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Chronic *l*-Dopa Fails to Lessen Rebound Enhancement of Self-Stimulation After Chronic Haloperidol[1]

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ROSE, I. C., M. MINTZ AND L. J. HERBERG. *Chronic l-dopa fails to lessen rebound enhancement of self-stimulation after chronic haloperidol.* PHARMACOL BIOCHEM BEHAV **30**(3) 585–588, 1988.—Chronic treatment with haloperidol (approximately 4.8 mg/rat/day PO for 18 days) severely impaired variable-interval hypothalamic self-stimulation. Cessation of treatment was followed by a strong rebound increase in response rates at submaximal currents, to well above pretreatment rates. The rebound increase in responding was not prevented (and at submaximal currents was actually enhanced) by treatment with *l*-dopa plus benserazide (respectively 240 and 60 mg/kg/day PO) for 6 days after withdrawal of haloperidol. This result is at variance with previously reported findings.

Benserazide Dopamine *l*-Dopa Haloperidol Neuroleptic Rat Reverse tolerance Self-stimulation Supersensitivity

BLOCKADE of dopamine (DA) receptors by neuroleptic drugs leads to an increase in receptor number [2,17] and consequently to supersensitivity to DA-receptor ligands. This becomes manifest as enhanced DA-mediated behavior if neuroleptics are discontinued [27,31] or if treatment is continued for many months [4]. Clinical manifestations of supersensitivity to DA may thus become a serious unwanted side-effect of treatment [15].

The factors affecting the duration and intensity of receptor supersensitivity, and the possibility of reversing it pharmacologically, are still under debate. Friedhoff and Alpert [7] have suggested that supersensitivity may be reversed by pharmacological means, by exposing the receptor to supranormal levels of agonist. Numerous investigators have indeed shown that increased activity and binding of DA by supersensitive preparations can be reversed experimentally by treatment with *l*-dopa, the precursor of DA, or with other DA agonists [3, 8, 10, 14, 20]. Such findings may have important implications for the clinical management of neuroleptic-induced dyskinesias [7] to the extent that these symptoms may be worsened by supersensitivity to DA [15]. However, it has also been known for some time that repeated administration of DA agonists can induce behavioral sensitisation to the agonists concerned (see Robinson and Becker [22] for review); there is thus a risk that treatment with DA agonists may successfully down-regulate receptor sensitivity, but may nevertheless have the opposite effect on DA-dependent behavior overall. Treatment with DA agonists might then prove counterproductive in the management of neuroleptic-induced dyskinesias.

Self-stimulation performance offers a convenient method for tracking and quantifying drug-induced changes in DA-dependent behavior in experimental animals [9,30]. Several investigators have shown that suppression of self-stimulation by treatment with neuroleptics is followed by a rebound enhancement of responding above pretreatment rates, persisting for several weeks after drug withdrawal [5, 21, 25]. A further finding of particular interest, by Seeger and colleagues [26], was that the rebound enhancement of self-stimulation could be partly reversed by a 7-day course of treatment with *l*-dopa; i.e., there was no sensitisation to DA-stimulant effects as seen in other investigations involving repeated administration of DA agonists (e.g., [1, 11, 12, 17, 22]). Unfortunately, the study by Seeger *et al.* [26] did not specify the selected intensities of the rewarding stimuli relative to the threshold or maximal level of responding. This is a crucial parameter, since high doses of DA-stimulants, and supra-optimal levels of dopaminergic activity, in rats that are already responding at maximal or near-maximal rates, may lead to *reduced* lever-pressing rates for brain-stimulation reinforcement [29,33], and it is thus uncertain whether the moderating effect of *l*-dopa observed by Seeger *et al.* [26] represented a decrease, or an increase, in DA neurotransmission. The present study sought to reexamine this question, but failed to replicate the reported reversal of supersensitivity by *l*-dopa.

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METHOD

Subjects

Male Lister hooded rats (Bantin and Kingman Ltd.) weighing 250–300 g at the time of surgery were housed in groups of 5 or 6 and allowed free access to food and water. Animals were anaesthetised with sodium pentobarbital (65 mg/kg IP) and atropine methylnitrate (0.25 mg/kg SC) and implanted with 0.25-mm diameter twisted bipolar stainless steel electrodes (Plastic Products Co.) aimed at the midlateral hypothalamus according to coordinates A6.2, L1.2, V7.8 of Paxinos and Watson [19].

Self-Stimulation

On recovery from surgery, rats were trained to operate a lever for a 0.5-sec 50-Hz sinewave constant-current stimulus available at randomly varied intervals of 10-sec mean duration in 1-hr daily sesssions; this reinforcement schedule (VI 10 sec) elicits a steady, relatively seizure-free rate of responding, on which stimulant or depressant effects can be imposed without appreciably affecting the rate at which stimuli are received. Current intensities were adjusted by successive approximations in 1-decilog steps to the lowest ('threshold') intensity that would support uninterrupted responding. When response rates were stable over 1-hr sessions, a 30-min pretreatment baseline rate was recorded at threshold current. The current was then switched off for 10–15 min to allow responding to extinguish. The current intensity was then adjusted to a value 6 decilog steps below threshold, and responding was recorded in a series of 13 5-min bouts, for which the current was progressively incremented in 1-decilog steps. A few priming stimuli were given at the start of each bout if the rat was not already responding.

Drugs

Haloperidol (Sigma) for oral administration was dissolved in a minimum volume of 1-M tartaric acid (BP) and diluted to a final concentration of 200 mg/l in tap-water sweetened with glucose BP (1.0 g/l) and sodium saccharine (75 mg/l). The mixture was continuously available in plastic bottles protected from light by an opaque wrap. Freshly prepared solutions were renewed at 24-hr intervals. Each rat was allowed approximately 24 ml/day, equivalent to an oral dose of haloperidol of 4.8 mg/rat/24 hr.

Levodopa and benserazide hydrochloride in proportions of 4:1 by weight were obtained from pharmaceutical capsules (Madopar 250, Roche) and suspended in tap-water in a concentration of 150 mg/ml. Suspensions were prepared immediately before use and administered twice daily by oral gavage in a volume of 1 ml/kg, equivalent to 240 mg/kg/day *l*-dopa and 60 mg/kg/day benserazide. Control rats received equivalent volumes of water by the same route.

Procedure

Rats were each given a pretreatment self-stimulation test, and allotted randomly to four groups. Groups H-D (n=6) and H-W (n=6) were treated with haloperidol tartrate in their drinking water for 21 days. Groups W-W (n=5) and W-D (n=6) were allowed plain tap-water during the same period. Self-stimulation was retested on the 18th day of treatment in all groups. Groups H-D and W-D were then given six daily doses of *l*-dopa/benserazide, Groups H-W and W-W were treated similarly with water, and self-stimulation tests were again repeated 3 days after the last treatment. Response rates at each current intensity for each rat were expressed as a percentage of the pretreatment rate recorded in the baseline session at threshold current. Scores were subjected to analysis of variance comprising the factors Group (4) × Session (3) × Current intensity (11).

RESULTS

Rats in Groups H-D and H-W experienced a 6% fall in mean body weight (from 343 to 324 g) while being treated with haloperidol, and showed an obvious reduction in spontaneous activity in their home cages. Pretreatment self-stimulation tests yielded a characteristic sigmoidal rate-intensity function (Fig. 1). Treatment with haloperidol produced a rise in self-stimulation threshold, together with a profound depression of performance at all current intensities, including the highest (asymptotic) intensities (see Fig. 1A and 1B, day 18). The fall in response rates with haloperidol differed significantly from the unchanged responding of the untreated groups (W-W and W-D) (Group × Session (1st vs. 2nd) interaction, $F(3,19)=14.7$, $p<0.0001$).

By the 9th day after withdrawal of haloperidol the depression of self-stimulation in Groups H-D and H-W (Fig. 1A and 1B, Day 18) had been more than reversed (Fig. 1A and 1B, Day 27 vs. Day 0) [Group × Session (3rd vs. 1st) interaction $F(3,19)=3.8$, $p<0.03$]. In Group H-W (Fig. 1B), increases above pretreatment levels occurred particularly at mid-range (nonasymptotic) current intensities (Session × Current-intensity interaction $F(10,50)=2.5$, $p<0.02$), the rate-intensity function thus showing a parallel shift to the left. In Group H-D, response rates again rose well above pretreatment levels, and over a wide range of intensities (Fig. 1A, Day 27 vs. Day 0) [Sessions effect $F(1,5)=8.7$, $p<0.03$]. Thus supersensitivity was not lessened by intervening treatment with *l*-dopa. Control rats treated solely with vehicle (Group W-W) or with *l*-dopa (Group W-D) showed unchanged responding throughout the 4-week period (Fig. 1C and 1D).

DISCUSSION

Low to moderate doses of neuroleptics given acutely depress self-stimulation performance without producing obvious signs of extrapyramidal or nonspecific motor impairment (see Liebman [13] for review). This is reflected by a 'parallel' shift to the right in the rate-intensity function, the maximal (asymptotic) rate of responding being unchanged [5,16]. In the present study, however, response rates after 18 days on haloperidol were depressed both at near-threshold and at maximal current intensities, suggesting that the daily dose of haloperidol was sufficiently large not only to affect mesolimbic motivational mechanisms, but also to act on motor mechanisms affecting physical performance [5,16].

Depressant effects had disappeared completely by the ninth day after stopping the haloperidol. Both haloperidol-treated groups by this stage showed a strong shift to the left relative to pretreatment scores, consistent with a heightened motivational response to brain-stimulation reward [5,16]. On the other hand, maximal rates of responding, which had been clearly depressed during treatment (presumably reflecting extrapyramidal motor impairment), reverted almost exactly to pretreatment levels (Group H-W, Fig. 1B, right-hand side), or to barely above pretreatment levels (Group H-D,

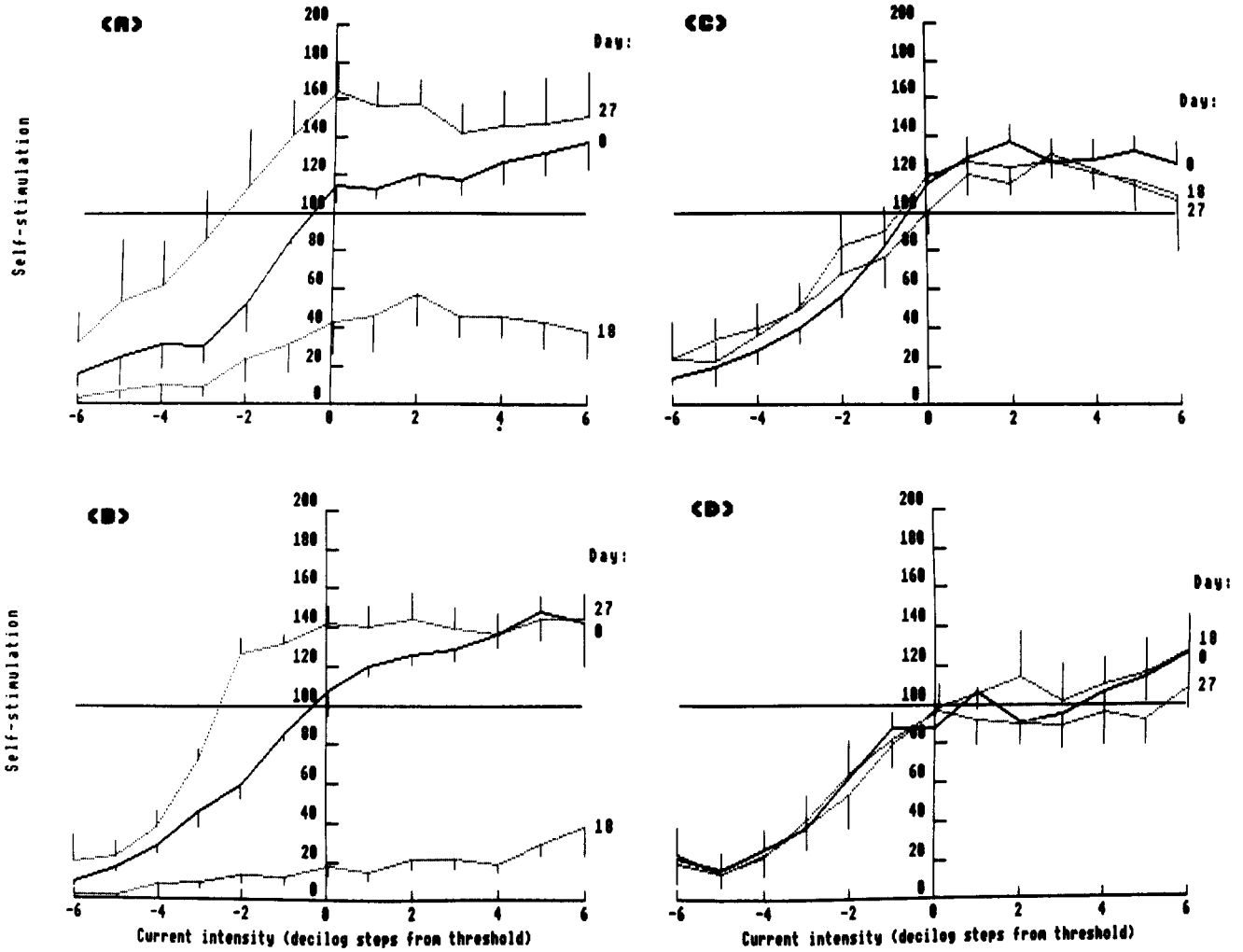

FIG. 1. Rate-intensity curves for self-stimulation responding of four groups of rats. Response rates are expressed as a percentage of each rat's rate of responding in a 30-min session at threshold current before the commencement of drug treatment. Vertical bars are standard errors. (A) *Group H-D.* Rats treated with haloperidol (ca. 4.8 mg/rat/day PO) for 21 days, followed by *l*-dopa for 6 days; self-stimulation tests were carried out on Day 0 (prehaloperidol), Day 18 (during haloperidol) and Day 27 (9 days after withdrawal from haloperidol, and 3 days after withdrawal from *l*-dopa). (B) *Group H-W.* Rats treated with haloperidol for 21 days, followed by water for 6 days; self-stimulation tests were carried out as in Group H-D. (C) *Group W-W.* Rats treated with water for 21 days, followed by water for 6 days; self-stimulation tests were carried out as in Group H-D. (D) *Group W-D.* Rats treated with water for 21 days, followed by *l*-dopa for 6 days; self-stimulation tests were carried out as in Group H-D.

Fig. 1A, right-hand side). This absence of appreciable rebound overshoot at the upper current intensities is consistent with other evidence that 'supranormal' striatal output fails to enhance (learnt) self-stimulation performance, though strongly accentuating simple (unlearnt) locomotor activity [32].

Rebound responding was at least as marked after haloperidol plus *l*-dopa as after haloperidol alone (Fig. 1A vs. Fig. 1B) even though exposure to *l*-dopa is known to down-regulate the supersensitive DA receptor. The effects of down-regulation were evidently overridden by behavioral sensitization, or reverse tolerance, induced by chronic *l*-dopa. 'Reverse tolerance' produced in this way does not appear to depend on an increase in the number [23] or sensitivity [1] of DA receptors, but may be associated with increased availability of releaseable transmitter, coupled with subsensitivity of inhibitory DA autoreceptors [12,17]. Another process that in principle may lead to reverse tolerance depends on learning: after repeated treatments the rat may learn to channel the stereotypy-inducing effects of DA into lever-pressing, or into whatever activity happens to be open to it at the time [24,33]. Studies of this phenomenon have shown, however, that substantial opportunity for learning, while drugged, is essential for the development of reverse tolerance to *d*-amphetamine in locomotor [28] and self-stimulation tests [11]. No opportunities for self-stimulation were given during the period of *l*-dopa administration in the present study, thus learning may not have played an important role in the apparent development of reverse tolerance in the present case.

It is uncertain why Seeger *et al.* [26] obtained the opposite effect to that in the present study, finding that the posthaloperidol rebound was diminished, rather than accentuated, by chronic *l*-dopa. As suggested above, it is possible

that the diminished responding in *l*-dopa-treated rats reflected a supraoptimal, rather than a lesser level of dopaminergic activity. Other important differences in the procedure followed by Seeger and colleagues included smaller daily doses of haloperidol (1.0 mg/kg/day by injection vs. approximately 18 mg/kg/day PO) and of *l*-dopa (100 mg/kg/day by injection vs. 240 mg/kg/day PO); and differing reinforcement schedules (continuous reinforcement (CRF), vs. VI 10 sec). Whatever the explanation for the differing outcome, it seems clear that treatment with *l*-dopa, at least in high doses, cannot be generally relied on to counteract the behavioral effects of DA supersensitivity, in animal models or in clinical practice, and may even have an effect opposite to that intended.

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