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Specific Modulation of Brain Stimulation Reward by Haloperidol[1]

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ESPOSITO, R. U., W. FAULKNER AND C. KORNETSKY. *Specific modulation of brain stimulation reward by haloperidol.* PHARMAC. BIOCHEM. BEHAV. 10(6) 937–940, 1979.—Low doses of haloperidol (3–18 μg/kg) caused dose related increases in reinforcing thresholds for self-stimulation to the medial forebrain bundle in rats. These effects, which were demonstrated completely independent of performance variables, indicate a direct modulation of central reinforcement processes by this drug, at doses which have highly selective action on dopaminergic neurotransmission.

Haloperidol Self-stimulation Reinforcement thresholds Dopamine

SEVERAL converging lines of research (i.e., anatomical, lesion, pharmacological) have rendered support to the hypothesis that the catecholamines are somehow critically involved in the phenomenon of brain stimulation reward [8,11]. Although there is widespread agreement that pharmacological interference with central dopamine systems will result in a general suppression of self-stimulation behavior, a remaining critical question is whether such suppression is due to an alteration of the rewarding value of the stimulation itself or alternatively to an impaired ability of the organism to perform the necessary operant response required to receive such stimulation. Evidence in favor of the specific reward explanation has recently been summarized by Wise [24]. Although cogent, this evidence is largely inferential (i.e. analysis of "extinction" patterns after drug administration), and to date there is no direct evidence demonstrating a neuroleptic induced alteration of self-stimulation behavior completely independent of motor impairment. After critically reviewing the evidence bearing on this issue, Fibiger [10] has concluded that resolution of the question will require techniques that clearly differentiate between the effects of drugs on motor function and central reinforcement processes. We presently report data demonstrating haloperidol induced increases in reinforcing thresholds for brain stimulation reward, completely independent of motor involvement.

METHOD

Animals and Apparatus

Four male albino Fischer rats (Charles River Breeding Laboratories), weighing approximately 300 g, were stereotaxically implanted with bipolar stainless steel electrodes (0.0127 cm in dia. and insulated except at the tips). The electrodes were aimed at the MFB-LH. Prior to surgery all animals were anesthetized with Equi-Thesin (0.3 ml/100 g body weight). Coordinates from bregma were −4.0 mm, anterior–posterior; ± 1.4 mm, lateral from the midline suture; and −8.5 mm, dorsal-ventral from the skull surface. The skull surface was levelled between bregma and lambda.

The animals were trained on a threshold procedure in a Plexiglas chamber (20×20 cm). Mounted in an opening in one wall of the chamber was a wheel manipulandum which was 15 cm long and 7.5 cm in diameter. Four equally spaced cams were positioned on one of the end plates such that they operated a microswitch when the wheel was rotated. Reinforcement was obtained only after closure of the microswitch (1/4 wheel turn). A constant current stimulator was used to deliver the stimuli which consisted of half-second trains of biphasic symmetrical pulses. Each train occurred at a frequency of 160 Hertz, with a pulse width of 0.2 msec, and a delay of 0.2 msec between the positive and negative pulses. Pulse amplitude was varied according to the procedural requirements for threshold determination.

Procedure

Determination of the threshold involved a discrete trial procedure identical in part to that used previously [9]. A trial began with the delivery of a noncontingent 0.5 sec pulse train. A response within 7.5 sec of this stimulus resulted in immediate delivery of a contingent stimulus, identical in all parameters to the noncontingent stimulus, and terminated the trial. Failure to respond has no scheduled consequences, and the trial terminated after 7.5 sec. Intervals between trials varied, with an average of 15 sec. Responses during the inter-trial interval resulted in a 15-sec delay before the start of the next trial. The initial noncontingent stimulation thus

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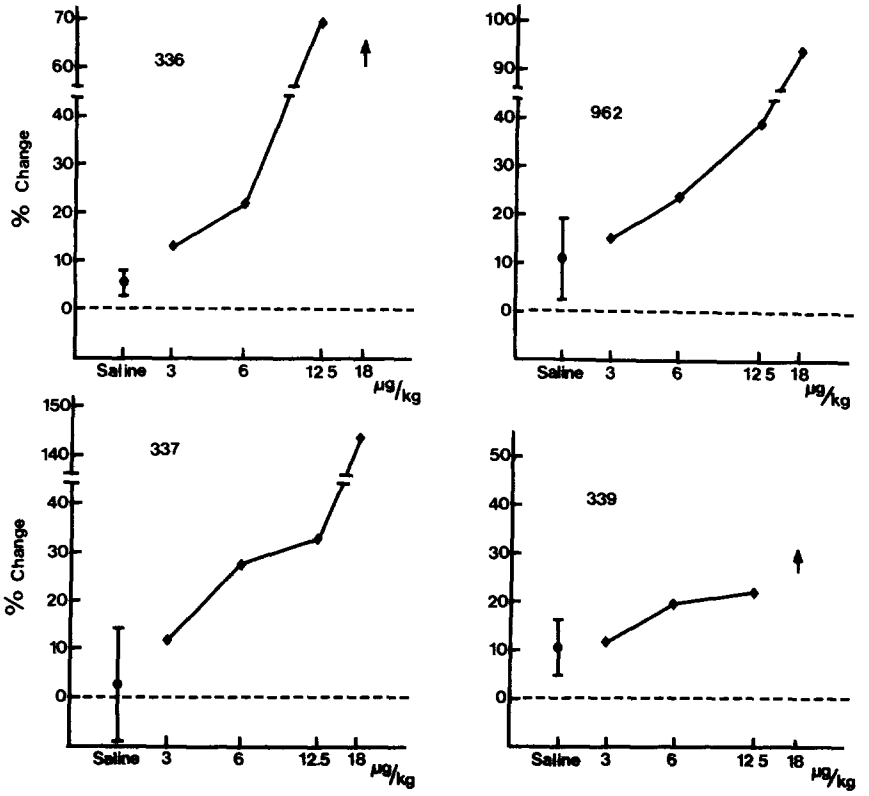

FIG. 1. Dose response data for all animals. The vertical bars to the left indicate the mean and standard deviation of percentage change value for a number (8-10) of saline control days Doses of drug administered are expressed in microgram/kilogram values, and plotted on a logarithmic scale on the abcissa. All injections were via the subcutaneous route. The arrows for animals 336 and 339, at the 18 μg/kg dose, indicate a lack of responding up to a level of 250 μa, the highest intensity employed. These animals, however, showed no gross signs of sedation at this dose level.

served both as a discriminative stimulus indicating availability of response-contingent stimulation, and as a comparative stimulus in the sense that it was a predictor of the parameters of the contingent stimulus. The latency to respond (time interval between the non-contingent stimulus and wheel-turning) was determined for each trial in which the animals responded. Total inter-trial or error responses were also calculated. These measures allowed for an assessment of behavioral impairment or disruptive responding.

Stimulus intensities for the threshold determinations were varied according to the classical method of limits with slight modification. Stimuli were presented in alternating descending and ascending series with a step size of 10 μA. Ten trials were given in succession at each step size or interval. A descending series was initiated at a previously determined intensity which invariably yielded a contingent response in at least nine out of ten trials, and then ten more successive trials were conducted at the next lowest interval and so on. Five or more responses at a particular intensity were arbitrarily scored as a plus for the interval, while less than five responses were scored as a minus for the interval. Descending series were conducted until minus scores were achieved in two successive intervals. An ascending series was started at one step size below the lowest intensity in the descending series, and continued until plus scores were achieved in two successive intervals, whereupon a descending series would be initiated at one interval above the last intensity used in the ascending series. Threshold was determined by calculating the arithmetic mean ($\bar{x}$) in microampers of the midpoints between the intervals in which the animal made greater than five responses (a plus score) and less than five responses (a minus score).

Each day the animals were given four test series (Session 1) before, and four test series (Session 2) after they were injected. After Session 1, the animals were injected subcutaneously with either saline or the drug, and then allowed 10 minutes to rest in the chamber before Session 2 was begun. The time needed to complete Session 1 or Session 2 varied from 60–90 minutes. The critical dependent measure was the percentage change in threshold from Session 1 to Session 2. (The percentage change was calculated as the Session 2 threshold minus the Session 1 threshold × 100 divided by the Session 1 threshold.)

The animals were trained until their thresholds stabilized and then were run for at least 4 days to determine the extent of the changes that occurred between Sessions 1 and 2 when the animals were injected with saline. They were then injected subcutaneously on test days with various single doses of haloperidol. Haloperidol was dissolved in 0.1 molar tartaric acid, diluted with isotonic saline and buffered with sodium hydroxide (pH=5.6). In between drug test days the animals were again tested after saline injections.

TABLE 1

LATENCY* OF RESPONSE IN SECONDS AT THRESHOLD, PRE AND POST, AT DOSES OF 6, 12.5, AND 18 μG/KG DOSES OF HALOPERIDOL

Animal	Dose μg/kg	Pre	Post	t	
962	6	4.59 ± 0.23	4.51 ± 0.20	0.26	
	12.5	4.82 ± 0.33	4.83 ± 0.59	−0.01	
	18	5.57 ± 0.38	4.59 ± 0.35	1.90	
337	6	4.33 ± 0.30	4.80 ± 0.40	−0 94	
	12.5	4.95 ± 0.32	4.14 ± 0.23	2.06	($p<0.05$)
	18	3.09 ± 0.42	5.02 ± 0.39	−3.37	($p<0$ 01)
336	6	4.77 ± 0.38	4.16 ± 0.38	1.14	
	12 5	3.74 ± 0.31	2.67 ± 0.43	2.02	
	18	†	†		
339	6	4.55 ± 0 36	4.59 ± 0.60	−0.06	
	12.5	4.76 ± 0.42	3.38 ± 0.44	2.27	($p<0.05$)
	18	†	†		

*Latency represents the average value at threshold intensity. When the threshold value did not fall on one of the 10 μA intervals, the value was rounded off to the nearest interval, and the latency value based on that interval. Latency values are presented as the mean (± ISEM).

†Indicates that too few responses were made in the postsession to make a meaningful comparison.

TABLE 2

NUMBER OF INTER-TRIAL (ERROR) RESPONSES, PRE AND POST, FOR ALL ANIMALS AT THE DOSES OF 6, 12.5, AND 18 μG/KG OF HALOPERIDOL BOTH PRE AND POSTSESSIONS CONSISTED OF APPROXIMATELY 200 TRIALS.

Animal	Dose μg/kg	Pre	Post
962	6	11	15
	12 5	7	10
	18	4	29
337	6	10	5
	12.5	5	5
	18	18	12
336	6	12	5
	12.5	7	10
	18	*	*
339	6	2	7
	12.5	6	5
	18	*	*

*Indicates that too few responses were made in the postsession to make a meaningful comparison

Following testing the animals were sacrificed and perfused intracardially with saline and then formalin. The brains were subsequently removed from the skull, fixed, embedded, and sliced at 40 μ. Mounted sections were stained with cresyl violet and luxol blue and examined under a light microscope. The electrode tips were located within the MFB at the level of the LH.

RESULTS

The effects of haloperidol on self-stimulation thresholds are illustrated in Fig. 1. As can be seen, through the dose range of 6–18 μg/kg, there were clear-cut increases in the reinforcing thresholds. It is of interest to note that these doses of haloperidol are significantly below those found to cause rate suppression in studies involving lever-pressing for brain stimulation reward (e.g. [23]). The pattern of responding after drug administration suggested an extinction pattern rather than a failure to detect the brain stimulation. Typically, on a descending series, the animals would give a few responses at the sub-threshold intensity, and then cease to respond entirely.

Threshold increases were unaccompanied by increases in response latencies (Table 1). In fact, there were instances of significant threshold increases with concomitant decreases in response latencies. Likewise the drug had no consistent effect on inter-trial or error responding (Table 2), and upon observation the animals revealed no overt signs of sedation.

DISCUSSION

The specific nature of these effects was made evident by the occurrence of threshold increases in the absence of concurrent increases in response latencies or inter-trial responses. These observations make it untenable to explain these results on the basis of a general performance impairment.

The extremely low doses of haloperidol employed in this study have been shown to have highly selective effects on dopaminergic neurotransmission [1, 2, 4, 22]. Although possible noradrenergic [21], adrenergic [12,13], serotonergic [16, 17, 18], and peptidergic [3] influences on self-stimulation behavior cannot be excluded, the present results argue for a direct role for dopamine in the modulation of brain stimulation re-

ward, in agreement with earlier studies that had suggested such a possibility [6,14]. Although the role that dopamine may play in the reinforcement process remains unspecified, a number of related findings provide some basis for speculation. First, it is noteworthy that previous work has found a strikingly high correlation between the ED_{50} values for neuroleptic induced inhibition of self-stimulation and ED_{50} values for reversal of amphetamine induced stereotypy [23]. Further, there is evidence which indicates an important role for the nigostriatal dopamine system in the mediation of amphetamine induced stereotypy (e.g. [5]). This dopamine system is involved in sensory-motor integration [15], and also has been implicated in self-stimulation on the basis of mapping, anatomical, and lesion studies [7, 11, 19, 20]. Thus, haloperidol may elevate self-stimulation thresholds by subtly disrupting higher order sensory-motor integration. As Wauquier [23] has suggested, neuroleptic treated rats may be unable to relate behavior with its consequences in situations involving relatively complex behaviors. In this sense haloperidol may disrupt the contingency between an operant and/or instrumental response and its consequence. A higher degree of stimulus "value" (increased stimulus intensity in our experiment) would thus be required in order to re-establish the relevant stimulus-response relationship. This attachment of stimulus "value" to appropriate response output may also involve other brain dopamine systems such as the meso-limbic and/or meso-cortical fibers.

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