DPI had an opposite effect. To our knowledge this is the first behavioral effect shown for DPI after systemic injection. These results with agonists and antagonists of a second system are the reverse of those found for EM-DA active drugs.

The present results suggest that the optimal processes in self-stimulation are all excitatory. A net increase in DA excitation may be achieved through either of two systems, one of which activates excitatory receptors and a second of which inhibits inhibitory receptors. Both increase net excitation and contribute to behavioral facilitation. Cools and Van Rossum (1976) have proposed a model which incorporates these findings. Behaviorally opposite effects for EM and IM-DA receptors have been found, for example, in the so-called turning syndrome (op cit.). These authors predict a number of cases of facilitation and inhibition across receptor types, both clinically and preclinically, and similar predictions might be made for self-stimulation as well. For example, apomorphine and piribedil might be predicted to have a cumulative effect upon reward and, conversely, DPI and pimozide to have a cumulative inhibitory effect. Both these predictions and additional anatomical studies are suggested by the present results.

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