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A Reward-Reduction Model of Depression Using Self Stimulating Rats: An Appraisal

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BINKS, S. M., J. K. MURCHIE AND D. T. GREENWOOD. *A reward-reduction model of depression using self stimulating rats: An appraisal.* PHARMAC. BIOCHEM. BEHAV. 10(3) 441–443, 1979.—A potential model of depression using a "reward reduction" technique with intracranial self-stimulation (ICSS) has been suggested. A number of rats with electrodes chronically implanted in the medial forebrain bundle were trained on this paradigm. The model involved the use of progressively increasing fixed ratio (IFR) schedules. Two tricyclic antidepressants, imipramine and protriptyline, were administered. Neither of these drugs resulted in the response enhancement which had been predicted. Only d-amphetamine (0.5 mg/kg) produced the predicted "antidepressant" action. It was concluded that response instability made this test difficult to operate and that even animals with adequately stable baselines did not produce a response pattern which could be categorised as specifically antidepressant.

Increasing FR Self-stimulation Depression Imipramine Protriptyline Amphetamine

THE IMPORTANCE of the catecholamines in the mediation of self-stimulation (ICSS) has been well established over many years [1–5]. There is conflicting evidence concerning the relative importance of dopamine and noradrenaline in this behaviour but this has to some extent been rationalized by Herberg *et al.* [4] who have developed a theory of the different but equally important role of both catecholamines in ICSS. In general, agents which enhance the effects of catecholamines tend to increase ICSS responding while those which impair catecholamine (CA) actions depress ICSS response rates. This broad relationship, however, holds true only where the contingency between the animal's response and neural transmission is maintained. Thus amphetamine, the releasing action of which is impulse-dependent, increases response rates [5] while tyramine and tetrabenazine, which destroy the contingency between response and neural impulse by a general release of amine, disrupt behaviour and decrease ICSS responding [2].

In view of the marked correlation between the functional availability of catecholamines and ICSS, the actions of tricyclic antidepressants appears anomalous. These drugs inhibit reuptake of released catecholamine and, clinically, exhibit a mood-elevating effect. Stein [6] suggests that the CA deficit in depressed patients occurs along the same CA pathways which mediate ICSS. The CA theory of ICSS should therefore predict that such drugs enhance ICSS. This is not the case. While there is some variability of response, the most commonly reported finding is a decreased rate of responding and a raised threshold of reward [7]. Only a limited amount of work has been done in an attempt to find a paradigm in which tricyclic antidepressants will potentiate ICSS responding. One such model has been suggested by Wauquier [8] who reported that, in a situation involving progressive fixed ratio schedules (i.e. where reinforcement required more and more effort), antidepressants enhanced responding which otherwise dropped gradually to zero. We were interested in the potential value of such a model and attempted to replicate Wauquier's work.

METHOD

A group of male rats (300 g) was implanted with bipolar electrodes in the medial forebrain bundle of the lateral hypothalamus (co-ordinates with incisor bar on same level as the intra-aural line were, Bregma −3 mm; lateral 1.5 mm with electrode precut to a length of 8.5 mm). The rats were trained to self-stimulate in a single lever Skinner box and then introduced to the progressive increasing fixed ratio schedule (IFR). In this study a pre-requisite for drug administration was two consecutive days of stable response baselines. Saline was administered on all non drug days and all administrations were by sub-cutaneous injection in a volume of 0.2 mls.

The basic procedure was that outlined by Wauquier (personal communication). The fixed ratio was increased every two minutes up to a maximum of 9 responses for every reinforcement. The final two minutes of each session was continuous reinforcement (CRF. 1:1) and the animals were given one priming stimulation at the commencement of this to revive responding. Thus, each session lasted 20 min and there were three consecutive sessions per day. High control variability in this test made interpretation difficult. Several

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modifications were therefore introduced. The fixed ratio was increased at three minute intervals up to a maximum of 9 responses for every reinforcement. The first and final three minutes were of continuous reinforcement (1:1 CRF) with the animals receiving a single priming stimulation at the commencement of the final CRF period to revive responding. An additional 3 min of CRF was introduced at the start of the experiment to allow acclimatisation before the experiment began. All drugs were administered 15 min prior to the start of the experiment.

RESULTS

In Wauquier's original experiments, [8] baseline responses were established in which ICSS increased up to FR3:1 then decreased to FR5:1 and eventually dropped to zero. The preliminary results from that work had indicated that animals treated with antidepressants responded for higher FRs than during control sessions.

The results from the present experiments are represented in Figs. 1–5. Imipramine at 3 mg/kg (Fig. 1) produced an overall depression of response of 8%. A similar response pattern was achieved at 10 mg/kg, where the average depression was 3–4% (Fig. 2). The results for imipramine 30 mg/kg (Fig. 3) show a much larger depression giving an overall decrement of 20%. The overall depression produced by protriptyline 10 mg/kg, (Fig. 4) was much greater than those seen with imipramine, giving an overall depression of 46.5%. The amphetamine response (Fig. 5) produced an enhancement especially evident at the higher ratios.

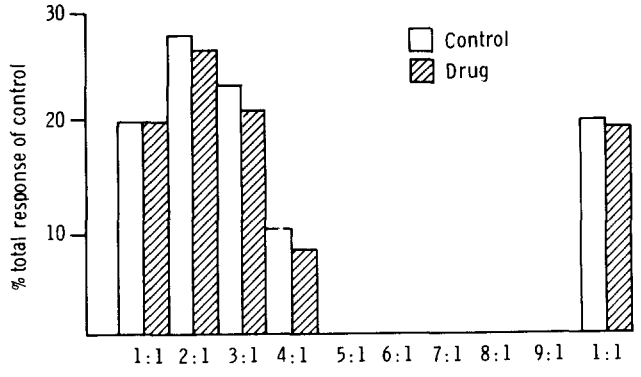

FIG. 1. Imipramine 3 mg/kg SC, 15′ pretreatment.

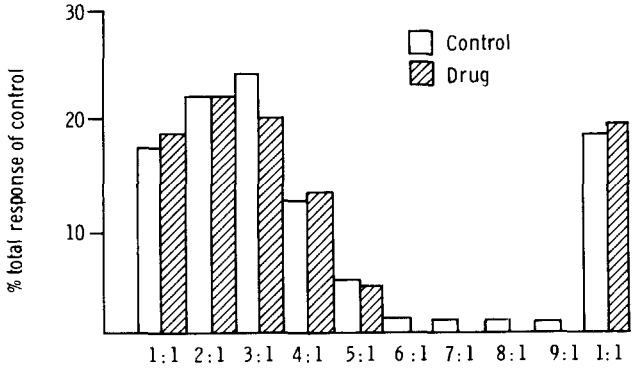

FIG. 2. Imipramine 10 mg/kg SC, 15′ pretreatment (pooled data).

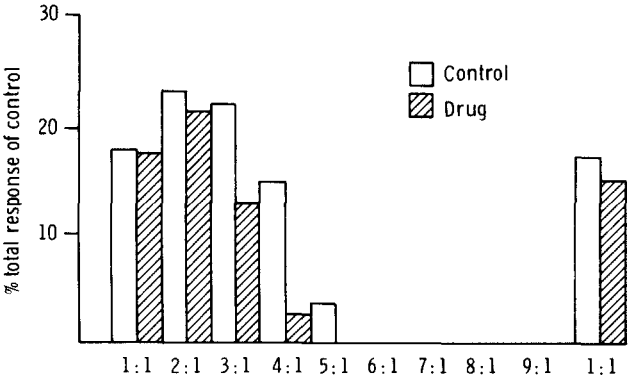

FIG. 3. Imipramine 30 mg/kg SC, 15′ pretreatment.

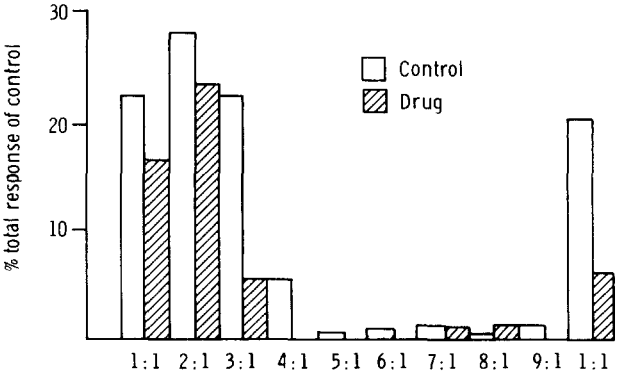

FIG. 4. Protriptyline 10 mg/kg SC, 15′ pretreatment (pooled data).

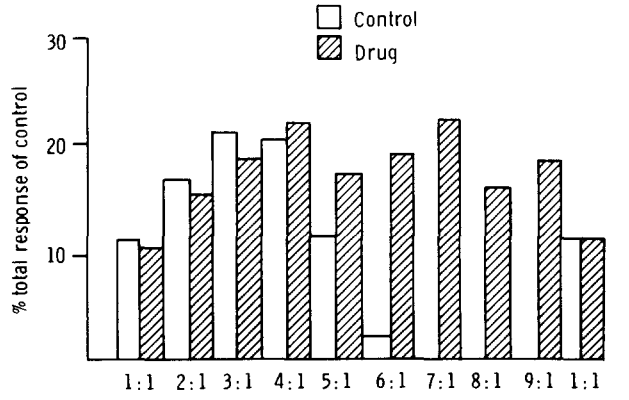

FIG. 5. Amphetamine 0.5 mg/kg SC.

DISCUSSION

Although this paradigm has been modified from Wauquier's original model, there is evidently no response-enhancement, such as that noted by Wauquier, with the tricyclics used. The basic differences are in the length of each fixed ratio period, increasing Wauquier's 2 mins to 3 mins and reducing the number of daily runs from 3 consecutive 20 mins (1 hr) to a single 30 min period which helped in stabilising basal responses.

Imipramine was used as a typical tricyclic antidepressant, the actions of which have been frequently studied on ICSS. Protriptyline was chosen because of the lack of effect of imipramine in producing the predicted increased response pattern. Protriptyline has certain activating as well as mood-elevating effects in the clinic and might have been expected to exhibit a more pronounced enhancement of response than tricyclics lacking this quality (e.g. imipramine). The results from the two animals studied did not support this hypothesis. Since protriptyline produced a response deficit more pronounced than even the highest dose of imipramine, additional work to produce a dose-response would be unlikely to show the response enhancement effect that was being sought.

d-Amphetamine was employed to show that it was possible to produce response enhancement on such an ICSS paradigm. The effect was very pronounced and unlike any other response pattern obtained in any animal with or without drugs. The single result was therefore useful in a qualitative rather than quantitative respect, the drug being employed as a tool rather than as a control.

In conclusion, it is apparent that there has been no response-enhancement produced by a tricyclic antidepressant, but that it is nevertheless possible to produce such an effect on such an ICSS model. It is appreciated that numerous modifications to the basic IFR paradigm could be made. However, in the light of our experience and Wauquier's [8], the variability of control basal response patterns is very great, despite a variety of modifications. It would appear that even had this model proved capable of specific drug sensitivity then control instability would make it difficult to implement as a specific screening test.

REFERENCES

1. Crow, T. J. The relationship between electrical self-stimulation sites and catecholamine containing neurones in rat mesencephalon. *Experientia* **27**: 662, 1971.
2. Franklin, K. B. J. and L. J. Herberg. Non-contingent displacement of catecholamines by intraventicular tyramine. Biphasic dose/response effects on self-stimulation. *Neuropharmacology* **16**: 53–55, 1977.
3. German, D. C. and D. M. Bowden. Catecholamine systems as the neural substrate for intracranial self-stimulation: A hypothesis. *Brain Res.* **73**: 381–419, 1974.
4. Herberg, L. J., D. N. Stephens and K. B. J. Franklin. Catecholamines and self-stimulation: Evidence suggested a reinforcing role for noradrenaline and a motivating role for dopamine. *Pharmac. Biochem. Behav.* **4**: 575–582, 1976.
5. Stein, L. Chemistry of purposive behaviour. In: *Reinforcement and Behaviour Chap. 11*, edited by J. T. Tapp. New York: Academic Press, 1968.
6. Stein, L. Psychopharmacological substrates of mental depression. In: *Proc. 1st Int. Symp. on Antidepressant Drugs*, edited by Garattini and Dukes. Amsterdam London: Excerpta Medica, 1967.
7. Stein, L. Effects and interactions of Imipramine, Chlorpromazine, Reserpine and Amphetamine on Self-Stimulation: Possible Neurophysiological Basis of Depression. In: *Recent Advances in Biological Psychiatry Vol. IV*, edited by J. Wortis. New York: Plenum Press, 1962.
8. Wauquier, A. *Brain Stimulation Reward*. New York, North Holland: American Elsevier, 1976, pp. 123–171.