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# Effects of Nomifensine (HOE 984) Upon Psychomotor Activity and Intracranial Self-Stimulation in the Rat

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KATZ, R. J., G. BALDRIGHI AND B. J. CARROLL. *Effects of nomifensine (HOE 984) upon psychomotor activity and intracranial self-stimulation in the rat.* PHARMAC. BIOCHEM. BEHAV. 7(3) 269–272, 1977. – The effects of nomifensine maleate (HOE 984) were evaluated using two behavioral tasks. The drug produced dose related increases in both psychomotor activity and operant responding for brain stimulation reward. These results may point to possible psychostimulant properties for the drug.

Activity Nomifensine Psychomotor Self stimulation Stimulant

NOMIFENSINE (HOE 984; 8 amino-2-methyl-4-phenyl-1, 2, 3, 4 tetrahydroisoquinoline) is an experimental thymoleptic drug with potential clinical utility and a number of unusual pharmacological properties [2, 8, 9, 11, 14]. Unlike many antidepressant drugs (e.g., imipramine and desipramine [4]) which depress motor activity at least certain dosages of nomifensine may in fact increase motor activity (e.g., turning behavior, stereotypy and general locomotion [2, 5, 8, 11]).

Since the drug may have an acute activating effect in several behavioral models the present tests attempted to quantify initial responses to drug administration upon two tasks – psychomotor activity upon an activity platform and intracranial self-stimulation. This choice of measures was intended both to supplement previous reports and to offer a preliminary assessment of this drug's potential psychostimulant properties, since psychostimulant drugs are known to increase both behaviors [12, 15, 20].

## EXPERIMENT 1: PSYCHOMOTOR EFFECTS

### METHOD

*Animals*

Thirty-two adult male Sprague-Dawley rats obtained locally (Charles River Farms, Portage, MI) and weighing 250–480 g each were maintained on ad lib food (Wayne Lab blox) and water, and normal day/night cycles of 12 hr each (light onset and offset were 8 and 20 hr EST). Animals were housed in groups of four.

*Apparatus*

Animals were individually tested in 50 x 40 x 22 cm polypropylene cages (Scientific Products Series 70) with a bedding of fresh pine chips. Cages were located upon field sensitive activity minotirs (Stoelting SA 1566, 1562, 1570) operating upon a selective mode for the detection of gross body movement. Four monitors calibrated to within 5% of each other were in use at a given time.

*Drugs.* Nomifensine hydrogen maleate was injected as a suspension in 0, 2.5, 5.0, 10.0 mg/kg dosages. Dosages were based upon previous reports [2, 5, 11] and all drugs were administered intraperitoneally in a volume of 1 cc/kg in a 0.9% saline vehicle.

*Procedure*

Animals were allowed 60 min to habituate to cages and ambient noise. Following habituation all rats were briefly removed and injected. Recording continued for an additional 120 min. Ten minute recording intervals were used throughout the entire 180 min session.

*Analysis.* Drug effects were evaluated via a Friedman 2-way analysis of variance [17] based upon the final 120 min (i.e., drug period) of each recording session.

### RESULTS

Results are presented in Fig. 1. It can be seen that initial exploration declined to a consistent low level at 60 min. Following injection nomifensine treated groups showed a dose related increase in activity which was significant ($\chi_r^2$ = 194, df = 3; $p<0.05$).

## EXPERIMENT 2

It is evident from the first experiment that nomifensine

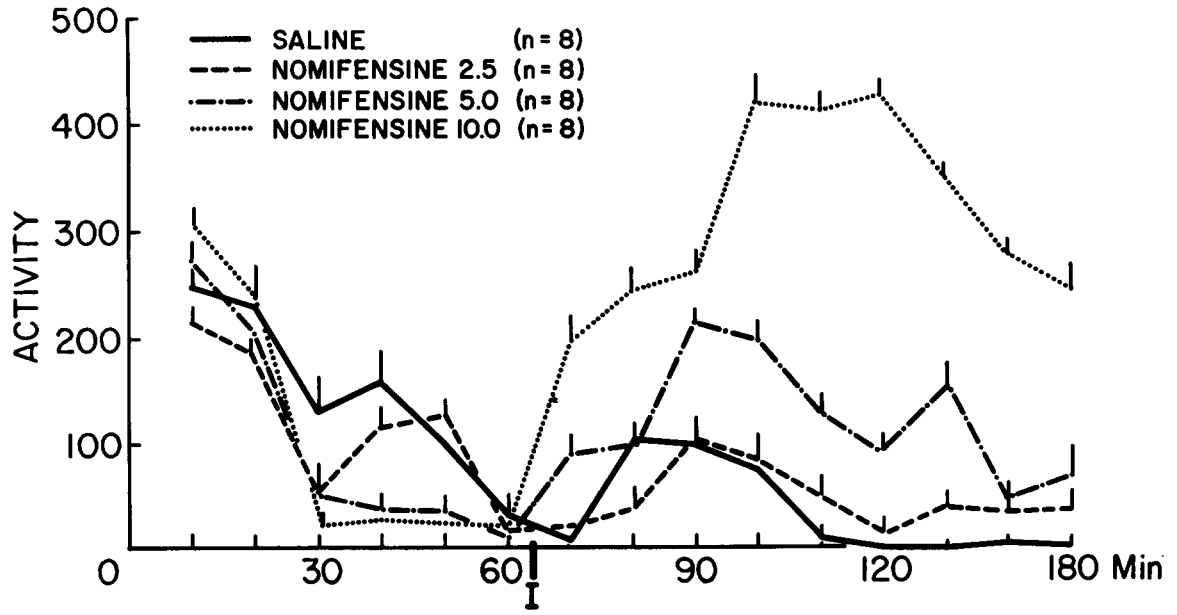


FIG. 1. Effects of nomifensine upon motor activity (mean + SEM).

has psychomotor stimulating properties. This is consistent with previous observations [5]. Experiment 2 evaluated the effects of nomifensine upon responding maintained by rewarding brain stimulation delivered to the medial forebrain bundle, a task which is also facilitated by a variety of stimulants [20].

## METHOD

### *Animals*

Sixteen rats equivalent in description to those employed in the first experiment were used. For recording purposes animals were housed individually.

### *Apparatus and Procedures*

The self-stimulation task of Wolf *et al.* [24] was used for behavioral testing. Surgical procedures, training, and apparatus were essentially similar to published reports [24]. In the self-stimulation task displacement of an overhead panel (a 14 × 16 cm steel plate located 14 cm from the cage floor) resulted in the delivery of a 0.3 sec train of a monopolar 60 cps sinusoidal current 50–300 $\mu$A in intensity via a head mounted brushing. At the close of testing all animals were killed with sodium pentobarbital and the brains were perfused and fixed for histologic examination. Twenty $\mu$ sections of brain were examined after staining with cresyl violet.

Behavioral testing consisted of injection of saline or drug (dosages and injection procedures were identical to Experiment 1) and recording total responses for a 4 hr period. Each animal was tested with several dose levels of nomifensine, and a recovery period of 72 hr intervened between injections. Gross observations of animals in Experiment 1 indicated behavioral recovery from the stimulating effects of the drug within 24 hr.

*Statistics.* Since individual animals showed widely differing albeit consistent rates of response the data are presented as percentage transformed scores in which the initial saline injected session was considered 100%. U tests were used to evaluate statistical differences [17].

## RESULTS

All electrode placements were located in the caudal medial forebrain bundle with the majority of sites clustered in an area immediately dorsal to the substantial nigra. It may be seen in Fig. 2 that nomifensine facilitated responding for stimulation and this was significant at the two highest levels of drug (respective U scores for the three drug dosages were 13, 5, 3 with the critical ($p<0.05$) U = 12. Saline injected animals showed minor and inconsistent changes across sessions.

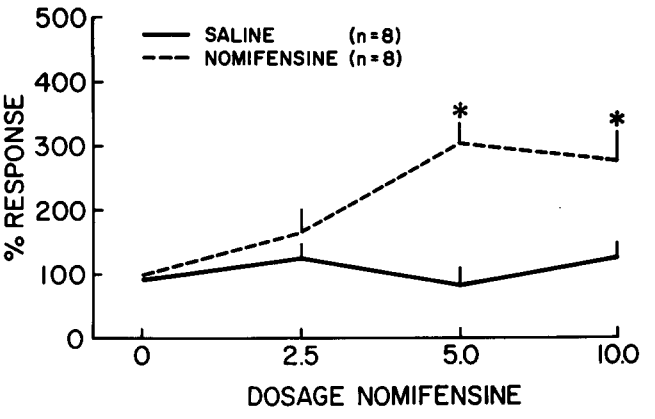


FIG. 2. Effects of nomifensine upon self stimulation (percent baseline + percent SEM)*; $p<0.05$.

## GENERAL DISCUSSION

Nomifensine has been shown to increase psychomotor activity and intracranial self-stimulation in rats. These results may have both preclinical and clinical implications. Looking first to their preclinical significance, the present report both confirms and expands previous observations regarding the drug's psychomotor effects. One previous report, which specifically examined general psychomotor patterns described biphasic effects with respect to time and dosage, i.e., lower dosages produced an initial period of motor inhibition followed by a later onset of excitation [8]. A consistent locomotor activation is reported after higher doses of nomifensine [5,8]. In the present report the predominant effect of nomifensine was activation. Figure 1 indicates also a slight initial motor depression at the lowest dosage level, which is consistent with the previous report [8]. Similar biphasic effects have been reported for a variety of direct and indirectly acting dopamine (DA) agonists (apomorphine [1] bromocryptine [18,19] and amantadine [21,22]). Since nomifensine is a potent DA agonist [2,5], the present motor effects may be related to facilitated transmitter release [9, 11, 14]. Direct and indirectly acting DA agonists have also been reported to augment self-stimulation [6, 7, 11, 13, 20, 23]. In general a presynaptic releasing action produces a more uniform increase in self-stimulation rates (e.g., [6, 7, 20]). The uniformity of the present results may argue indirectly for a presynaptic mode of action. It should be stressed, however, that nomifensine bears little structural similarity to psychostimulants, and upon purely structural criteria a direct post synaptic mode of action cannot be excluded [10]. Nomifensine differs from psychostimulants clinically as well as structurally, since stimulant drugs are of quite limited utility in the treatment of endogenous depression. Nomifensine is therefore unique in a variety of ways – it is both clinically effective, structurally unique, and possibly related to indirectly acting sympathomimetics on psychopharmacological grounds (e.g., [5,9], also the present tests).

Our results also have a number of clinical implications; on the one hand, they suggest that nomifensine is likely to produce an initial activation and mood elevation in clinical use – this property might prove useful in the treatment of mood disorders, especially since most thymoleptic agents show a delayed onset of action, often lasting up to two weeks. On the other hand, however, it should be stressed that nomifensine, which resembles psychostimulants upon several behavioral tests may also share with them a potential for abuse. While most antidepressants lack serious abuse potential, this has been reported occasionally with the monoamine oxidase inhibitors [16]. Our results suggest that the abuse potential of nomifensine should be evaluated quite carefully.

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