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16. The dye WW802, [1,3-dipentylbarbituric acid-(5)]-[1-*p*-sulfophenyl-3-methyl-5-pyrazolone-(4)]-pentamethinoxonol, was our best choice (*12*), yet it is still a poor probe because photodynamic damage and dye bleaching limit the duration of the experiments and make them difficult. However, photodynamic damage was reduced at least 100-fold by removing oxygen from the saline (*11*). We think that by alternately perfusing oxygen-free and oxygen-enriched solutions, much longer experiments, employing signal averaging for better resolution, would be feasible without anoxia.
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19. We are grateful to Y. Kimhi and D. Saya for growing the cells, to W. Ross for his contribution to preliminary experiments, and to B. Salzberg, L. Cohen, and R. Llinas for their critical reading of the manuscript. Supported in part by PHS grant NS14716, a grant from the United States–Israel Binational Science Foundation, and a grant from the Muscular Dystrophy Association.

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Intravenous Self-Administration of Nomifensine in Rats: Implications for Abuse Potential in Humans

Abstract. *Rats acquired and maintained intravenous self-administration of nomifensine, a new antidepressant compound. Additional experiments implicated dopamine-containing neurons in this behavior. These findings, along with the marked pharmacological similarities between nomifensine and such drugs as cocaine and methylphenidate, indicate a potential for nomifensine abuse by humans.*

The tetrahydroisoquinoline nomifensine is a member of a new class of compounds that have significant antidepressant properties in man (*1*). The compound is being used clinically in Europe and is being considered for use in North America. The pharmacological and biochemical properties of nomifensine differ somewhat from the classic tricyclic antidepressants. The compound shares with tricyclic compounds the common property of inhibiting the uptake of norepinephrine into brain nerve endings (synaptosomes), but differs in that it is also a potent inhibitor of dopamine (DA) uptake by synaptosomes obtained from brain regions that are rich in DA (*2, 3*). Furthermore, unlike many tricyclic compounds, nomifensine is a weak inhibitor of synaptosomal uptake of serotonin (*3, 4*).

In rats nomifensine has been found to increase locomotor activity and, at higher doses, to produce stereotyped behavior (*5*). These effects are commonly induced by drugs known to increase the activity of central DA systems and are consistent with the effect of nomifensine on DA uptake (*6, 7*). The fact that 6-hydroxydopamine lesions of the ascending DA systems or reserpine treatment abolishes nomifensine-induced stereotypy confirms that nomifensine is an indirectly acting DA agonist (*8*). Apart from motor stimulation and stereotypy, another universal property of such indirectly acting DA agonists as cocaine, amphetamine, and methylphenidate is that they can be self-administered intravenously by animals (*9*) and have the potential for abuse by humans (*10*). Because the pharmacological profile of nomifensine appears to be very similar to that of cocaine and methylphenidate, we sought to investigate its potential for abuse by determining whether the compound would support self-administration behavior in the rat.

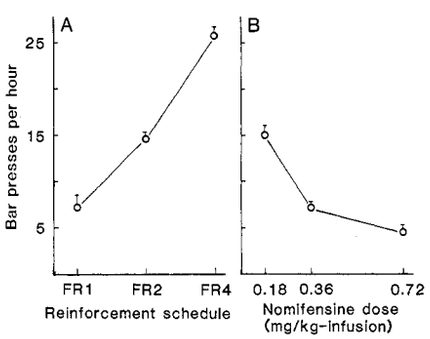

Fig. 1. (A) Number of bar presses per hour to obtain nomifensine (0.36 mg/kg per infusion), as a function of reinforcement schedule. On the FR1 schedule every bar press resulted in an intravenous infusion of nomifensine, whereas on the FR2 and FR4 schedules every second and fourth bar press produced an infusion. (B) Number of bar presses per hour (on an FR1 schedule) to obtain nomifensine, as a function of dose per infusion. Each data point represents the mean ± standard error for seven animals. Six rats with no history of drug self-administration bar-pressed for saline (operant level) at the rate of 0.15 ± 0.01 presses per hour.

Male Wistar rats weighing 300 to 320 g at the time of surgery were implanted with a Silastic jugular catheter under pentobarbital anesthesia (*11*). One or two days later, they were given access for 4 to 6 hours per day to a lever mounted on one wall of the cage. Each depression of the lever produced a 4-second infusion of 0.2 ml of nomifensine hydrochloride (0.6 mg/ml) solution through the catheter. In the first experiment, self-administration of cocaine (1.25 mg/ml) was established (*12*). After 4 to 5 days of stable responding, the animals were transferred to nomifensine to determine whether the compound would cause them to maintain bar pressing. In subsequent experiments, naïve animals were given immediate access to nomifensine to determine whether they would initiate and maintain bar pressing to obtain the drug.

Nomifensine caused maintained self-administration behavior in the animals that had previously acquired the behavior with cocaine reinforcement. More important, nomifensine was effective in causing the initiation and maintenance of bar pressing in the naïve animals. Typically, the rate of bar pressing was somewhat erratic for the first few days and then stabilized within 3 to 5 days. To establish that the animals were responding to maintain a relatively constant blood level of nomifensine, several additional experiments were conducted. First, the schedule of reinforcement was varied so that the animals had to press either once (FR1), twice (FR2), or four times (FR4) for each infusion (*13*). Second, the amount of nomifensine per infusion was varied.

The results of these experiments are shown in Fig. 1. The rate of bar pressing varied significantly ($P < .001$, analysis of variance) as a function of the operant schedule. This relation appeared to be linear, with the rate on the FR4 schedule being approximately four times greater than that on the FR1 schedule (Fig. 1A). The rate of responding also varied significantly ($P < .001$) as a function of the dose per infusion (Fig. 1B). Both experiments demonstrate that intravenous nomifensine is reinforcing and that animals will work to maintain relatively constant serum (and presumably brain) concentrations of the drug. At the end of the experiments with nomifensine, the animals were transferred to solutions containing imipramine (0.5 mg/ml). In accordance with the results of experiments on monkeys (*14*), imipramine did not cause

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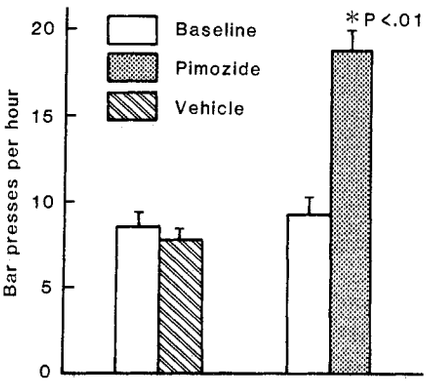

Fig. 2. The effect of prior treatment with pimozide (0.25 mg/kg) or vehicle (tartaric acid) on the rate of bar pressing to obtain nomifensine (0.36 mg/kg per infusion) on the FR1 schedule. Each column represents the mean ± standard error for seven animals.

maintained intravenous self-administration behavior.

In a final experiment, we investigated the effect of prior treatment with the relatively specific DA receptor antagonist pimozide on nomifensine self-administration (*15*). Previous studies have demonstrated that low doses of pimozide or other neuroleptics can increase the rate of self-administration of psychomotor stimulants (*12, 16, 17*). It was suggested that this increase is due to partial blockade of central postsynaptic DA receptors involved in mediating the reinforcing properties of psychomotor stimulants and that higher concentrations of these stimulants are therefore required to produce maximally reinforcing effects (*17*). Further evidence for a dopaminergic mechanism underlying self-administration of psychostimulants is the finding that lesions of DA terminals in the region of the nucleus accumbens abolishes self-administration of cocaine and *d*-amphetamine (*12, 18*).

The results of this experiment are presented in Fig. 2. In accordance with previous observations for other indirectly acting DA agonists, pimozide (0.25 mg/kg) significantly increased the rate of self-administration of nomifensine ($P < .01$), while prior treatment with the vehicle had no significant effect. Regardless of the precise basis of this effect, these results implicate dopaminergic mechanisms in nomifensine self-administration.

The present experiments provide evidence that nomifensine is self-administered intravenously by the rat. This finding supports the generalization that compounds which block the uptake or increase the release of DA by central dopaminergic neurons will maintain self-administration behavior in a variety of animals including man (*1, 10, 19*). In terms of its effects on central monoaminergic systems, nomifensine is remarkably similar to cocaine and methylphenidate, and therefore its ability to support self-administration behavior might have been predicted. All three compounds potently inhibit the synaptosomal uptake of both DA and norepinephrine, and the stimulating effects of each drug are blocked by reserpine but not by the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine (*6, 20*). The latter observation has been taken to indicate that these compounds primarily release granular stores rather than newly synthesized DA. In this regard it should be noted that, although these compounds block DA uptake, there is no evidence that they increase the release of DA from synaptosomes or brain slices in vitro (*21*). However, in vivo all three compounds appear to increase DA release in the central nervous system (*6, 22*).

On the basis of their observation that nomifensine increases the rate of intracranial self-stimulation in rats with electrodes in the medial forebrain bundle, Katz *et al.* (*23*) cautioned that this compound may share with other psychostimulants the potential for abuse. In one unpublished report, however, Leuschner (*24*) claimed that nomifensine (0.02 to 0.18 mg/kg per injection) was not self-administered by monkeys that self-administered cocaine and amphetamine. The reason for this discrepancy is not readily apparent (*25*).

To our knowledge there have been no clinical reports of nomifensine abuse by humans. In addition, clinical trials on healthy volunteers have failed to identify euphoric or other pleasant effects of the compound (*26*). Nevertheless, the intravenous self-administration paradigm has proved reliable for identifying compounds with the potential for abuse by humans. The present demonstration provides evidence that nomifensine may have this potential. The remarkably similar pharmacological profiles of nomifensine and compounds that are abused by humans reinforce this conclusion.

Further clinical research on nomifensine is needed. If nomifensine does not have the potential for abuse by humans and yet supports self-administration in animals, then it would represent a truly novel class of compounds.

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