Self-administration in baboons and the discriminative stimulus effects in rats of bupropion, nomifensine, diclofensine and imipramine

R.J. Lamb and Roland R. Griffiths
The Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Division of Behavioral Biology, Baltimore, MD 21225, USA

Received April 4, 1989 / Final version March 3, 1990

Abstract. The behavioral effects of the antidepressants nomifensine, diclofensine, bupropion, and imipramine were examined using a cocaine substitution drug self-administration procedure in baboons and a cocaine drug discrimination procedure in rats. Intravenous self-administration of the antidepressants was examined in baboons under conditions in which baseline responding was maintained by intravenous injections of cocaine HCl (0.32 mg/kg/injection). Drug was available under a fixed-ratio 80-response or 160-response schedule of intravenous injection. Each drug injection was followed by a 3-h time-out allowing a maximum of eight injections per day. The antidepressants or their vehicles were substituted for cocaine for a period of 15 days, followed by a return to the cocaine baseline. Nomifensine, diclofensine, and bupropion all maintained self-administration behavior at levels above those maintained by their respective vehicles. Some doses of nomifensine, diclofensine, and bupropion maintained levels of behavior similar to those maintained under baseline cocaine conditions. High doses of imipramine maintained levels of behavior above those maintained by its vehicle, but the amount of behavior maintained under these conditions was extremely small. In a second experiment rats were trained to discriminate 32 μmol/kg cocaine (IP 10 min presession) from no drug in a two-lever food reinforced drug discrimination procedure in which responding on one lever was reinforced following ten consecutive responses when the session was preceded by cocaine administration, while responding on the other lever was similarly reinforced in the absence of cocaine pretreatment. Cocaine, nomifensine, diclofensine, and bupropion all dose-dependently occasioned cocaine-appropriate responding. Imipramine did not occasion cocaine-appropriate responding over a range of behaviorally active doses.

Key words: Self-administration – Drug discrimination – Nomifensine – Bupropion – Diclofensine – Imipramine – Cocaine – Drug abuse – Baboon – Rat

Some recently developed antidepressants have pharmacological properties reminiscent of those of psychomotor stimulants, such as amphetamine and cocaine. The present research examined the self-administration of three such compounds by the baboon using a cocaine substitution procedure. In addition, we examined the ability of these three compounds to occasion cocaine-appropriate responding in rats trained to respond on one lever following an injection of cocaine and on another lever in the absence of a cocaine injection. The prototypical tricyclic antidepressant imipramine was included in these studies for comparative purposes. The three novel compounds studied were nomifensine (8-amino-4-phenyl-1,2,3,4-tetrahydroisoquinoline maleate; Merital) (Brogden et al. 1979), bupropion d, l-t-butylamino-3-chloropropiophenone HCl; Wellbutrin (Dufrense et al. 1985), and diclofensine (racemic 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline HCl; Ro 8-4650) (Gentili et al. 1984; Omer et al. 1984). All three of these compounds contain the phenylethylamine skeleton found in a number of psychomotor stimulants, e.g. amphetamine. All three compounds have phenyl substitutions that might be expected to lessen some of their amphetamine-like properties; similar substitutions have been shown to lessen the amphetamine-like properties of other compounds containing the phenylethylamine nucleus (cf Houlihan and Biel 1970; Babington 1979).

The neurochemical and behavioral effects of these atypical antidepressants more closely resemble cocaine or amphetamine than tricyclic antidepressants, such as imipramine. For instance, nomifensine, diclofensine, and bupropion, like cocaine, are inhibitors of dopamine reuptake (Kruse et al. 1977; Ferris et al. 1981; Keller et al.
1982). While imipramine can inhibit the reuptake of dopamine, it does so only at very high concentrations (Koe 1976). Nomifensine and bupropion inhibit cocaine binding (Kennedy and Hanbauer 1983); while imipramine would be expected to do so only at very high concentrations (Ritz et al. 1987). Further, nomifensine, diclofensine, and bupropion increase locomotor activity, and decrease food intake (Katz et al. 1977; Soroko et al. 1977; Keller et al. 1982; Johanson, 1986). These effects are more typical of stimulants than of tricyclic antidepressants. Also, nomifensine and bupropion increase low rates of operant responding in the rat and squirrel monkey (Mc Kearney 1982; Rastogi and Mc Millan 1985). Again, these effects are more typical of stimulants than of tricyclic antidepressants (e.g. Rastogi and Mc Millan, 1985). Most importantly, nomifensine and bupropion, but not imipramine, share discriminative stimulus properties with psychomotor stimulants (Colpaert et al. 1979; Jones et al. 1980), and serve as reinforcers in the rhesus monkey and the rat (Hoffmeister and Goldberg 1973; Spryaki and Fibiger 1981; Yanagita et al. 1981; Woods et al. 1983; Winger and Woods 1985; Johanson 1986). However, in humans neither nomifensine nor bupropion reliably produce stimulant-like effects (Wittenborn et al. 1976; Hindmarch and Parrott 1977; Peck et al. 1979; Chan et al. 1980; Hamilton et al. 1983; Miller and Griffith 1983).

As is apparent from the foregoing discussion, nomifensine, bupropion, and diclofensine in many ways have more in common pharmacologically with psychomotor stimulants than with tricyclic antidepressants. An important practical consideration is whether these three antidepressants share with cocaine its high potential for abuse. This paper reports the results of an examination of the effects of these three antidepressants and imipramine in two procedures used for detecting a cocaine-like potential for abuse. Drug discrimination procedures have proven useful in categorizing psychoactive drugs into different classes, and thus provide information on the extent to which a compound may produce some types of cocaine-like effects. Drug self-administration procedures have been used to examine the defining characteristic of drugs of abuse, that they can serve as reinforcers. The particular procedure used was a cocaine substitution procedure with which the reinforcing effects of a number of psychomotor stimulant drugs have been documented (Griffiths et al. 1976, 1979).

Materials and methods

Self-administration

Four male baboons (Papio anubis) weighing 23–25 kg served as experimental subjects. Baboon GI was experimentally naive prior to the beginning of this study. The other three baboons had been subjects in previous self-administration experiments (baboon GA with sedatives, baboon ZE with phenylpropanolamine, and baboon DI with buspirone and 3,4-methylenedioxymethamphetamine). Baboons were housed within standard primate cages that also served as experimental chambers. These cages were enclosed by sound and light attenuating cubicles (Lukas et al. 1982). Intravenous catheters were implanted using sterile technique in either femoral or jugular veins under pentobarbital anesthesia using methods described in Lukas et al. (1982). Catheters were protected by a harness/tether system, which allowed baboons virtually unrestricted movement within the cage (Lukas et al. 1982). The infusion system was similar to that described in Findley et al. (1972). Baboons had free access to water through a drinking tube, and received daily rations of fruit and vitamin supplements.

A 0.7 x 1.0 m aluminum panel was mounted on one wall of the experimental chamber. Mounted on the panel were a Lindsley lever (Gerbrands, No. G6310) (lower left of panel) with an associated jewel light (approximately 1.5 cm diameter), a leaf lever (lower right of panel) with an associated jewel light, a food hopper with an associated light (lower left or center of panel), and a 5 x 5 cm translucent panel (upper left corner) that could be transilluminated. Baboons could respond on the leaf lever under a fixed-ratio 30-response schedule of food pellet (1 g Noyes or BioServ banana flavored) delivery (i.e., every 30th response delivered a food pellet and produced a brief flash of the hopper light) 24 h per day. The availability of an injection was indicated by a 5-s tone followed by illumination of a jewel light over the Lindsley lever. When the jewel light was illuminated, each response produced a brief feedback tone (approximately 0.1 s). Upon completion of 80 responses (baboons GI and GA) or 160 responses (baboons ZE and DI) on the Lindsley lever following illumination of the jewel light, the jewel light over the lever was extinguished, the drug injection was begun, the 5 x 5 cm translucent panel was illuminated for a 1-h period, and a timeout period of 3 h was begun. This schedule of drug availability permitted a maximum of eight injections per day. There was no time limit for completion of the fixed-ratio response requirement. Data were collected each day at approximately 8 a.m. and drug changes were made at this time, if indicated.

The self-administration of these antidepressants was evaluated using a cocaine substitution procedure (Griffiths et al. 1976). Experiments ran continuously 7 days per week. Three days during which 0.32 mg/kg/injection cocaine HCl (dissolved in saline) maintained six or more injections per day preceded the substitution of each dose of antidepressant or antidepressant vehicle (imipramine HCl and buspirone HCl-normal saline; diclofenac HCl-sterile water; nomifensine maleate-minimum amount 1.0 N HCl and sterile water to volume). Following substitution of antidepressant or antidepressant vehicle for approximately 15 days, cocaine was again available. This procedure of replacing cocaine with a dose of antidepressant or vehicle was continued throughout the study. Due to severe stimulant effects, testing with diclofenac 1.0 mg/kg/injection was terminated after 4, 14, 3, and 7 days for baboons GI, ZE, DI, and GA respectively. Baboon DI's catheter was found to be unattached on day 15 of 0.32 mg/kg/injection nomifensine substitution, therefore the catheter was reattached, and the substitution was continued for 11 additional days. Baboon GA's substitution with 0.10 mg/kg/injection nomifensine was inadvertently stopped after 14 days. Drug or vehicle injections were 5 ml and each injection was followed by a 5 ml, flush of normal saline. These injections each took about 90 s to complete. All drug doses are expressed as the salt.

Using paired t-tests, drug response rates were compared to vehicle response rates for days 11–15, while food consumption data during drug availability were compared to that during vehicle availability for days 1–5. Data for injections per day for days 11–15 were compared to vehicle using a signed rank test (Wilcoxon 1945). Since 1 mg/kg/injection diclofenac was tested for shorter periods of time, data for this dose were analyzed using the last 5 days (or fraction thereof) for response rate and injections per day data, and using the first 5 days (or fraction thereof) for food consumption data.

Drug discrimination

Five individually housed male rats (Sprague-Dawley; CD strain from Charles River) were subjects. Rats were experimentally naive.