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Rate Dependent Inhibition of Self-Stimulation by Apomorphine

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CAREY, R. J. *Rate dependent inhibition of self-stimulation by apomorphine.* PHARMAC. BIOCHEM. BEHAV. 16(5) 859–861, 1982.—The effect of three doses of apomorphine 0.125, 0.25 and 0.5 were studied on self-stimulation generated by three levels of current intensity. Eight rats exhibited overall dose dependent decreases in self-stimulation obtained at the two lowest current intensities. Self-stimulation at the highest current intensity, however, was unaffected by even the highest dose level of apomorphine (0.5 mg/kg) despite typical signs of stereotypy exhibited by the rats in their home cages. Additionally, self-stimulation obtained under the 0.5 mg/kg dose of apomorphine underwent extinction when reinforcement was discontinued. Thus, brain stimulation can be an effective reinforcement when an animal is given a stereotypy inducing dose of apomorphine if the current intensity is of sufficient magnitude and if the response manipulandum is not compatible with stereotypic responses. These observations appear consistent with a dopaminergic involvement in the response rather than reinforcement aspect of self-stimulation.

Self-stimulation Apomorphine Dopamine Stereotypy Extinction

THE well known efficacy of neuroleptics as potent inhibitors of self-stimulation behavior has provided an important line of evidence implicating brain dopamine in the mediation of reinforcement [10]. The opposite pharmacological manupulation; namely, stimulation of dopamine receptors, has not yielded such consistent findings. Apomorphine, a direct acting dopamine agonist [1], has been reported to inhibit as well as facilitate self-stimulation [2, 6, 8, 11]. While inhibition and facilitation of self-stimulation by the indirect acting dopamine agonist amphetamine has been frequently reported, this result has been shown to be a response rate dependent phenomenon; i.e., facilitation low but reduction of high rates of responses [5]. The present experiment was undertaken to determine if the effects of apomorphine on self-stimulation also exhibited the response rate dependent characteristic.

METHOD

Subjects

Adult male Sprague-Dawley rats were used as subjects. From an original group of 10 implants, eight rats were obtained with electrodes which reliably generated self-stimulation behavior. The rats were housed in individual cages in a room with controlled temperature (22.0±1°C), humidity (60%±5%) and light-dark cycle (12:12 hr). Purina Rat Chow and tap water were always provided.

Surgery and Histology

Rats were implanted with bipolar platinum electrodes (Plastic Products Company, Roanoke, VA) insulated except for the cut end [4]. Surgery was aseptic and performed while the rats were under deep anesthesia (Equi-thesin 0.3 ml/100 g). A Kopf stereotaxic instrument was used to situate the electrode into the brain and it was bonded to a roughened skull with Cranio-plastic cement. The electrodes were aimed at the lateral hypothalamic area using the following coordinates: 1.2 mm posterior to bregma, 1.5 mm lateral to the midline sinus and 9.0 mm ventral to the skull surface. The incisor bar was placed 3.2 mm above the interaural line. Following surgery, each rat received several days of IM injections of procaine penicillin.

Upon completion of the study, rats were sacrificed by ether anesthesia and then intracardially perfused with 0.9% saline followed by a 10% Formalin solution. The electrodes were removed with the skull held in the stereotaxic instrument using the electrode carrier. After 10 days of fixation in 10% Formalin an approximately 3 mm section containing the electrode tract was removed from each brain and embedded with paraffin. From this tissue block, 12 micron sections were cut, mounted and stained with luxol fast blue and cresyl violet [7]. The stained sections were evaluated microscopically and the electrode tips were generally localized to the lateral hypothalamic area between the fornix and internal capsule.

Apparatus

Self-stimulation testing was conducted in three 26×24 cm operant chambers located within sound attenuating enclosures (B.R.S./L.V.E. No. 1417). Each chamber contained a response lever (Ralph Gerbrands Co., No. G6312) mounted in the center of a chamber wall 3.5 mm above the grid floor. A 28 V DC miniature lamp (No. 304) illuminated each chamber and white noise was broadcast whenever stimulation was available. Relay circuits with timers and digital counters programmed reinforcement, recorded bar presses and controlled session duration.

A Grass Brief-Pulse Biphasic stimulator Model BPS 1 was the source for the brain stimulation reinforcement. The stimulation delivered pairs of biphasic rectanglular 0.1 msec pulses separated by a 0.1 msec interval between positive and negative pulses. The frequency of stimulation was 100 pulses/sec and the train duration was 0.2 sec. Current intensity was measured and monitored continuously on each of three oscilloscopes (Textronix No. 502A) from the voltage drop across a 1-K resistor in series with the animal. The rat was connected to the stimulator through a mercury swivel commutator mounted above each chamber.

Procedure

After a two week postoperative recovery period, the rats were trained to lever press for brain stimulation. After the lever press response was reliably trained the current intensity was systematically adjusted in order to generate optimal rates of response at the lowest current setting [9]. After response rates stabilized at this current intensity, current intensity was reduced by 25% on successive tests. Current intensities which generated low (less than 15 responses per minute) medium (approximately half-maximum) and maximum response rates were selected. Several rate-intensity determinations were made at these current intensities with slight adjustments made to obtain the low, medium, high response rates. After the rate-intensity performance was stabilized, the drug testing procedure was initiated with no further changes in current intensities.

Three dose levels of apomorphine HCl were tested 0.125, 0.25 and 0.5 mg/kg. The apomorphine was dissolved in a 0.4 mg/cc solution of ascorbic acid to retard oxidation. The self-stimulation testing commenced 5 mintues after the IP injections of apomorphine and the rats were tested in successive 5 minute intervals at the low, medium and high current intensities with a 5 minute non-stimulation interval in the home cage separating changes in current intensity. Thus, the total testing took place within 30 minutes after the apomorphine injections.

After assessment of the effects of the three doses of apomorphine on self-stimulation under the three current intensities the rats were tested at the highest dose of apomorphine at the highest current intensity. This test was conducted to assess if the responding under apomorphine might simply be a matter of response stereotypy rather than reinforcement contingent responding. In this test procedure the rats were injected with 0.5 mg/kg apomorphine and then 10 minutes later tested for 15 minutes of self-stimulation and then put on extinction for 5 minutes. If the responding was a response stereotypy, then the animals would be expected to continue responding after the current was turned off. Again, the test procedure was completed within 30 minutes after the apomorphine injections.

RESULTS

Figure 1 shows the effect of the three dose levels of apomorphine on self-stimulation. It is evident from Fig. 1 that the effect of apomorphine is dose and response rate dependent. Increasing dose levels of apomorphine produce increasing reductions of lower rates of self-stimulation responding. Consistent with Fig. 1, Fig. 2 shows that the highest dose level of apomorphine used, 0.5 mg/kg, had no dicernible effect on the highest self-stimulation response rate, but that this responding was contingent in that when brain stimulation was discontinued responding subsided. Figure 3

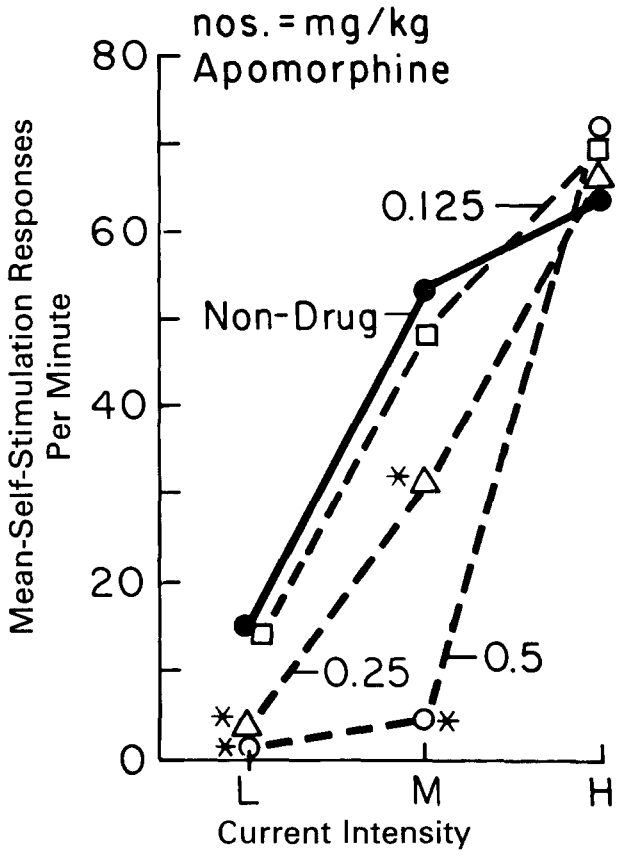

FIG. 1. Effect of three dose levels of apomorphine on self-stimulation performance generated by three levels of current intensity (L=low, M=medium, H=high). (*Indicates $p<0.05$ drug versus non-drug comparisons with t-tests).

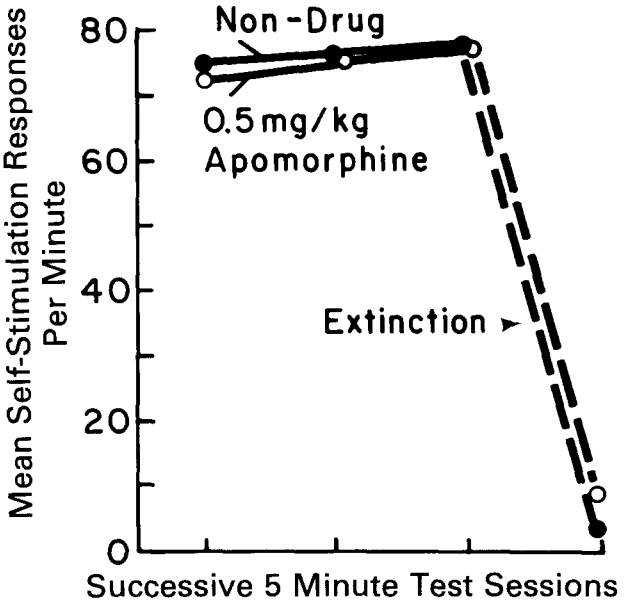

FIG. 2. Effect of 0.5 mg/kg apomorphine on self-stimulation performance in three successive five-minute sessions with brain stimulation followed by a five-minute extinction session.

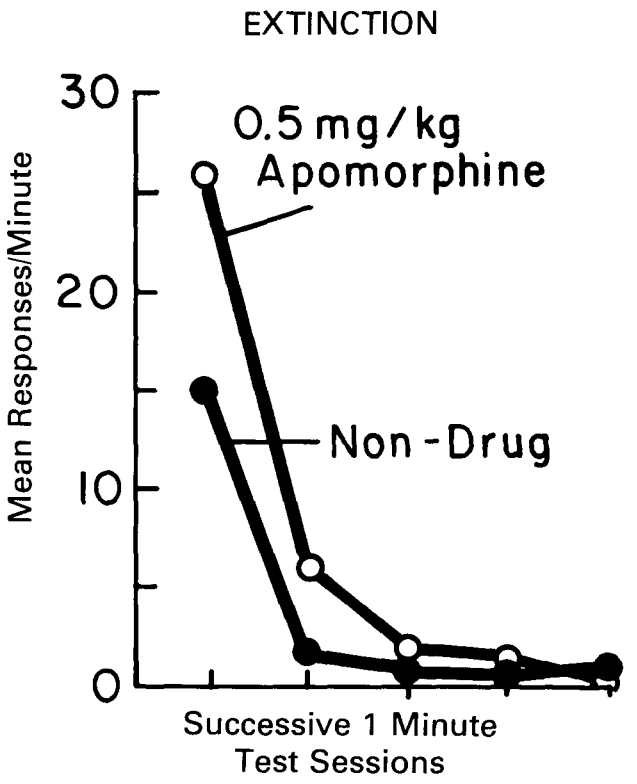

FIG. 3. Effect of 0.5 mg/kg apomorphine on extinction of self-stimulation over five successive one-minute intervals.

shows that the progression of extinction over the 5 minute extinction interval was similar for the drug and non-drug conditions. The overall difference between drug and non-drug conditions in terms of the total number of responses emitted, however, was statistically significant ($t=3.4$, $p<0.01$). It should also be noted that this 0.5 mg/kg dose of apomorphine reliably produced the typical symptoms of stereotypy when the rats were observed in the home cage (i.e., constant intense sniffing and licking the cage floor in the characteristic hunched posture).

DISCUSSION

The results of the present study show that the effects of apomorphine on self-stimulation are rate-dependent. In contrast to the results reported for amphetamine, however, low rates were suppressed but high rates were unaffected. Observation of the animals suggested that at the lower current intensities, apomorphine generated behavior which distracted or interfered with the brain stimulation. This was particularly evident at the highest dose level when the rats were being primed for the self-stimulation test at the lower intensities and the stimulation did not interrupt the animals' stereotypy. Seemingly, at the highest current intensity used, the stimulation was of sufficient magnitude to compete with the stereotypy and at least direct the responding at the response lever. The extinction data indicate that the responding for self-stimulation at the highest current intensity was not simply a response stereotypy. Possibly the extinction was fortuitous in that the rounded shape of the manipulandum made it awkward for the animal to bite or position itself in such a way as to sustain a stereotyped response. Presumably, with a manipulandum better suited to sustain a response stereotypy such as biting or licking, the animal would have continued the response after the termination of reinforcement. Thus, if a manipulandum cannot differentiate between a simulation contingent versus a drug-induced stereotyped response, it could be readily deduced that the animal was unresponsive to the brain stimulation. This consideration may explain the reported failure of rats treated with apomorphine to extinguish responding for self-stimulation after current is no longer applied to the electrode. The present study, therefore, suggests that apomorphine can have marked effects on self-stimulation but that these effects are probably secondary to competing motoric response patterns rather than an effect on reinforcement per se. Since impairments in the dopamine system either by neuroleptic treatment or 6-hydroxydopamine injections also produce severe motoric dysfunction [3], it becomes apparent that dopamine related performance deficits in self-stimulation are difficult to attribute to possible modifications in reinforcement efficacy.

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REFERENCES

1. Andén, N. E., A. Rubenson, K. Fuxe, T. Hökfelt. Evidence for dopamine receptor stimulation by apomorphine. *J. Pharm. Pharmac.* **19:** 627–629, 1967.
2. Broekkamp, C. L. E. and J. M. Van Rossum. Effects of apomorphine on self-stimulation behaviour. *Psychopharmacologia* **34:** 71–80, 1974.
3. Calne, D., T. H. Chase and A. Barbeau. Dopaminergic mechanisms. *Adv. Neurol.* **9:** 1–418, 1975.
4. Carey, R., E. Goodall and S. Lorens. Differential effects of amphetamine and food deprivation on self-stimulation of the lateral hypothalamus and medial frontal cortex. *J. comp. physiol. Psychol.* **88:** 224, 1975.
5. Dews, P. B. Analysis of effects of pharmacological agents in behavioral terms. *Fedn Proc.* **17:** 1024–1030, 1958.
6. Hasegawa, K. Roles of noradrinergic and dopaminergic systems in the substantia nigral self-stimulation behavior. *Folia pharmac. jap.* **72:** 827–835, 1976.
7. Kluver, H. and E. Barrera. Method for combined staining of cells and fibers in the nervous system. *J. Neuropath. exp. Neurol.* **12:** 400–403, 1953.
8. Liebman, J. and L. L. Butcher. Effects on self-stimulation behavior of drugs influencing dopaminergic neurotransmission mechanisms. *Naunyn-Schmiedeberg's Arch. Pharmac.* **277:** 305–313, 1973.
9. Lorens, S. A. Effect of lesions in the central nervous system on lateral hypothalamic self-stimulation in the rat. *J. comp. physiol. Psychol.* **62:** 256–262, 1966.
10. Wauquier, A. and C. J. E. Niemegeers. Intracranial self-stimulation in rats as a function of various stimulus parameters. II. Influence of haloperidol, pimozide and pipamperone on medial forebrain stimulation with monopolar electrodes. *Psychopharmacologia* **27:** 191–202, 1972.
11. Wauquier, A. and C. J. E. Niemegeers. Intracranial self-stimulation in rats as a function of various stimulus parameters. III. Influence of apomorphine on medial forebrain bundle stimulation with monopolar electrodes. *Psychopharmacologia* **30:** 163–172, 1973.