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Catecholamines and Self-Stimulation: Reward and Performance Effects Dissociated[1]

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FRANKLIN, K. B. J. *Catecholamines and self-stimulation: Reward and performance effects dissociated.* PHARMAC. BIOCHEM. BEHAV. 9(6) 813–820, 1978.—Drug-induced changes in the specifically rewarding effect of brain stimulation can be shown by shifts in the location of the sharp rise in the function (reward summation function, RSF) which relates running speed in an alley to the number of pulses received as a reward.This method was used to characterize the depressions of self-stimulation induced by the dopamine antagonist pimozide (0.2–0.9 mg/kg) and clonidine, a drug which acts on presynaptic α-adrenoceptors to inhibit noradrenaline release. Pimozide shifted RSFs in the direction indicating a reduced rewarding effect of brain stimulation but did not proportionately depress the maximum running speed. The larger doses of pimozide led to extinction of alley running. Clonidine (0.03 and 0.15 mg/kg) similarly reduced the rewarding potency of brain stimulation but also depressed running speed. Piperoxane antagonized clonidine's effect on the RSF location but added to the depression of running speed, thus confirming that drug effects on reward are dissociable from performance effects with the RSF method. In the light of these and other recent findings it is suggested that dopaminergic mechanisms are directly involved in the putative reward system and noradrenaline may be indirectly involved in self-stimulation via an effect on cerebral metabolism.

Self-stimulation   Reward   Reinforcement   Catecholamines   Noradrenaline   Dopamine
Pimozide   Clonidine   Piperoxane   Presynaptic α-receptors

SELF-STIMULATION is depressed or abolished by drugs which inhibit noradrenaline (NA) or dopamine (DA) transmission in the brain [13, 26, 30] but there is disagreement as to whether the loss of responding is due to reduction of the rewarding properties of brain stimulation [32,33] rather than to sedation or impaired motor ability [10, 11, 28, 29]. This controversy has arisen because rate of lever pressing, the response measure commonly used to demonstrate self-stimulation, does not discriminate between reward and performance effects. Reduced reward, sedation, and motor impairment can all lead to slower lever pressing. In addition, brain stimulation has an exciting after-effect (the 'priming' effect) which decays rapidly with time and which influences the probability and vigor of a succeeding response [6]. Thus, drug treatments which interfere with the execution of the response may increase the intervals between brain stimulations and lead to a reduction in the motivation for brain stimulation.

Gallistel and his associates [7,9] have devised a method which takes account of these difficulties. An animal is run between a start box in which it receives 'priming' stimulation and a goal box at the other end of an alley where it presses a lever for brain stimulation reward. By independently varying the parameters of the priming and rewarding stimulation it is possible to determine the functions which relate changes in performance to changes in the parameters of brain stimulation. With priming held constant the function which relates running speed to the number of electrical pulses the rat receives as a reward (reward summation function, RSF) has a distinctive shape. With short pulse trains the running speed is low but as train length is increased the running speed suddenly increases to an asymptote. The location (on the pulse train length axis) of the sharp rise in the RSF is a measure of the reward value of brain stimulation which is relatively unaffected by factors which alter the general level of performance. Treatments which alter the animal's level of arousal or its motor abilities raise or lower the maximum running speed but produce little change in the location of the sharp rise in the curve [7].

Recently, Edmonds has used an automated version of this method [9] to investigate the effects of inhibition of catecholamine synthesis by α-methyl-p-tyrosine on brain stimulation reward and found that reward was reduced in some cases [8]. Since α-methyl-p-tyrosine depletes both NA and DA it is not clear which amine is essential to maintain the rewarding effect of brain stimulation. To distinguish the relative contributions of NA and DA the present study used Edmonds' method to examine the effects on RSFs of

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pimozide, a specific DA antagonist, and clonidine, which inhibits NA release by an action on presynaptic α-receptors [14,30]

METHOD

Animals

Animals used were 14 adult male hooded rats which self-stimulated through stainless steel electrodes (Plastic Products, Roanoke, VA) implanted, under nembutal anaesthesia, in the lateral hypothalamic area (8 rats) or the ventral tegmental area (6 rats). Four of the electrodes aimed at the lateral hypothalamus were bipolar, all the rest were monopolar. Ground leads were connected to the skull screws.

Apparatus

Animals were tested in a 200×18×18 cm runway with a 30×30 cm start box at one end and a motor operated door separating the start box and runway. This door dropped beneath the floor at the beginning of a trial. A retractable lever protruded through the end wall of the runway (the goal lever) and a second retractable lever protruded through the wall of the start box opposite the door.

Brain stimulation of 100 Hz, 1.0 msec cathodal pulses was delivered by a Grass SD5 stimulator through a 1.0 μF capacitator via a mercury slip ring. Stimulation current was monitored on an oscilloscope. The parameters of brain stimulation and the sequence of events in the runway were controlled by solid state programming equipment. The latency between the drop of the start box door and the rat's depression of the goal lever was recorded on an electronic timer and transformed to running speeds (1/latency×200).

Drugs

Clonidine hydrochloride (Boehringer) was used from ampoules and diluted with 0.9% saline as required. Piperoxane (RhonePoulenc) was dissolved in distilled water immediately before use. Pimozide (Janssen) was dissolved in a vehicle of 3% tartaric acid.

Pretraining Procedure

A rat first learned to lever press for brain stimulation of 64 pulses per reward (PPR) in a conventional Skinner box before it was transferred to the runway and given 2, 15-min sessions of self-stimulation on the goal lever. To shape alley running the rat was placed further and further back from the lever and allowed 10 rewarded lever presses (64 PPR) every time it returned to the goal lever. When the rat was running the length of the runway the start box lever was introduced and the rat was allowed 10 rewarded lever presses per trial on it as well. When the rat was shuttling reliably between start box and goal lever the motor operated door was raised to delay the rat's exit from the start box to the runway for 5 sec. The apparatus was then put on the following program of trials used throughout the rest of training and testing.

A trial began when the start box door dropped away allowing the rat to run to the goal end. When the rat pressed the goal lever it received a single train of brain stimulation (128 PPR) and the lever retracted. The rat was then free to wander in the apparatus for 25 sec before the start box lever extended, signalling that stimulation was available in the start box. The rat was allowed 10 reward presses of the start box lever (64 PPR). These served as priming stimulation for the next trial. The first press of the start box lever closed the door and on the 10th press the lever retracted. Five sec later the goal lever extended and the door dropped away to begin a new trial. If the rat failed to press the goal lever within 30 sec it was forced to the goal lever and made to press it. If, as rarely happened, the rat failed to press the start box lever the experimenter delivered the priming stimulation. Aftec 2, 1-hr sessions on this program the rat was introduced to the test procedure.

Test Procedure

Each test session began with the rat running 15 trials to a high reward of 128 PPR. Stimulation at the goal lever was then reduced to 2 PPR until the rat stopped running. The number of pulses was then set at the highest value for which the experimenter was sure the rat would not run and increased from there in 0.3 logarithmic steps until the rat was running at asymptotic speed (i.e., running speed did not increase by more than 15% between successive reward settings). Ten trials were run at each reward train setting, except, if running speed was particularly variable up to 15 trials were run. If a rat failed to run within 30 sec it was forced to the goal lever. Four forced trials out of 5 successive trials terminated a reward setting. The *median* running speed for the last 6 trials at a reward setting was used as the representative running speed for that reward train length.

Priming stimulation was always 10 trains at 64 PPR of the same current as the reward (goal stimulation) and were delivered as a burst of responding lasting less than 10 sec.

Reward Summation Functions

Reward summation curves were constructed by plotting median running speeds against the common logarithms of the number of pulses in the rewarding train. To locate the sharp rise in the RSF a horizontal line was drawn through the curve halfway between zero and the maximum running speed. The abscissa for the intersection of this horizontal line and the summation curve represents the RSF 'locus'. (For discussion of this procedure, see Gallistel *et al.* [9].) The maximum running speed was taken to represent the asymptote of the RSF.

During training the stimulation current was adjusted so that the RSF locus for each rat was as close as possible to 16 PPR (1.2 log PPR). Training continued at 1 session per day until the RSF locations were stable. This required 6 to 10 sessions.

Drug Treatments

Each rat was run under as many drug conditions as possible. At least 48 hr separated any 2 tests with the same drug or its control and at least 6 days separated tests with different drugs. Reward summation curves were obtained in the order of: clonidine, piperoxane, clonidine plus piperoxane, and pimozide, except for 3 rats which received pimozide before the other treatments. All injections were given IP in a volume of 1 ml/kg. The numbers of rats treated and the doses and orders of treatments were as follows:

1. Clonidine. Eight rats with lateral hypothalamic electrodes (LH rats) and 6 with ventral tegmental electrodes (VT rats) were tested with saline, clonidine 0.03 mg/kg, clonidine 0.15 mg/kg and again with saline. Injections were given 60 min prior to testing.

2. Piperoxane and clonidine. Four LH and 4 VT rats,

previously tested with clonidine alone, were tested with piperoxane alone, piperoxane plus clonidine 0.03 mg/kg, and piperoxane plus clonidine 0.15 mg/kg. Piperoxane was given 75 min prior to testing in a dose of 5 mg/kg. Clonidine was injected 15 min later.

3. Pimozide. Three LH and 3 VT rats were treated with vehicle, 0.1, 0.2, 0.3 and 0.5 mg/kg pimozide in different order for each rat. An additional 3 LH received vehicle, 0.3 mg/kg pimozide and 0.9 mg/kg pimozide and 3 VT rats received vehicle, 0.3, 0.5 and 0.9 mg/kg pimozide. Pimozide or its vehicle were injected 4 hr before testing.

RESULTS

1. Clonidine. Figure 1 shows the effects of clonidine on the location of the sharp rise in the RSF ('location' or 'locus' of RSF) for LH and VT rats. In both groups clonidine shifted RSF location towards longer pulse trains in a dose dependent manner (Friedman $\chi_r^2=14.4$ and 10.34; $p<0.002$ for LH and VT, respectively). Clonidine also caused a dose-dependent depression of running speed in LH ($\chi_r^2=12.25$, $p<0.001$) and VT rats ($\chi_r^2=9.33$, $p<0.006$). As there were no significant differences between the LH and VT rats at any dose or condition these data were combined for all further analyses.

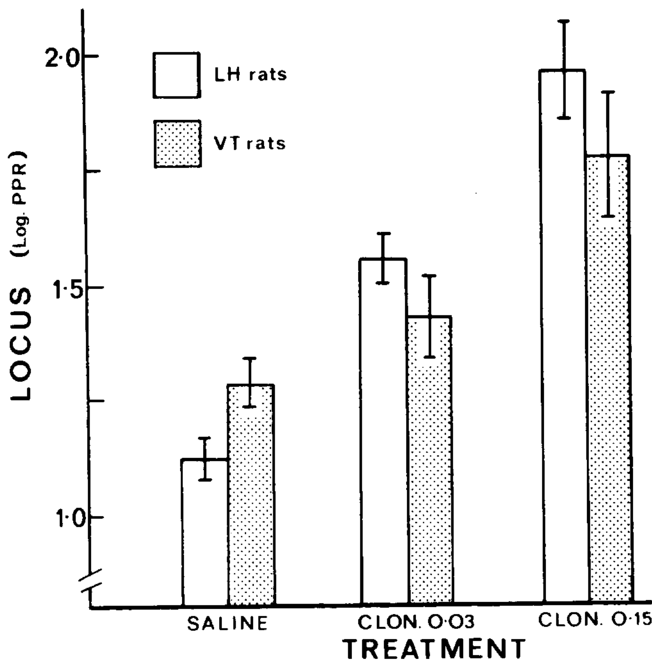

FIG. 1. Mean locus of reward summation functions for 8 LH and 6 VT rats after treatment with saline, 0.03 mg/kg clonidine, and 0.15 mg/kg clonidine. Ranges are standard errors.

The upper panels of Figs. 2 and 3 show RSFs of two animals which illustrate the effect of clonidine. It can be seen that both the location and the asymptotic speed are shifted by clonidine treatment but the general form of the curves is unaltered. The sharply rising asymptotic curves shown in Fig. 2 are typical of RSFs in both drugged and undrugged rats (see also Fig. 7) though a few rats (3/15) produced less markedly asymptotic RSFs (e.g., Rat 5, Fig. 3). Regardless

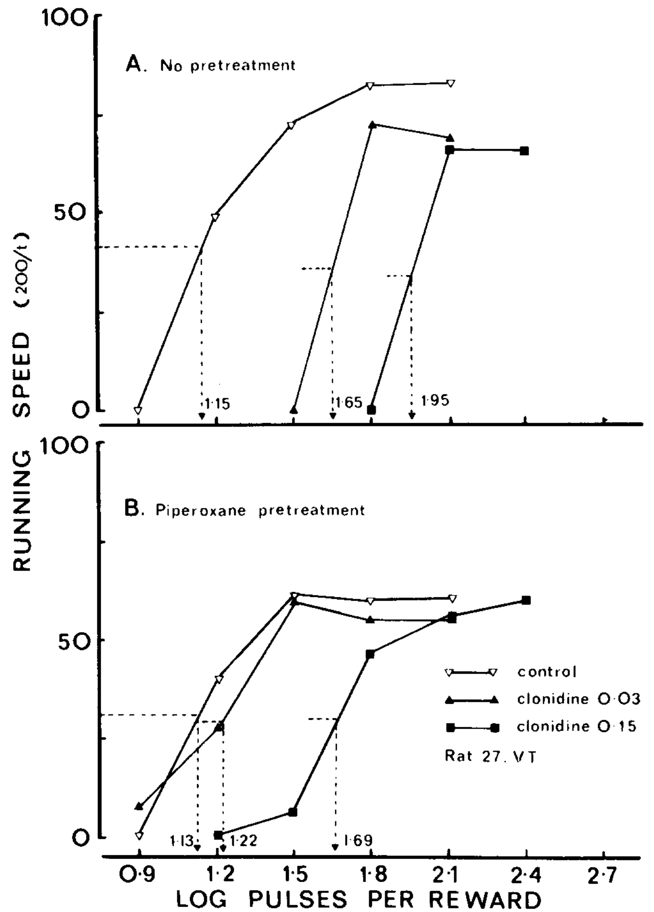

FIG. 2. Reward summation functions for Rat 27 under control conditions and after 0.03 and 0.15 mg/kg clonidine with no pretreatment (Panel A) and pretreatment with 5 mg/kg piperoxane (Panel B). Dotted lines and their adjacent numbers indicate the loci of individual reward summation functions.

of the shape of the curves of individual rats, RSFs under clonidine were roughly parallel to control RSFs. Major irregularities in the curves were rare. On only two occasions was the location of the rise in the RSF ambiguous and in both cases the conservative (i.e., least change from control) alternative was taken. RSFs were also quite stable from session to session. In 8 rats (4 LH, 4 VT) which were tested 3 times under saline—before, during and after the series of clonidine treatments—the small sample standard deviations for RSF location of individual rats ranged from 0.005 to 0.165 (log PPR) with a mean standard deviation of 0.093. In contrast the mean shift in location produced by 0.03 mg/kg clonidine (0.336) was more than three times the size of this session to session variation.

2. Piperoxane plus clonidine. Figure 4 and the lower portions of Figs. 2 and 3 show the effect of clonidine and piperoxane on the locus of the sharp rise in RSFs. The effects of clonidine, $F(2,35)=39.21$; $p<0.001$, was highly significant and there was a significant interaction between clonidine and piperoxane treatments, $F(2,35)=5.33$; $p<0.05$. Multiple comparisons (Tukey's HSD=0.233, $\alpha=0.05$) showed that clonidine 0.03 and 0.15 mg/kg shifted RSF loca-

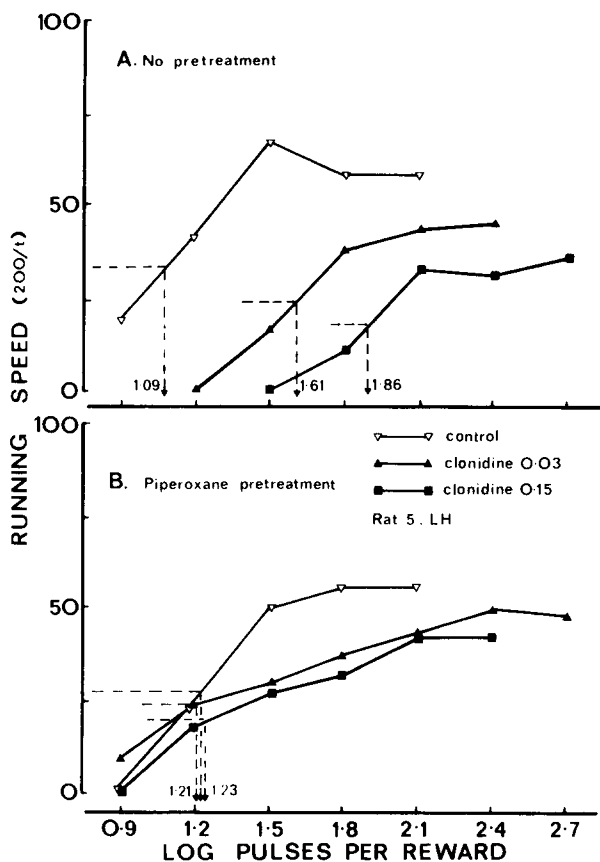

FIG. 3. As in Fig. 2 for Rat 5.

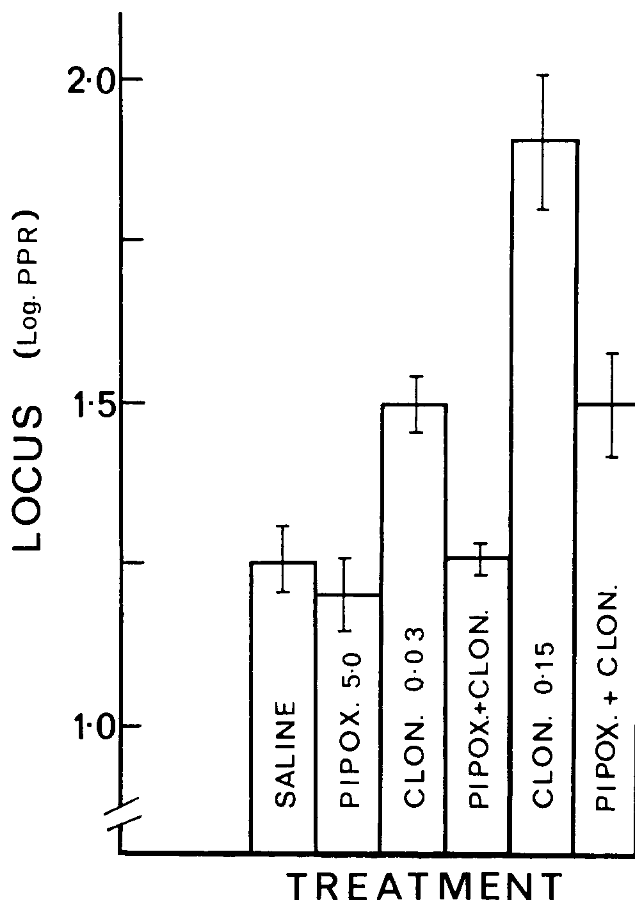

FIG. 4. Mean locus of reward summation functions after treatment with saline, piperoxane 5 mg/kg, clonidine 0.03 or 0.15 mg/kg, and piperoxane 5 mg/kg plus clonidine 0.03 or 0.15 mg/kg. Ranges are standard errors.

tion towards longer reward trains while piperoxane eliminated the effect of 0.03 mg/kg clonidine and reduced the effect of 0.15 mg/kg clonidine. Piperoxane itself had no effect on RSF locus.

The effects of clonidine and piperoxane treatment on asymptotic running speed are shown in Fig. 5. Both treatments depressed running speed, $F(2,35)=21.83$; $p<0.001$; $F(1,36)=8.36$; $p<0.01$, respectively, and their action was additive, $F(2,35)=2.73$, NS.

3. Pimozide. In all rats pimozide shifted RSFs towards long pulse trains. This effect was so strong that at doses above 0.2 mg/kg an increasing proportion of rats would not sustain running for the longest pulse trains the apparatus could deliver (512 PPR). Thus affected were 3/12 rats tested with 0.3 mg/kg, 7/9 at 0.5 mg/kg and 7/7 at 0.9 mg/kg. Figure 6 shows the dose dependent shift of RSFs produced by the 3 lower doses of pimozide ($\chi_r^2=13.8$; $df=3$, $p<0.01$). To estimate the effect of 0.3 mg/kg pimozide the 2 rats which failed to run for 512 PPR were given scores of 2.85 log PPR, that being the lowest score they could have attained if longer pulse trains could have been tested.

Pimozide also depressed the asymptotic running speed of most animals but this depression did not parallel the shift in RSF location. At 0.1 mg/kg pimozide did not significantly shift RSF locus (T=2, N=6, NS, Wilcoxon) but depressed maximum running speed by 26% (T=0, N=6, $p<0.05$). Increasing pimozide dose to 0.2 mg/kg produced a fourfold increase in the number of pulses required as a reward (see Fig. 6) but no further drop in running speed (mean drop 9.9%, T=3, N=6, NS). Overall there was no consistent relationship of running speed to RSF shift. For example, at 0.2 mg/kg the rat most depressed in running speed (44%) also showed the largest shift in RSF (1.41 log PPR) but the rat with the second largest RSF shift (1.02 log PPR) ran slightly faster than it did under control treatment (see Fig. 7). This latter rat was one of 3 in which pimozide produced large shifts in RSF locus (0.6 to 1.1 log PPR) but small changes (<10%) in running speed. At doses of 0.3 mg/kg and above, in the majority of rats, asymptotic speed could not be accurately estimated because RSFs were shifted too close to the limit of 512 PPR. However, for 11 out of the 12 rats tested under pimozide there was at least one pimozide dose for which a complete RSF was available. Pooling rats and doses there were 18 RSFs under pimozide for which both locus and asymptote could be computed. For these 18 tests the correlation between the RSF shift and the change in asymptotic running speed was insignificant ($r_s=0.098$).

As already noted, RSFs could not be plotted for the largest doses of pimozide but these treatments did reveal an interesting effect which occurred during the 15 warm-up trials (at 128 PPR) given at the start of every session. The first time a rat was run under one of these doses it ran the first trial of the session at its usual speed and slowed to a stop

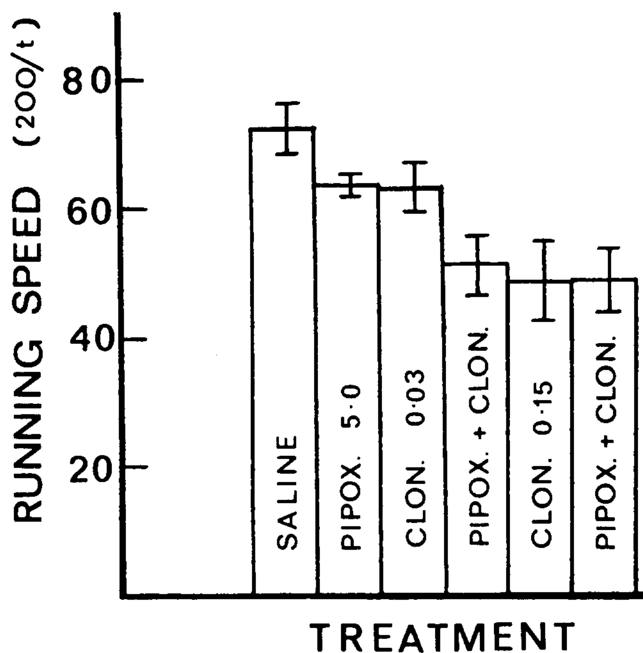

FIG. 5. Mean (n=8) maximum running speeds after treatment with saline, piperoxane 5 mg/kg, clonidine 0.03 or 0.15 mg/kg, and piperoxane 5 mg/kg plus clonidine 0.03 or 0.15 mg/kg. Ranges are standard errors.

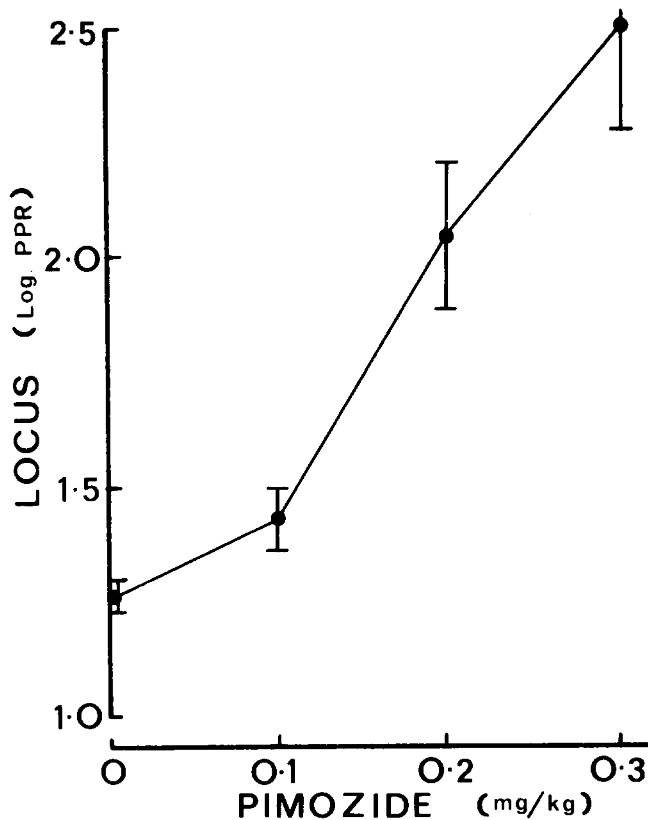

FIG. 6. Mean locus of reward summation functions (n=6) after different doses of pimozide and after vehicle (0 mg/kg). Ranges are standard errors.

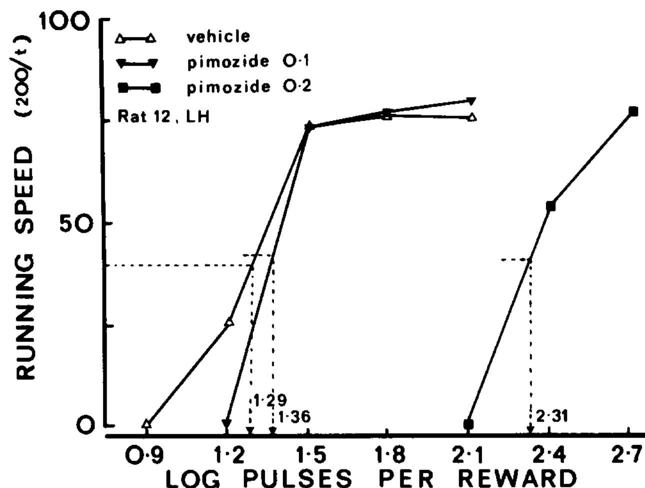

FIG. 7. Reward summation functions for Rat 12, 4-hours after injection of pimozide (0.1 or 0.2 mg/kg) or its acid vehicle. Rat 12 was one of three rats in which pimozide produced a large shift in the loci of reward summation functions without depressing the maximum running speed. Dotted lines and adjacent numbers indicate loci of individual reward summation functions.

over the next 3 to 9 trials (mean 5.67 trials, N=12) Rat 34 (see Panel A, Fig. 8) was typical of the majority of rats (10/12) which always ran spontaneously on the first trial of the day. Under pimozide Rat 34 ran the first 3 trials at normal speed, slowed, and refused to run on Trial 6. Later Rat 34 recommenced running for 512 PPR. Panel B of Fig. 8 shows one of the 2 rats which usually required several forced trials before it ran spontaneously. Under pimozide it also required forcing but nevertheless ran spontaneously before again refusing to run. For all twelve rats the median running speed under pimozide did not differ from that on control days on the first (56.5 vs 56.7, T=30, NS, Wilcoxon) or second (65.4 vs 72.2, T=20.5, NS) spontaneous run but on Trial 3 rats ran slower under pimozide (69.6 vs 81.6, T=8, $p<0.02$). This pattern of responding occurred reliably only on the first occasion rats experienced a large dose of pimozide. On subsequent tests most rats ran slowly or not at all. However, since doses of pimozide were tested in different orders for each rat it is possible to examine the effect of dose on the decline in running. It can be seen from Table 1 that the dose of pimozide is not related to the number of trials to extinction of running (Kruskal-Wallis H=0.55, NS). Moreover, on the first spontaneous run there was no correlation between the dose of pimozide and change in running speed (control minus pimozide speed) produced by pimozide ($r_s = -0.095$).

Electrode Placements

Of the electrodes aimed at the LH 5 were found in the MFB at the level of De Groot planes A5·0–A5·2 and 1 in the MFB at A3·8. In VT rats electrodes were found near A2·8, 4 in the ventral tegmental nucleus and 1 in the nucleus parafasciculus of the thalamus. The brains of 3 rats (1 VT, 2 LH) were not available for histology.

Rats varied in their sensitivity to pimozide and clonidine but RSFs of all animals were shifted by both drugs. As previously noted, the VT and LH groups of rats responded equally to pimozide and clonidine. Furthermore, ignoring

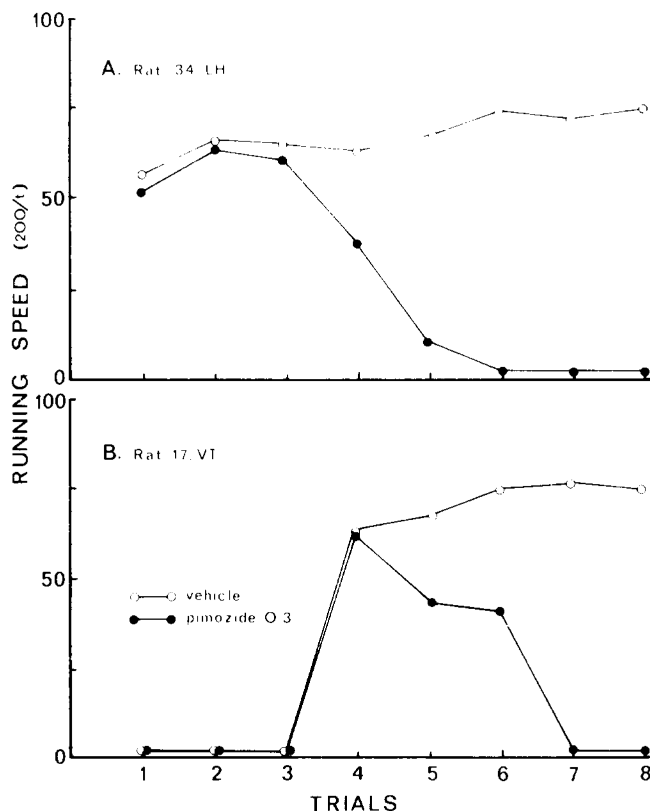

FIG. 8. Running speeds of Rats 34 and 17 on the first 8 trials run (128 PPR) 4-hours after injection of pimozide 0.3 mg/kg or its acid vehicle.

TABLE 1

MEAN NUMBER OF TRIALS TAKEN TO CEASE RUNNING FOR BRAIN STIMULATION REWARD OF 128PPR AFTER DIFFERENT DOSES OF PIMOZIDE

Pimozide Dose (mg/kg)	0.2	0.3	0.5	0.9
Trials to Cease Running	6.00	5.25	6.00	5.66
Number of Rats	1	4	4	3

electrode site, there was no significant correlation between the response to clonidine (0.03 mg/kg) and the response to pimozide (0.3 mg/kg) for the 11 rats which received both drugs (r_s=−0.373, NS).

DISCUSSION

Edmonds and Gallistel [7] have shown that the location of the sharp rise in RSFs is very sensitive to changes in the parameters of brain stimulation delivered as a reward but insensitive to priming effects of brain stimulation, the physical demands of the response, or the animal's physical fitness. These latter "performance variables" do, however, affect the optimum running speed. In the present experiments both clonidine, an alpha-adrenergic agonist which inhibits NA release, and pimozide, a DA antagonist, shifted the locus of the sharp rise in RSFs towards longer pulse trains, thus showing that interfering with NA or DA transmission reduces the rewarding effect of brain stimulation. This interpretation of the RSF data is reinforced by the finding that drug effects on running speed and RSF locus were dissociable. While clonidine shifted RSF locations and depressed the maximum running speeds, piperoxane added to the depression of running speed and at the same time antagonised the clonidine-induced shift in RSF location. This finding also confirms that clonidine reduces brain stimulation reward by inhibiting NA release [14,18] since piperoxane is a selective antagonist of clonidine's effect on presynaptic alpha-receptors [30]. The pharmacological basis of clonidine's effect on maximum running speed is not known but might involve acetylcholine [23].

The effects of pimozide were also selective. 0.1 mg/kg pimozide depressed maximum running speed but did not shift RSF locus while 0.2 mg/kg pimozide produced a 17-fold shift in RSF locus but had no further effect on the maximum running speed. Considering all rats and doses of pimozide there was no consistent relationship between depression of asymptotic running speed and the shift in the locus of RSF. Even doses of pimozide as high as 0.9 mg/kg did not prevent rats from running at normal speed in the first few trials of the session though running speed did decline rapidly. Such extinction-like decrements in responding have been previously reported [12,33] and are consistent with the view that the shift in RSF locus indicates loss of reward. The decrements were observed under doses of pimozide which would have raised the threshold of reward well above the 128 PPR (e.g., Fig. 7, RSF for 0.2 mg/kg) which rats were receiving when the decrements occurred. Moreover, there was no correlation between number of trials to extinction and the dose of pimozide that produced it. This would be expected if pimozide acted on reward, since once reward is reduced below threshold the effect of any further increase in dose should be undetectable. On the other hand, if the response decrement had been due to pimozide making it difficult or exhausting to run the decrement would be expected to increase with the dose. Moreover, in the later case the initial running speed would be inversely related to the dose of pimozide and again this was not the case.

The finding that pimozide does not reduce running speed in the first few trials of a session also suggests that the neural substrates of 'priming' and reward are not identical. Self-stimulating animals usually require several trains of brain stimulation to begin responding or to reach their maximum running speed [6]. In the present experiments, priming stimulation was delivered before each trial so that most rats ran near maximum speed on the first trial of the day. The effectiveness of this pre-trial stimulation was apparently not reduced by pimozide (e.g., Fig. 8A) and even the few rats that normally required several bouts of stimulation to begin running were successfully primed (e.g., Fig. 8B). The priming effect therefore does not depend on DA. Furthermore, since priming apparently occurs when the rewarding effect is blocked, priming is not dependent on the rewarding effect of brain stimulation.

Edmonds and Gallistel [8] have reported that α-methyl-p-tyrosine, which depletes both NA and DA, reduced brain stimulation reward at some hypothalamic sites but not at others. In the present data no relationship was found between the site of brain stimulation in LH or VT and the effect of clonidine or pimozide. The data do not suggest whether the difference in results was due to the particular drugs used or the particular sites of stimulation tested but the

latter alternative is likely since the neurochemical substrate of self-stimulation varies within the MFB [31]. However, it should be noted that the effects of clonidine do not vary with self-stimulation site [17].

Implications for Theories of Brain Stimulation Reward

These results confirm that both NA and DA activity contribute to the rewarding effect of brain stimulation [17] but in the light of other recent findings it may be argued that they play different roles.

It has been shown that DA systems are essential for self-stimulation [3,11] and that reward is produced by direct stimulation of DA receptors with apomorphine [2]. Furthermore, the specific DA antagonist pimozide causes an extinction-like decline in learned responding when the response is rewarded by brain stimulation ([12] this paper), by intravenous amphetamine [33,34], or food [34]. The pattern of this decline in responding resembles that seen when reward is omitted and has been interpreted [12,33] as showing that pimozide blocks the neural substrate of reward. The present results strongly support this interpretation by showing that pimozide reduced the rewarding potency of brain stimulation and that large reductions in rewarding potency led to the extinction-like deficits previously reported. Moreover, these effects were not correlated with signs of motor impairment nor accompanied by loss of the "priming" effects of brain stimulation. The evidence is thus consistent in indicating that DA mechanisms are a component of the putative reward system, or selectively modulate it.

NA seems to be less selectively involved in reward than DA. Though pharmacological blockade of NA frequently abolishes self-stimulation [13, 14, 32] NA appears not to be essential for self-stimulation [3], nor even for self-stimulation of NA-containing sites [5]. In addition, the loss of self-stimulation after NA blockade does not resemble extinction [12]. Nevertheless, in the present experiments depression of NA activity by clondine was found to produce a reduction of the rewarding potency of brain stimulation. This contradiction might be resolved by considering the general actions of NA. Endogenous and exogenous NA in the brain greatly increase cerebral blood flow and metabolism [21,22]. Self-stimulation is known to be accompanied by high levels of NA release [1,25] so that, during self-stimulation, the neural substrate of brain stimulation reward will normally be in a state of high metabolic activity. An acute reduction of NA release (e.g., by clonidine) would be expected to reduce brain blood flow, depress metabolism, and thus possibly reduce the sensitivity of the reward substrate to brain stimulation. The net result would be a diminution of the specifically rewarding effect of brain stimulation trains brought about by an indirect, non-specific means. Similar considerations might also suggest why NA seems to be involved in a number of processes including feeding [15], the sleep-waking cycles [20], and memory [16,27] but is not essential for any of them [4, 19, 24]

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