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Noradrenaline, Dopamine, and Brain-stimulation Reward[1]

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ROLLS, E. T., P. H. KELLY AND S. G. SHAW. *Noradrenaline, dopamine, and brain-stimulation reward.* PHARMAC. BIOCHEM. BEHAV. **2**(6) 735–740, 1974. – Attenuation of self-stimulation produced by blockade of noradrenaline receptors (phentolamine) or inhibition of noradrenaline synthesis (disulfiram) was associated with sedation (defined by decreased locomotor activity and decreased rearing) in rats. Attenuation of self-stimulation produced by blockade of dopamine receptors was associated with only minor sedation. Thus when both arousal and self-stimulation are measured, it is found that noradrenaline is less specifically involved in self-stimulation than dopamine. The noradrenergic theory of reward cannot be accepted until it is shown that noradrenaline has an effect on reward aspects of self-stimulation independently of its general effects on behavior measured here by locomotor activity and rearing.

Noradrenaline Dopamine Self-stimulation Reward Arousal

IT has been suggested that the release of noradrenaline from noradrenaline-containing neurons mediates brain-stimulation reward (see [25, 26, 37–44]). Much of the evidence for this 'noradrenergic theory of reward' is, we believe, weak in two respects (see also [31,32]). First, many of the treatments used to support the theory are pharmacologically non-specific, and affect catecholamines apart from noradrenaline, for example dopamine. For example, the treatments such as amphetamine, methamphetamine, and α-methyl-m-tyrosine or tetrabenazine after monoamine oxidase inhibition which release noradrenaline from nerve terminals and facilitate self-stimulation [25, 37–40] also release dopamine [1, 6–8, 19, 22, 46].

Similarly the treatments which attenuate self-stimulation [1, 7, 11, 12, 26, 37–40] such as α-methyl-p-tyrosine, reserpine and tetrabenazine which reduce brain concentrations of noradrenaline, and haloperidol and chlorpromazine which block noradrenaline receptors also reduce brain concentrations of dopamine [7, 22, 24, 35, 47] and block dopamine receptors [2]. Further, 6-hydroxydopamine attenuates self-stimulation [41,44] but in the doses used reduces brain concentrations of both noradrenaline and dopamine [4, 5, 45]. Thus these treatments provide only poor evidence that one particular catecholamine, noradrenaline, is involved in brain-stimulation reward. Second, many of the treatments used to support the noradrenergic theory of reward are behaviorally non-specific, and affect behavior apart from brain-stimulation reward, for example arousal. For example, amphetamine increases, and α-methyl-p-tyrosine decreases, both self-stimulation rate and arousal measured by stimulus-bound locomotor activity comparably [15]. The decrease in self-stimulation rate which occurs with α-methyl-p-tyrosine could be due to sedation, and much more evidence is required to show that the release of noradrenaline mediates reward, and does not affect self-stimulation only by behavioral side effects.

There have been few studies of the effects on brain-stimulation reward of treatments which alter the activity in specific catecholaminergic systems. One agent, disulfiram, which depletes the brain of noradrenaline (NA) but not of dopamine (DA) by inhibiting the enzyme dopamine β-hydroxylase [13,21] can abolish self-stimulation [27,48] but also produces some sedation.

Two main points therefore require further investigation. The first is whether it is noradrenaline or dopamine which is involved in self-stimulation. The second is whether the release of noradrenaline (see also [43]) (or dopamine) mediates reward produced by brain stimulation as opposed to affecting self-stimulation rate by an indirect effect on, for example, arousal. The experimental design we chose to investigate these points was to compare the effects on both self-stimulation and arousal of interference with noradrenaline or dopamine. In Experiment 1 we measured the effects of disulfiram (which decreases the synthesis of NA but not DA), phentolamine (which blocks receptors sensitive to NA but not DA receptors – [23]) and spiroperidol (which blocks DA but not NA receptors – [2]) on self-stimulation rate and two measures of sedation. The level of sedation was measured by spontaneous locomotor activity (for details see [33]) and by spontaneous rearing, a good measure of arousal/sedation [3].

EXPERIMENT 1

Method

Spontaneous locomotor activity was measured in a cage 27 × 27 × 27 cm [32]. The cage had a false floor

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supported on four microswitches, which depressed if a rat stood over the switch. Four counts were produced if the rat walked once round the cage. Sometimes the rats reared (lifted both forepaws high off the ground), and this was counted.

Eight male rats (3 albino Wistar and 5 hooded Lister) were tested while each of the drugs was active, or after a placebo. A test consisted of a 5 min measurement of spontaneous locomotor activity and rearing followed by a 10 min test of lateral hypothalamic self-stimulation rate [31].

The level-head co-ordinates for the lateral hypothalamus were 3.0 mm behind bregma, 1.5 mm lateral to the midline, and 7.6 mm beneath the dura. Examples of the self-stimulation sites determined with the aid of frozen 25 μ thionin-stained sections are shown in Fig. 1. The electrodes were 00 size stainless steel insect pins insulated except for 0.2 mm at the tip. All drugs were injected intraperitoneally (i.p.). Disulfiram (200 mg/kg) was injected as a suspension in 2 ml of 1% methyl cellulose 2 hr before testing. Phentolamine mesylate (10 mg/kg), dissolved in M/100 tartaric acid, was injected 40 min before testing. Spiroperidol (Janssen) (0.1 mg/kg) dissolved in M/100 tartaric acid was injected 2 hr before testing. Pilot experiments had shown no differences between the three possible placebo treatments, and therefore only one placebo, M/100 tartaric acid injected 2 hr before testing, was included in the experiment. Except for the disulfiram the injection volume was 2 ml/kg. The animals were divided randomly into 4 groups of 2. Every animal was tested 4 times, once after each of the 4 treatments. Tests were separated by at least 48 hr. An animal was always tested at the same time each testing day. The order of the treatments was balanced between the groups. After injection the animal was replaced in its home cage until required for the 5 min locomotor activity and rearing test. Then the animals were induced to self-stimulate by priming and, if necessary, by placing the animal on the lever. The first 3 min of the 10 min self-stimulation test were considered as a warm-up period and were not included in the computation of self-stimulation rate.

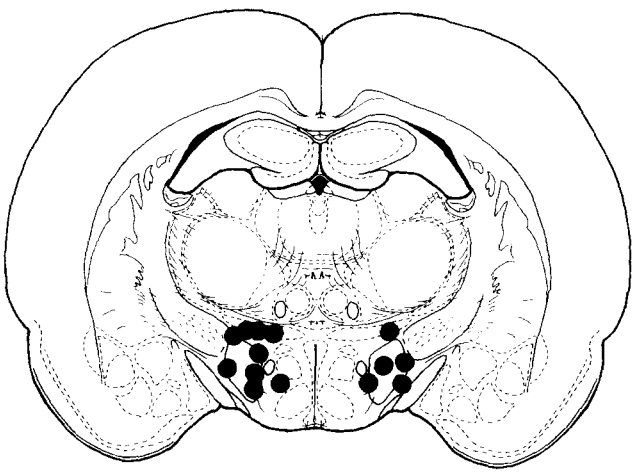

FIG. 1. Examples of the lateral hypothalamic self-stimulation sites used in this study.

Results

The bar histograms in Fig. 2 show that when disulfiram or phentolamine produced a modest reduction in self-stimulation rate (from 70 to about 42 bar-presses/min), the animals were very drowsy, as measured by the decrease in rearing and the decrease in locomotor activity. The animals also looked drowsy. Therefore inhibition of the synthesis of NA (disulfiram treatment) or blockade of noradrenaline receptors (phentolamine treatment) does reduce self-stimulation rate, but at the same time produces drowsiness. It is also shown in Fig. 1 that treatment with spiroperidol reduced self-stimulation rate from 70 to 10 bar-presses/min, and left rearing and locomotor activity relatively high (compared to disulfiram and phentolamine). Therefore a pharmacological treatment, spiroperidol, can be found which appears to attenuate reward aspects of self-stimulation more specifically with respect to arousal than disulfiram and phentolamine.

Discussion

It can be concluded that the effects of interference with noradrenaline (disulfiram and phentolamine treatments) on brain-stimulation reward are relatively non-specific since a large effect on arousal relative to the effect on self-stimulation is produced.

The disulfiram and phentolamine treatments probably act here through an effect of noradrenaline on the brain because these effects of disulfiram can be reversed with intraventricular injections of noradrenaline [48]; intraventricular infusions of noradrenaline in the normal rat produce arousal [11] and intracranial injections of 20 μg of phentolamine in the normal rat produce sedation (personal observations).

EXPERIMENT 2

Because the results of Experiment 1 indicate that the roles of noradrenaline and dopamine in brain-stimulation reward must be reconsidered, the results were extended in Experiment 2 by performing dose-response curves of the effects of disulfiram and spiroperidol on locomotor activity and self-stimulation rate. New groups of rats were used in this experiment, but the apparatus and general procedure were as in Experiment 1.

Method

Each rat was tested for both locomotor activity and lateral hypothalamic self-stimulation after an i.p. injection of disulfiram, spiroperidol, or placebo. A number of rats were tested at more than one drug dose. The rate of self-stimulation or amount of locomotor activity of each rat was measured as in Experiment 1 and expressed as a percentage of the group mean under the placebo condition.

Results

It was found that treatment with disulfiram produced a greater reduction of locomotor activity than of self-stimulation at all drug doses (Fig. 3). In contrast, spiroperidol produced a greater reduction of self-stimulation than of locomotor activity at all drug doses (Fig. 3). This confirms the results of Experiment 1: when compared to spiroperidol, treatment with disulfiram decreases arousal more than self-stimulation rate.

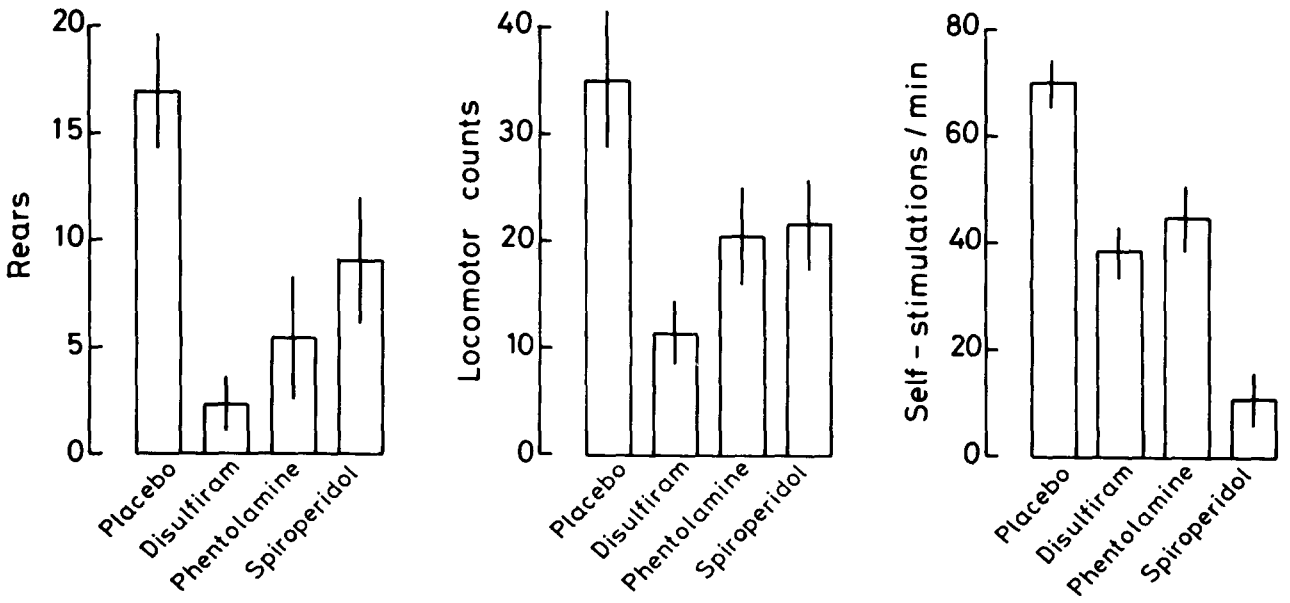

FIG. 2. The effects of spiroperidol (0.1 mg/kg), disulfiram (200 mg/kg), and phentolamine (100 mg/kg) on rearing, locomotion and self-stimulation in eight rats. The histograms represent the means ± S.E. Associated with a partial attenuation of self-stimulation, disulfiram and phentolamine produce sedation. In contrast, spiroperidol attenuates self-stimulation much more than arousal. Relative to the placebo, the effects of disulfiram and phentolamine on rearing, of disulfiram on locomotor activity, and of spiroperidol on self-stimulation, are significant at the 0.01 level. Relative to the placebo, the other effects are significant at approximately the 0.05 level (Mann-Whitney U-test).

Further evidence that the attenuation of self-stimulation produced by disulfiram is relatively non-specific follows from an additional observation. Even at a dose of 200 mg/kg disulfiram did not produce a large attenuation of self-stimulation. A larger attenuation of self-stimulation after two hours was found using the procedure [48] of allowing the animals to self-stimulate continuously following the drug injection (see Fig. 3). This greater attenuation of self-stimulation was accompanied by a greater depression of locomotor activity, in line with the conclusions from the main part of this experiment (Fig. 3). That this degree of attenuation of self-stimulation by disulfiram is not a specific effect on brain-stimulation reward follows from the finding that 4 of the 8 rats on this condition died as a result of the procedure.

DISCUSSION

When the functions of noradrenaline and dopamine in self-stimulation are considered in the light of these experiments in which both self-stimulation and arousal were measured, two main conclusions follow. First, treatments which affect noradrenaline and attenuate self-stimulation produce general effects on behavior. These general effects were measured in this study by decreased locomotor activity and rearing, and are referred to here as sedation, or decreased arousal. The animals certainly looked sedated. The sedation produced by disulfiram is relatively great in that another agent (spiroperidol) which attenuates self-stimulation produces much less sedation. These findings show that alterations of noradrenaline affect many types of behavior including self-stimulation. It cannot be concluded that the release of noradrenaline mediates reward until it is shown that the effect of altered noradrenergic activity on self-stimulation is a direct effect on reward, and is not mediated by an indirect effect. For example, it has to be excluded that the drowsiness produced by disulfiram does not account for the effect of disulfiram on self-stimulation. It is not enough to state that barbiturates do not always decrease self-stimulation rate (Wise and Stein [48]), because these drugs affect many types of behavior, e.g., frustrative non-reward [14], have some stimulant properties [18], and may facilitate or depress self-stimulation [20]. Such observations do not remove the necessity for performing adequate behavioral controls when a specific effect of a drug on reward is claimed [48]. It can be noted that arousal probably normally does affect self-stimulation rate [20, 27, 28, 32]. Because manipulations of noradrenaline affect arousal, the noradrenergic theory of reward [37–44, 48] cannot be accepted until controls for this (and other) side-effects have been performed. If it can be shown that noradrenaline affects reward independently of its effects on other types of behavior such as locomotor activity, then the noradrenergic theory of reward can be accepted.

The second main conclusion is that the blockade of dopamine receptors attenuates self-stimulation relatively specifically with respect to arousal. (The experimental design allows the conclusion that the relatively small degree of sedation produced by spiroperidol does not account for the attenuation of self-stimulation, in that a similar degree of sedation following disulfiram produced only a minor attenuation of self-stimulation – see Fig. 3.) Whether or not the attenuation of self-stimulation produced by

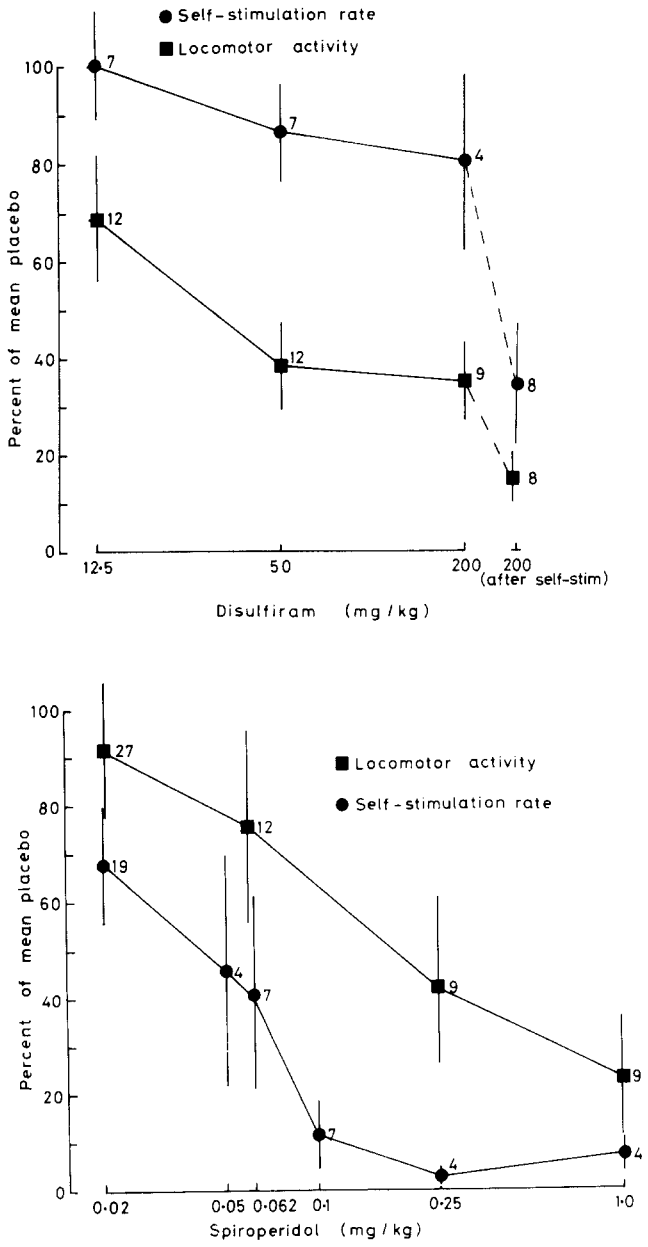

FIG. 3. Dose-response curves of the effects of disulfiram (upper) and spiroperidol (lower) on self-stimulation rate and locomotor activity. Disulfiram attenuates locomotor activity more than self-stimulation rate. In contrast, spiroperidol attenuates self-stimulation rate more than locomotor activity. Each point represents the mean ± S.E. The number of rats is indicated beside each point. On the disulfiram dose-response curve the 200 mg/kg (after self-stimulation) condition refers to 8 rats allowed to self-stimulate continuously and tested 2 hr after the disulfiram injection on both locomotor activity and self-stimulation.

dopamine-receptor blockade is due to a blockade of transmission in reward pathways remains to be shown. It has been shown that the degree of motor impairment produced by doses of spiroperidol which attenuate self-stimulation is small, and that the treated rats are still able to perform the motor response of bar-pressing rapidly [16,34]. Nevertheless the possibility that a motor impairment accounts for the effects of spiroperidol on self-stimulation cannot be excluded [34].

There is other evidence that dopamine is involved in

self-stimulation of at least some sites. Crow *et al.* [10] obtained self-stimulation when electrodes were near the dopamine-containing cell bodies (especially the Group A 10) in the ventral mesencephalon. The dopamine-receptor blocking agent pimozide attenuates MFB self-stimulation [17,46]. We [16,34] have shown that self-stimulation of many different sites (the septal area, nucleus accumbens, anterior hypothalamus and midbrain tegmentum) is attenuated by spiroperidol. It should be noted that the lateral hypothalamic self-stimulation sites used in this study are near axons of noradrenergic and of dopaminergic neurons.

There have been extrapolations from the noradrenergic theory of reward to abnormal human emotional behavior [37–41, 44]. Given the evidence above that the noradrenergic theory of reward is far from proven, any extrapolation to the etiology of schizophrenia or depression [37–41, 44] must be considered to be very tentative.

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