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Effects of Peripheral and Central Dopamine Blockade on Lateral Hypothalamic Self-Stimulation: Evidence for Both Reward and Motor Deficits

JAMES R STELLAR, ANN E KELLEY[1] AND DALE CORBETT

Department of Psychology and Social Relations, Havard University
33 Kirkland Street, Cambridge, MA 02138

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STELLAR, J R , A E KELLEY AND D CORBETT *Effects of peripheral and central dopamine blockade on lateral hypothalamic self-stimulation Evidence for both reward and motor deficits* PHARMACOL BIOCHEM BEHAV **18**(3) 433–442, 1983 —The effects of dopamine receptor antagonists on lateral hypothalamic self-stimulation were analyzed using a reward summation function (RSF) technique This paradigm relates running speed in a runway to the number of stimulation pulses received as a reward, and it is able to separately characterize changes in reward pulse effectiveness and motor performance Pimozide, administered peripherally (0 125, 0 25, 0 5 mg/kg, IP), dose-dependently shifted the RSF toward higher values of number of pulses indicating reduced reward Pimozide also reduced the asymptotic running speed of the RSF, indicating a deficit in motor performance In a second experiment, α-flupenthixol infused directly into the nucleus accumbens (0 5 μg–0 5 μg, bilaterally) induced changes in the RSF similar to those obtained with peripheral neuroleptic treatment These findings are discussed from the perspective that dopamine is involved both in the perception of reward value and in the performance of the response to obtain reward

Self-stimulation Lateral hypothalamus Dopamine blockade Reward and motor effects Nucleus accumbens

THE neurotransmitter dopamine has been implicated by a number of investigators in the rewarding effect produced by electrical stimulation of the lateral hypothalamus [5, 19, 54] Much of the supportive evidence has come from studies showing that pharmacological interference with dopamine function leads to decreased self-stimulation [14, 15, 16, 31, 32, 40, 52] Since dopamine is known to play a major role in motor function [1, 13, 22], many studies have appropriately avoided using simple rate of response as an index of reward value For example, Fouriezos and Wise [15] have observed that rats trained to self-stimulate will show extinction-like patterns of responding under the influence of a dopamine receptor blocker, pimozide However, most of these techniques do not readily permit quantitative estimates concerning the reward decrement and motoric deficit induced by neuroleptic drugs Thus, claims for the effectiveness and selectivity of various drug treatments range from a fairly selective reward blockade or "anhedonia" [15,55] to substantial motoric impairment [9,49]

The reward summation function (RSF) technique developed by Edmonds and Gallistel [6] is better able to distinguish reward from motor effects on performance during self-stimulation behavior and it is able to provide information on the quantitative extent of the reward alteration induced by a drug or other physiological manipulation The RSF technique assumes that the electrical stimulation generates a reward signal that is partially dependent upon the number of individual square-wave pulses given in one stimulation burst If more pulses are added, the reward is increased Previous work [6, 7, 16, 48] has shown that running speed in a runway for one burst of lateral hypothalamic stimulation reward is a function of the number of pulses given in the reward burst, and depending upon the current and other parameters, rats typically begin running at about 5–15 pulses in the burst and asymptote at about 30–50 pulses Any reduction of the impact of individual pulses on the brain, e g , lowering the stimulating current, causes a shift in the RSF curve such that more pulses are required to offset the decreased effective-

[1]Present address Laboratoire de Neurobiologie des Comportements, Universite de Bordeaux II 146 Rue Leo Saignat, 33076 Bordeaux, Cedex, France

ness of each pulse Thus the number of pulses required to reach a previously determined behavioral criterion will increase as pulse effectiveness decreases Edmonds and Gallistel [6] chose as the behavioral criterion one half of the asymptotic running speed They then calculated the number of pulses required to reach this criterion and termed this value the "locus of rise " They show that the locus of rise of the RSF shifts to higher numbers as the effectiveness of the pulses is decreased, but does not change if, for example task difficulty is increased In contrast, the asymptotic running speed does change with task difficulty Thus, the locus of rise of the RSF provides a measure of the pulse effectiveness in producing reward, while asymptotic performance level reflects performance capability Furthermore, these measures have been empirically verified [6,48]

An additional benefit of the RSF technique is that it permits a rough calculation of the percentage shift in the effectiveness of reward pulses following a manipulation by ascertaining the number of pulses required to offset the effect of the manipulation For example, if pimozide at a given dose causes a shift in the RSF curve such that there is a doubling of the number of pulses required to achieve locus of rise, then the pulse effectiveness in producing reward is decreased by 50%

In the present study, the RSF technique was used to assess the quantitative effects of dopamine receptor blockade on lateral hypothalamic self-stimulation The first experiment was an attempt to replicate the earlier findings of Franklin [16] who reported a relatively selective interference with the rewarding effects of lateral hypothalamic stimulation following peripherally administered pimozide The second experiment examined the effects of brain injection into the nucleus accumbens

GENERAL METHOD

Subjects and Surgery

The subjects were male albino rats of the Sprague-Dawley strain They were stereotaxically implanted under Chloropent anesthesia (3 cc/kg) with 4 stainless steel monopolar electrodes constructed from size "00" insect pins insulated with Formvar enamel which were aimed at the medial forebrain bundle at the level of the lateral hypothalamus The level-skull coordinates for these electrodes were 2 0 mm posterior to bregma ±1 8 mm lateral, 8 5 mm ventral from skull, −4 0 mm posterior, ±1 4 mm lateral, 9 0 mm ventral The assembly of electrodes was anchored to the skull with stainless steel screws which also served as the return path for stimulating current Animals were allowed 4 days of recovery before the start of behavioral testing

Training Procedure and Apparatus

Brain stimulation consisted of cathodal monophasic, square-wave pulses of 0 1 msec in duration, and was delivered from a constant-current source Pulse frequency was always fixed at 100 pulses per second while number of pulses and current were adjusted as described below

Rats were tested for self-stimulation on each of four electrodes in a free lever press situation Burst duration was 0 5 seconds and current varied from 100–300 μA The electrode which at any current supported the highest, steadiest rate of responding was selected for inclusion in this study Rats were then trained to run a 1 meter runway and press a lever to receive a reward of one burst of pulses through the stimulation electrode

Following preliminary training, rats were adapted to the following schedule of discrete runway trials A single trial in the runway began with 10 bursts of free, noncontingent, priming stimulation delivered in a waiting box outside the runway Each burst of priming contained 60 pulses and the bursts occurred at the rate of 1 per second After priming stimulation had terminated, a six second interval elapsed during which the rat was transferred by the experimenter to the start box of the runway At the end of this interval a door separating the start box from the alley of the runway dropped and the rat was allowed to run the runway press the lever, and obtain a single burst of brain stimulation Performance was measured as the time elapsed from the drop of the door to the press of the lever Overall speed was calculated by dividing the distance (1 meter) from the door to the lever by the time elapsed After a run, the rat was removed from the runway by the experimenter and placed in the waiting box where a 20 second intertrial interval elapsed before priming stimulation began again Further details concerning this apparatus and procedure can be found in other reports [6,48]

Priming current was adjusted in individual rats to produce clear signs of behavioral arousal (e g , sniffing locomotion) but no signs of aversiveness (e g , attempts to escape from the waiting box, vocalization) Reward current was set to produce vigorous running at 64 pulses per burst As a final step in training, rats were adapted to changing levels of reward by undergoing a series of extinction and acquisition conditions In the acquisition condition, rats were given 11 successive trials of high reward (64 pulses) This was directly followed by trials of low reward (1 pulse) until a criterion of 4 consecutive trials of no running (i e , more than 20 seconds running time or less than 5 cm per second running speed) occurred Rats that did not run the runway within 20 seconds were placed on the reward lever, the reward was delivered, and a speed score of zero was entered These conditions of high and low reward were alternated until after each reward change the rat's running speed stabilized at the new level within 5 trials or less

A reward summation function (RSF), was generated by testing a series of reward conditions in which the number of pulses in the reward burst was varied Within a single condition reward was held constant and 11 trials were run The first four trials of each conditions were discarded to allow the animal to adjust to the new reward condition and the median of the last seven trials was taken to represent the animal's performance at that number of pulses One RSF was generated per day and the number of pulses was varied as follows first a warm-up condition was given, consisting of a high level of reward (64 pulses) This was followed by an extinction condition (1 pulse) which was judged complete when the rat did not run the runway (see above) in 4 out of 5 successive trials The reward condition was then progressively increased every 11 trials in a series of 0 3 log unit steps by doubling the number of pulses (i e , 2, 4, 8 16) until maximum running speed was obtained

EXPERIMENT 1 SYSTEMIC DOPAMINE BLOCKADE

METHOD

Procedure

In this experiment, 4 rats served as subjects After the

animals stabilized on the RSF procedure, baseline (non-drug) data were collected for 5–7 daily sessions before the neuroleptic, pimozide, was administered Pimozide (Janssen) was dissolved in tartaric acid (9 parts to 1 part pimozide), and was administered in 3 doses of 0 125, 0 25, and 0 5 mg/kg, in random order Injections were given intraperitoneally 4 hours before testing Animals were typically tested 3 to 4 times/week with only one session occurring under the influence of pimozide For each subject the stimulating current (in μA), given as reward and priming stimulation respectively, was TD17, 100, 300, JS95, 400, 300, JS98, 100, 200 KS11, 375, 200

Data Analysis

Data were analyzed for each RSF by calculating the locus of rise value and noting the asymptotic running speed Locus of rise was determined by first finding half of the asymptotic speed for that RSF and then by calculating the number of pulses required to sustain that level of running To determine statistical significance of drug effects, modified 95% confidence limits were constructed about the mean (non-drug) baseline for the locus of rise and for the asymptotic running speed by multiplying each standard deviation by ± 1 96 [21] Any point which fell outside these confidence limits was suggested to represent a significant deviation from the baseline control This procedure is comparable to the criterion of Edmonds and Gallistel [7]

Confidence limits are usually constructed about means using the standard error and refer to locations where new sample means are likely to occur [21] In our case, "confidence limits" were constructed about baseline means of the locus of rise, but used the standard deviation These modified confidence limits were taken as rough guides to where individual observations of locus of rise were likely to occur As such, they function as simplified versions of the criterion of Edmonds and Gallistel [7], the derivation of which is more complex, and the reader is referred to their paper for a detailed discussion of the statistical analysis of RSF shifts There was no difference in the outcome of the statistical analysis when these criterion [7] were applied to our data It should also be noted that the locus of rise determination is not based on the data from a single trial, but is the interpolation between two points on the RSF, each of which is the median of 7 trials Finally, data from asymptotic running speed were analyzed in the same way as data from the locus of rise

Histology

At the conclusion of the experiment subjects were deeply anesthetized and perfused through the heart with isotonic saline followed by 10% Formalin Brains removed from the skull were soaked for 1 week in 10% Formalin and 2 days in 20% sucrose Formalin They were sectioned on a freezing microtome at 40 μm, mounted, and stained with cresyl violet Electrode tips or cannula tracks were then found and sites reconstructed on the atlas of Konig and Klippel [28]

RESULTS

Histological examination indicated that all electrode tips were located in the medial forebrain bundle as shown in Fig 1 Pimozide altered the RSF in all subjects The RSF data from one subject, TD17, are shown in detail in Fig 2 Here all baseline control and drug RSF's are presented as individual curves to show the representative patterns of variability observed in baseline testing These data and the data from other subjects are summarized for each rat in Fig 3 As can be seen from Fig 3, pimozide produced shifts of the curve to the right and down on these axes The shifts in the RSF under pimozide were analyzed into independent changes in locus of rise and asymptotic running speed, and are presented in Fig 4 (In one case, JS 98, the baseline RSF of Fig 3 includes a terminal point that is derived from fewer observations than the other points in this RSF This point was not included in the analysis in Table 1, making this analysis more conservative) The highest dose of pimozide, 0 5 mg/kg, significantly increased the locus of rise and markedly decreased

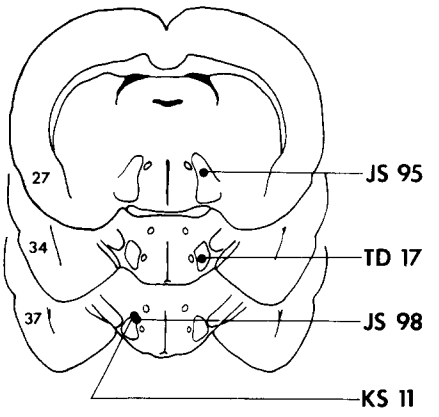

FIG 1 Electrode tip locations plotted on plates from the atlas of Konig and Klippel [28] Plate numbers are given on the left of each section

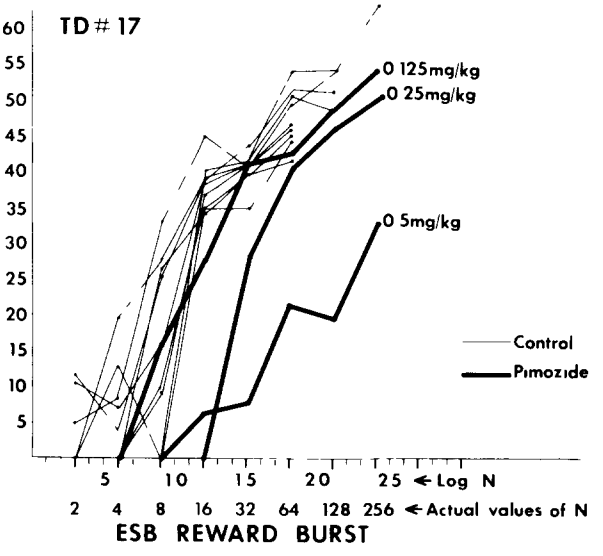

FIG 2 Data from subject TD17 The light lines indicate repeated individual baseline control reward summation functions Note that 0 25 mg/kg of pimozide produced a clear shift of the curve to the right along the abcissa without any decrement in asymptotic running speed This is not true for the 0 5 mg/kg condition

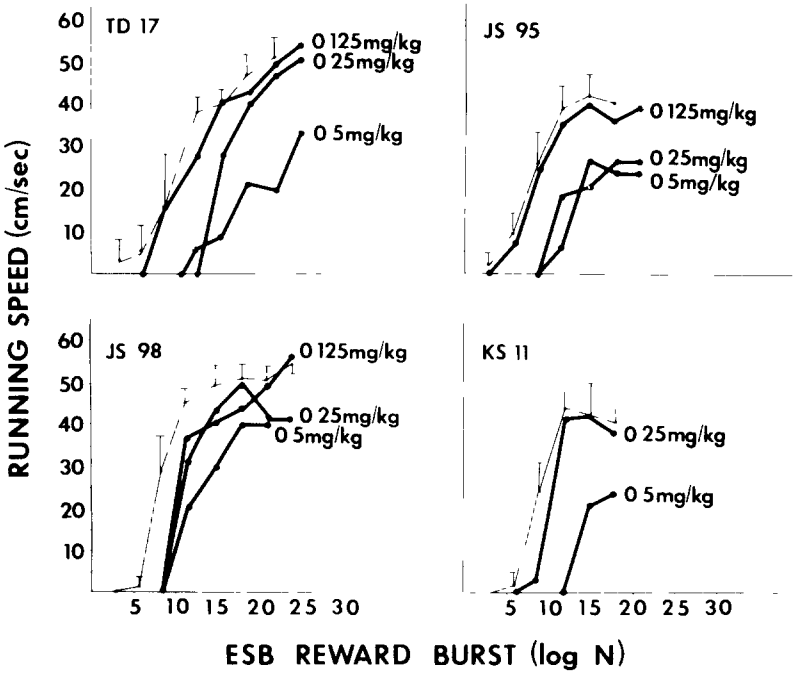

FIG 3 Data from all subjects given pimozide Control conditions are shown in the light line and drug conditions in heavy lines Data from the subject in Fig 2 are replotted in this figure Control curves were calculated by finding the mean performance in each condition of pulses over a number of sessions Error bars indicate one standard deviation from that mean

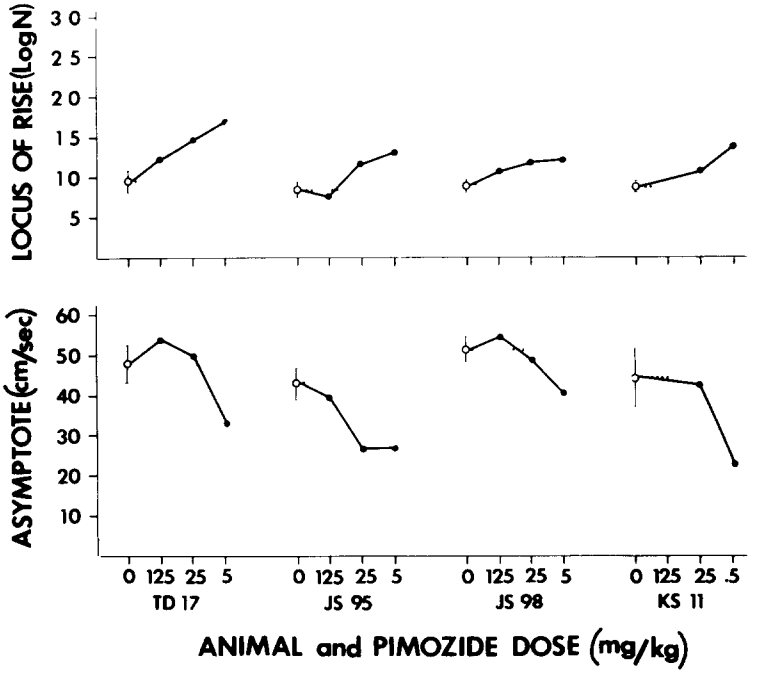

FIG 4 Changes in locus of rise and in asymptotic running speed of the reward summation function shown for all subjects at each dose of pimozide The locus of rise measurement can be seen to be steadily rising in a dose-dependent manner This indicates a decrease in reward pulse effectiveness The asymptotic speed can be seen to be lower in the high drug conditions This indicates a drop in overall performance capability The statistical analysis of these data is presented in Table 1

TABLE 1

Animal	Baseline Mean	Baseline SD	Baseline D	After Pimozide (mg/kg) 0 125	0 25	0 5
Locus of Rise (log N)						
TD17	0 96	0 18	9	1 20	1 45	1 70
JS95	0 83	0 07	4	0 73	1 15	1 30
JS98	0 89	0 06	8	1 13	1 15	1 20
KS11	0 88	0 04	8	—	1 05	1 35
Maximum Running Speed (cm/sec)						
TD17	48 8	6 6	9	54 0	50 0	32 5
JS95	43 1	4 0	4	40 0	26 3	27 0
JS98	51 4	3 4	8	54 6	49 0	40 1
KS11	44 1	6 9	8	—	43 0	23 3

Underlining signifies that the '95% confidence limit ' (see text) has been exceeded
SD=Standard deviation
D=Number of baseline control days

the maximum running speed It is noteworthy that in all rats, this dose produced an increase in the locus of rise which exceeded 0 3 log units, the criterion used for a statistically significant shift by Edmonds and Gallistel [7] At the intermediate doses of pimozide (0 25 mg/kg), increases in the locus of rise also exceeded the 95% confidence limits in all animals, although only one animal, JS95, showed a significant decrease in asymptotic running speed The lowest dose (0 125 mg/kg) had no effect on running speed, and only in one rat, JS98, was there a significant increase in the locus of rise

DISCUSSION

Two observations can be made from the results of this experiment First, dopamine receptor blockade with systemically administered pimozide induces a dose-dependent decrement in the effectiveness of lateral hypothalamic stimulation This phenomenon is observed in all rats at the intermediate dose (0 25 mg/kg) and is even more apparent at the high dose (0 5 mg/kg) It is manifested as a requirement for increased number of reward pulses to achieve locus of rise or any other criterion level of performance Second, it is clear that pimozide also impairs performance ability, an effect which is most obvious at the high dose This motor impairment is manifested by a failure of increases in number of reward pulses in the pimozide condition to achieve the same asymptotic level of running speed reached in baseline conditions It is interesting to note that at the intermediate dose of pimozide most subjects did not show significant decreases in asymptote, suggesting a possible "selective" effect on reward at this dose of the drug

In regard to the amount of reward alteration produced, at high doses of pimozide (0 5 mg/kg) the maximum loss of pulse effectiveness in producing reward ranged from 51% to 84% The intermediate dose (0 25 mg/kg) which was relatively free of performance disabilities, produced a 34% to 67% decrement in pulse effectiveness Reward pulse effectiveness can be calculated by assuming that for every doubling of our number of pulses (increase of 0 3 log units) required to reach the locus of rise, reward pulse effectiveness had dropped 50% The formula for calculating the proportional loss of pulse effectiveness would then be

$$100\left(1-\frac{1}{2^{n/0\,03}}\right)=P,$$

where n=the increase in locus of rise in log units and P=percentage of pulse effectiveness lost This calculation slightly overestimates the actual percentage decrease unless the reward burst duration is held constant, something that was not done in either our first experiment or in Franklin's report [16] This overestimation is due to the fact that longer reward burst durations offer a greater opportunity for decay of excitation [17]

The above values reflect pimozide's considerable ability to degrade the reward of lateral hypothalamic stimulation, but it should be noted that in this study, pimozide does not produce complete anhedonia Previously, the observation of extinction behavior on a task rewarded with hypothalamic stimulation following pimozide administration has been taken to reflect an anhedonic state [54,55], however, extinction could be attributed in part, to a decrease in pulse effectiveness below the level of reward needed to sustain behavior Effects of a given dose level will depend on the initial reward pulse effectiveness and the task chosen but complete anhedonia is unlikely to be achieved, at least in the dose range (<0 5 mg/kg) where pimozide may act selectively on reward

In comparing our study to that of Franklin's [16], in which he also analyzed the effects of pimozide on the reward summation function (RSF), we find agreement on the attenuation of reward, but he reports much less of a motor impairment than we do One difference between the studies is that despite using the same stimulation frequency, Franklin may have used less effective stimulating pulses The evidence for this difference is in the no-drug condition where the logarithmic locus of rise values for our subjects (mean=0 89, S E M =0 05) were much lower than for his subjects (mean=1 25, S E M =0 05) Therefore, fewer stimulation pulses were required to reach the behavioral criterion in our report, giving us a larger operating range Consequently, we were able to make locus of rise and asymptote determinations at doses of 0 5 mg/kg while Franklin was not, and it was at this dose level that significant motor effects were observed In the absence of complete RSF's, Franklin did note that at 0 5 mg/kg and 0 9 mg/kg, rats often showed extinction behavior, with running beginning at the same speed as in the undrugged condition Franklin [16] and others [14, 15, 55] have used this initial similarity of running speed in the drug and non-drug conditions to suggest that little, if any, motor deficit was present Yet, some [48,49] have argued that responding under dopamine receptor blockade is not functionally equivalent to the extinction condition We agree that pimozide likely induces a significant and relatively selective reward decrement at doses less than 0 5 mg/kg, but we suggest caution at making similar interpretations at this dose level or above

EXPERIMENT 2 NUCLEUS ACCUMBENS DOPAMINE BLOCKADE

The findings from the first experiment suggest that peripheral neuroleptic treatment degrades both reward and per-

formance factors associated with lateral hypothalamic self-stimulation However, peripheral administration affects all dopamine receptors which have very different anatomical connections [26,33], and likely quite different functions [1, 22, 26] Therefore, a more selective effect on reward might be obtained with local injections of dopamine blockers, and the nucleus accumbens stands out as a good candidate Current evidence suggests that myelinated reward relevant fibers may pass from the lateral hypothalamus to the ventral tegmental area [18, 46, 48] The ventral tegmental area is rich in dopamine and projects heavily to the nucleus accumbens [10,51] Functionally, dopaminergic impairment of the nucleus accumbens attenuates hypothalamic and ventral tegmental self-stimulation [31, 32, 34, 36, 40]

METHOD

Procedure

Five rats were implanted with two electrodes as described previously The level-skull, bregma-based coordinates were 4 0 mm posterior, ±1 4 mm lateral, and 9 0 mm ventral Additionally, rats were bilaterally implanted with 22 gauge stainless steel guide cannulae directed 3 mm above the nucleus accumbens, using the following coordinates 1 9 mm anterior, ±1 5 mm lateral and 4 4 mm ventral Except during brain injection, the guide cannulae contained stainless steel obturators

Apparatus, electrode selection procedure, training and testing were the same as in Experiment 1 with the exception that reward stimulation burst duration was held constant at 1 0 seconds as number of pulses were varied Thus frequency covaried with number of pulses in the reward burst For each subject the stimulating current (in μA) given as reward and priming, respectively, was AK2, 400, 300, AK4, 400, 200, AK5, 350, 225, AU3, 400, 200, AU6, 300, 150 α-Flupenthixol (Lundbeck) mixed in a saline vehicle was used in place of pimozide as the dopamine receptor blocking drug, to avoid using a tartartic acid vehicle These two neuroleptics are believed to be equal in potency and specificity [44] α-Flupenthixol was administered bilaterally by means of a 30 gauge injector cannula which was inserted into the guide cannulae in awake, unanesthetized animals Injector cannula tips extended 3 0 mm beyond the tip of the guide cannula 0 5 μg of α-flupenthixol in a volume of 0 5 μl of saline was administered over a 1'25" period by a hydraulic system driven by a Razel pump, followed by one minute diffusion time Animals were returned to their home cage for 5 to 10 minutes after injection before being tested in the runway Each animal received in random order one α-flupenthixol infusion and one control infusion (0 5 μl saline) with the exception of one animal (see below) Data analysis and histology were performed as in the first experiment

RESULTS

α-Flupenthixol infused into the nucleus accumbens altered the RSF in all subjects, as shown in Fig 5 Infusion of saline alone had no effect These shifts of the RSF were then analyzed into changes of locus of rise and asymptotic running speed, and the results are displayed in Fig 6 From this figure, it can be seen that α-flupenthixol significantly raised the locus of rise above baseline in 3 out of 5 cases and depressed asymptote in 4 out of 5 cases

One rat, AK5, would not run the runway at all after infusion of 0 5 μg of α-flupenthixol In later trials, the dose was reduced to 0 25 and 0 125 μg in 0 5 μl ("a" and "b," respectively in Fig 5) for this rat, in order to generate a RSF At 0 25 μg dose, the animal would still not run, however the lowest dose, 0 125 μg α-flupenthixol, produced a large increase in the locus of rise without affecting asymptote Saline vehicle alone induced no shifts in either locus of rise or asymptote These data are statistically analyzed in Table 2 where it can be seen that only in the case of α-flupenthixol infusion was there a shift in either asymptote or locus of rise that exceeded the 95% confidence limits

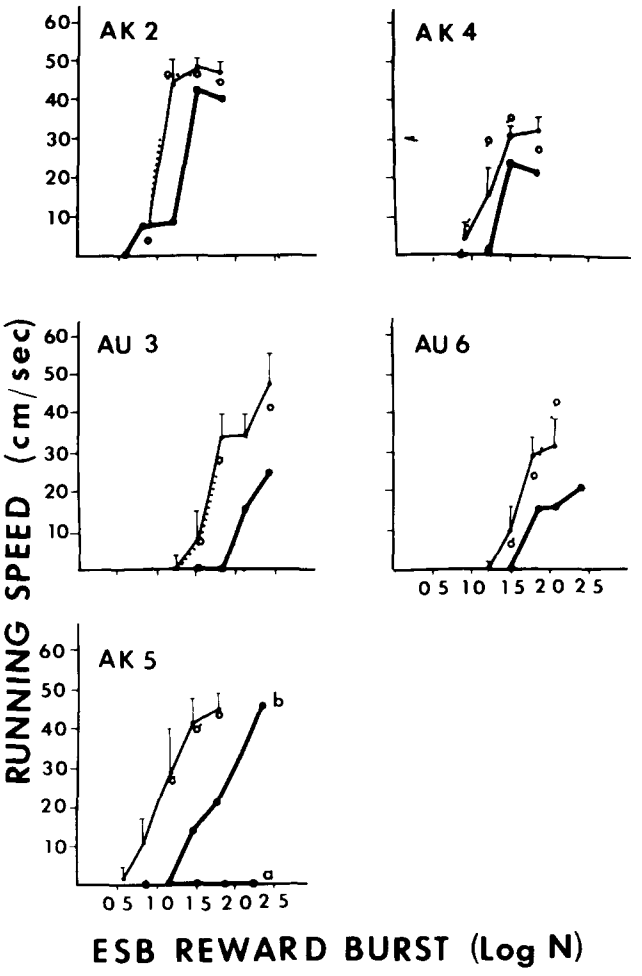

FIG 5 Reward summation function data for all subjects receiving brain injections The lighter lines indicate mean performance under control conditions and the brackets indicate one standard deviation Dashed lines indicate the saline session and heavy lines indicate sessions run under bilateral α-flupenthixol injections of 0 5 μg/0 5 μl into the nucleus accumbens Symbols a" and b ' indicate drug doses of 0 25 μg/ and 0 125 μg/0 5 μl, respectively

Histological examination (Fig 7) revealed that all electrodes were located in the medial forebrain bundle, and in every rat, the cannula tip was located in the nucleus accumbens medial to the anterior limb of the anterior commissure In rats AU3 and AU5 the cannula was in the anterior accum-

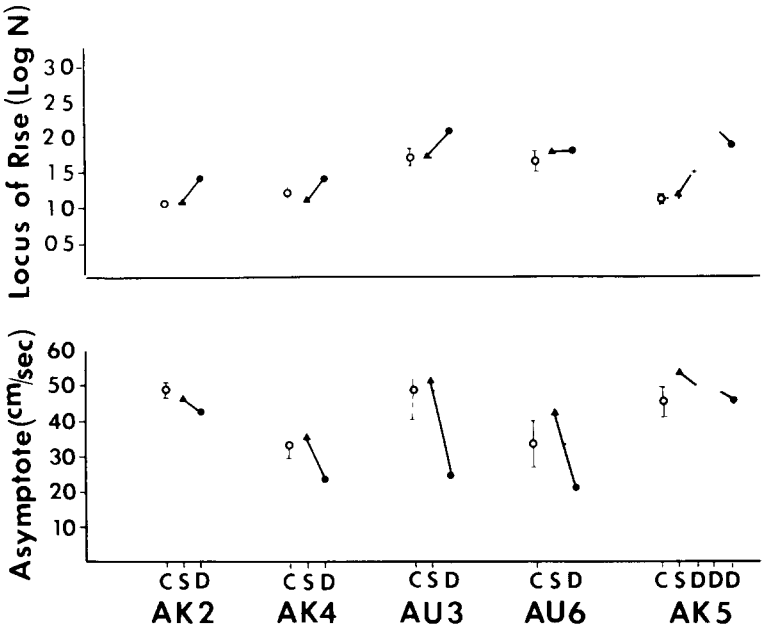

FIG 6 Locus of rise and asymptotic calculations from the data presented in Fig 5 Control, saline, and drug conditions are indicated by the symbols "C," ' S," and "D," respectively Control brackets indicate one standard error of the mean The second and third drug conditions under animal AK5 indicate reduced drug doses of 0 25 μg and 0 125 μg/μl, relatively

TABLE 2

	Baseline			After Accumbens Injection	
Animal	Mean	SD	D	Saline	α-Flupenthixol
Locus of Rise (log N)					
AK2	1 06	0 06	5	1 06	1 34
AK4	1 19	0 18	8	1 10	1 38
AU3	1 70	0 10	9	1 77	2 05
AU6	1 60	0 09	9	1 77	1 74
AK5	1 09	0 06	12	1 16	*, *†, 1 84‡
Maximum Running Speed (cm/sec)					
AK2	48 4	2 6	5	46 0	42 0
AK4	33 0	4 1	8	34 9	23 3
AU3	47 9	7 6	9	46 0	24 1
AU6	32 8	6 8	9	42 0	20 1
AK5	45 2	4 3	12	53 0	*, *†, 46 0†

Underlining signifies that the "95% confidence limit ' (see text) has been exceeded
SD=Standard deviation
D=Number of baseline control days
*Trials on which the animal did not run
†‡α-Flupenthixol at dose of 0 25 μg and 0 125 μg, respectively

bens, while in the remaining 3 rats it was somewhat more posteriorly placed However, based on these rats, no specific correlation could be made between cannula localization within the nucleus accumbens and behavioral results

DISCUSSION

In general, the results of this experiment are similar to those of the first experiment That is, dopamine receptor blockade of the nucleus accumbens induces a decrement in the effectiveness of lateral hypothalamic stimulation pulses in producing reward, and appears also to induce a decrement in performance ability Thus, it does not seem that reward can be selectively blocked by α-flupenthixol infusion into this brain site at this dose One could argue that at lower doses one might obtain a pure reward shift, since at 0 125 μg α-flupenthixol rat AK5 showed the greatest shift in locus of rise with no drop in asymptote However, this rat was particularly sensitive to the neuroleptic, and in the other rats 0 5 μg was enough to induce a just significant shift in the locus of rise It also might be argued that the drop in asymptote observed here is due to some spread of the drug to the caudate-putamen by leaking up the sides of the cannula shaft This possibility can only be tested adequately by making injections of α-flupenthixol at more dorsal sites within the caudate itself However, the relatively small volume (0 5 μl) and low dosage (0 5 μg) of α-flupenthixol injected make it unlikely that diffusion to distant sites via the ventricular system could account for the present results due to the great dilution of the drug which would accompany such diffusion

On the trials in which RSF's were generated, calculated percent reduction in pulse effectiveness decreased by a range of 48% to 82%, with a mean of 62% and standard error of 10% The decrements of pulse effectiveness seen here are comparable to those seen in the first experiment Thus, roughly speaking the two methods of drug treatment are approximately equal, with the brain infusion possibly being slightly more effective This strongly implicates the dopa-

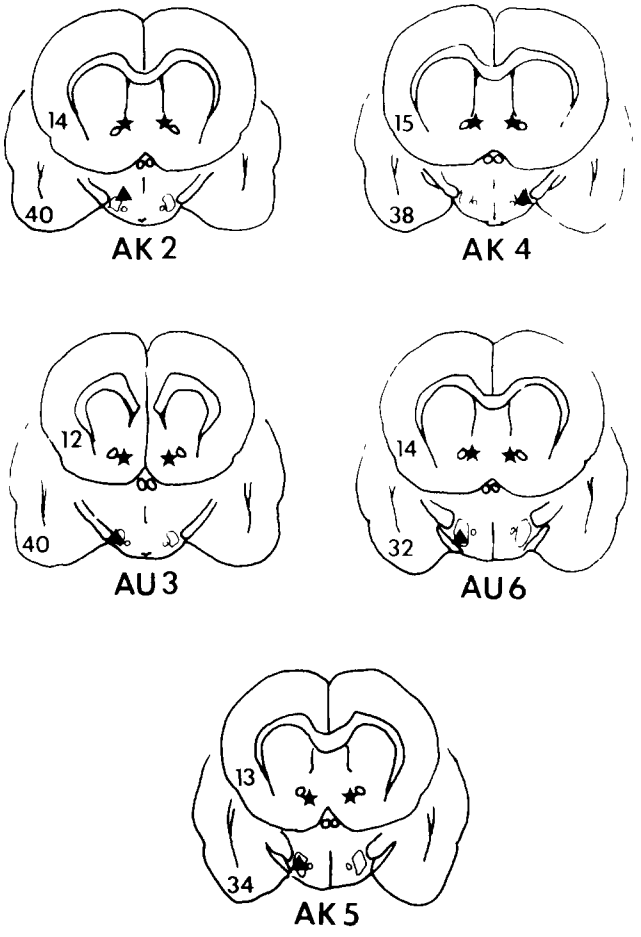

FIG 7 Electrode tip and cannulae tip locations plotted on plates from the atlas of Konig and Klippel [28] Plate numbers are given on the left of each section One representative 40 μm section through a cannulae injection site is shown

mine input to the nucleus accumbens in the process of hypothalamic stimulation reward, and agrees with other similar findings [32, 34, 36] particularly those of Mogenson and colleagues [31,40] who showed that, ipsilateral, but not contralateral injections of spiroperidol into the nucleus accumbens attenuated responding for nucleus accumbens self-stimulation [40] as well as ventral tegmental self-stimulation [31] However, an assessment of the effects of neuroleptic infusion into the many subregions of the striatum on this paradigm would be needed in order to ascertain the contributions of these regions to reward perception and performance It is possible, for example, that only a performance deficit might be obtained after neuroleptic blockade of the major motor area (anterodorsolateral) of the striatum [25]

GENERAL DISCUSSION

The present study has investigated the effects of blockade of dopaminergic transmission on lateral hypothalamic self-stimulation, employing the reward summation function (RSF) paradigm The objective of this study was not to demonstrate that dopamine is involved in this phenomenon, for which there is considerable previous evidence [3, 4, 5, 14, 15 16 31 32, 33 36, 40, 53, 54], but to dissociate and quantitatively characterize the consequences of dopamine-receptor antagonists on two factors involved in self-stimulation behavior responding to obtain reward, and reward value itself The major conclusions which can be drawn from our observations are the following (1) widespread blockade of dopamine receptors with the peripherally administered neuroleptic pimozide substantially decreases the effectiveness of hypothalamic stimulating pulses in generating reward and impairs motor performance of the response, (2) local infusion of the neuroleptic α-flupenthixol directly into the nucleus accumbens produces a similar result It should also be noted that complete anhedonia was not achieved even when substantial motor impairments were observed in task performance

Although it has been known for some time that systemic blockade of dopaminergic receptors has a considerable suppressing effect on self-stimulation [11 41 52 53, 54] the question of whether the suppression of self-stimulation rates is due to an attenuation of the reinforcing value of brain stimulation, or due to a deficit in the motor expression of reward, has recently become a central and controversial issue For example, a number of studies have shown that neuroleptics can impair motor function in a variety of conditioned and unconditioned behavioral paradigms [8 9 12 42, 49, 50] and lead to the interpretation that the neuroleptic-induced decrease in self-stimulation is due to a non-specific attenuation of motor performance or response artifact On the other hand groups which have studied self-stimulation with rate-free paradigms have argued that neuroleptics can, at some doses, selectively block the rewarding effects of brain stimulation [14, 15 16] and lead to the interpretation that these drugs induce a state of anhedonia in which the perception of stimulation is either largely diminished or completely blocked Thus it appears that the major question being debated is whether dopaminergic neurons have a major involvement in reward processes, or whether their role falls exclusively in the domain of motor or sensorimotor function

In an attempt to confront this issue it is helpful to remember that a large body of data outside the field of self-stimulation supports the concept of the involvement of dopamine in both the mediation of the hedonic value of stimuli and in the initiation and execution of complex motor acts For example the self-administration of psychostimulant drugs appears to be dependent on the dopaminergic neurons [39,56], further the discriminative properties of these drugs are mediated by dopamine [45] The rewarding effects of conditioned reinforcers are enhanced by amphetamine and amphetamine-like drugs [38] and diminished by pimozide [2] There is some evidence that neuroleptics attenuate the hedonic value of saccharin reward [43] and the euphoria noted in humans induced by amphetamine or cocaine is blocked after administration of dopamine-receptor blockers [20] Further, it has been demonstrated that normal human subjects prefer to self-administer low doses of amphetamine over placebo and that amphetamine enhances positive aspects of mood [24], suggesting that selective activation of the dopaminergic neurons is rewarding There is equally strong evidence that blockade of dopaminergic transmission induces a general motor depression, evident in humans in the syndrome of tardive dyskinesia [1] also a major symptom of Parkinson s disease is the inability to initiate and maintain

movement [22] Large dopamine lesions induce a state of complete dyskinesia, revealing the importance of the dopamine systems in many aspects of motor behavior [29,30] The results presented in our study quantitatively characterize these two functions of dopamine and provide additional evidence that it is likely spurious to claim that dopamine is involved solely in reward or motor processes [37,50]

In regard to the more specific study of local dopamine projections, it is generally acknowledged that dopamine receptors in the mesolimbic system mediate the motivational-affective role of dopamine, while dopamine in the striatum is responsible for facilitating complex motor responses [23] The nucleus accumbens is often cited as a structure linked with the reward role of dopamine [31, 32, 34, 36, 40, 54], and indeed one might have predicted that selective blockade of this structure would affect only reward and not motor capacity in the RSF paradigm However, this clear dissociation was not found It may be that while separating the concepts of motor function and reward-motivation is important on a psychological level, the ability to make this distinction is much less clear on a neural level For example, it is clear that the output of the nucleus accumbens plays a role in locomotion [23], locomotion is certainly motor behavior, yet it also can be the behavioral expression of an ongoing reward process in the limbic system, as in the case of amphetamine-induced locomotion [26] Anatomical descriptions indicate that the circuits underlying motor and motivational processes are inextricably linked in that both the nucleus accumbens and the rest of the striatum are decisively influenced by the limbic system [25], and both function in behavioral output [26,33] Perhaps, then, the goal of future research in this domain should lie not so much in separating reward from motor function, but in investigating how they interact via the dopamine systems

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