Effects of nimodipine on the discriminative stimulus properties of d-amphetamine in rats

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Abstract. The discriminative stimulus (DS) properties of d-amphetamine (AMP) are thought to be mediated by enhanced release of catecholamines, which may involve neuronal calcium influx through voltage sensitive channels. The present study examined the influence of nimodipine, a calcium channel blocker, on the DS properties of AMP. Rats (N = 8) were trained to discriminate AMP (0.5 mg/kg, IP) from saline in a two-lever, food-reinforced, drug discrimination paradigm. Nimodipine alone (2.0–5.6 mg/kg, IP) did not substitute for AMP. When given in combination with AMP, 2.0 mg/kg nimodipine increased by less than 2-fold the AMP dose necessary to induce AMP-appropriate responses. Higher doses of nimodipine combined with AMP did not increase the magnitude of this effect. Nimodipine enhanced the effects of AMP on response rate. Haloperidol (0.125 mg/kg) increased by approximately 4-fold, whereas diazepam (0.5 or 1.0 mg/kg) and morphine (5.0 mg/kg) increased by approximately 2-fold the AMP dose necessary to induce AMP-appropriate responses. The interaction with AMP was associated with enhanced reduction of response rate in the tests with diazepam and morphine but not haloperidol. These results suggest that nimodipine attenuates the DS properties of AMP, probably in a non-specific way, due to the ability of nimodipine itself to induce a discriminable internal state.

Key words: Drug discrimination – d-Amphetamine – Nimodipine – Diazepam – Morphine – Haloperidol – Calcium channel – Behavior – Rat

To the extent that subjective effects play an important role in the dependence potential of psychoactive drugs, drugs that block those effects may prove useful in the treatment of drug dependence. The discriminative stimulus (DS) properties of drugs are often predictive of their subjective effects (Schuster et al. 1981; Woolverton and Schuster 1983). Therefore, pharmacological agents that block the DS properties of a drug may also attenuate its subjective effects. For instance, opiate antagonists attenuate both the DS and subjective effects of opiate agonists (Martin et al. 1973; Shannon and Holtzman 1976).

In the case of psychomotor stimulants, attention has mainly focused on drugs that alter catecholamine (CA) function on the assumption that these neurotransmitters are responsible for the DS effects of this group of compounds (Lewander 1977). For instance, drugs that deplete dopamine (DA) (e.g., 6-hydroxydopamine, alphamethylparatyrosine) or block DA receptors (e.g., haloperidol, pimozide) have been reported to attenuate the DS properties of psychomotor stimulants (Colpaert et al. 1978; Ho and Silverman 1978; Nielsen and Jepsen 1985; Woolverton and Cervo 1986).

Another approach to attenuating the discriminative stimulus effects of psychomotor stimulants might be to modify CA release pharmacologically. However, the neuronal mechanisms responsible for drug-induced CA release are not clear. Under physiological conditions, stimulus-secretion coupling in monoaminergic terminals involves a redistribution of transmembrane cations, particularly calcium (Zucker and Lando 1986). Therefore, it is possible that amphetamines, for example, facilitate monoamine release by altering cation redistribution, as suggested by the recent finding that AMP activates a K-dependent ATPase (Angel et al. 1985). In addition, several antidopaminergic compounds that inhibit AMP effects have been found also to function as calcium channel blockers (Gould et al. 1983; Flaim et al. 1985; Wolfe and Brostrom 1986).

Recently, there has been substantial interest in the possibility that calcium channel blockers may attenuate the effects of drugs of abuse. For instance, it has been found in mice that AMP-induced circling (Fung and Uretsky 1980) and phencyclidine-induced locomotor stimulation (Grebb 1986) can be attenuated by calcium antagonists. In addition, calcium channel blockers have been suggested as antagonists of the toxic effects of cocaine (Nahas et al. 1985). The present experiment was designed to evaluate the effects of pretreatment with nimodipine on the DS effects of AMP in rats. Nimodipine is a calcium-channel blocker, which has been found to cross the blood-brain barrier and to have behavioral effects characterized by mild sedation and enhancement of reserpine-induced catalepsy (Hoffmeister et al. 1982). In addition, nimodipine enhances hypothermia produced by both ethanol and diazepam (Draske et al. 1985; Isaacs et al. 1985). The effects of nimodipine were compared with the effects of haloperidol, diazepam, and morphine.
Materials and methods

The subjects were eight male Sprague-Dawley rats (Holzman Co., Madison, WI) that were maintained at 80% of their initial free-feeding body weights. Seven of the rats were experimentally naive at the beginning of the present experiment. The eight had been tested with a number of compounds in combination with AMP before beginning the present experiment. The rats were individually housed in stainless steel cages in a room maintained at 24°C and on a 12 h light-dark cycle (light 6 a.m.–6 p.m.). In addition to the 45-mg food pellets (P.J. Noyes Co., Lancaster, NH) delivered during the experimental sessions, the diet was supplemented with Teklad 4% Mouse and Rat Diet (Winfried, IA) to maintain stable body weights. Water was continuously available except during experimental sessions.

Operant chambers for rats (Ralph Gerbrands Co., model D-1), in which a food receptacle was mounted on one wall between two response levers, were used as experimental chambers. Each chamber was illuminated during experimental sessions by a single 6 W light located on the wall opposite the levers. Extraneous noise was diminished by enclosing each chamber in an insulated picnic chest and by operating ventilation fans mounted on the outside of each chest. Electronic equipment (Aim 65 Microprocessor, Dynatemp Incorporated, Irvine, CA), located in the adjacent room, controlled stimulus events and recorded lever presses.

The rats were randomly assigned to the four experimental chambers. In each chamber one lever was designated the saline (S) lever and the other, the drug (D) lever. Experimental sessions, which lasted 15 min, were conducted daily, 5 days a week. A training schedule was used in which saline (1.0 mg/kg, IP) and AMP (0.5 mg/kg, IP) pretreatment sessions were conducted in a double alternation sequence (i.e., S, S, D, D, S, S, ...). In order to prevent odor from exerting discriminative control of behavior, this sequence was offset by one day in the two groups of four so that the condition in effect for one rat on a given day was not predictive of the conditions for the next rat in the same chamber. At 10 min after injection the house light was illuminated and food was available for every response on the S lever during a S session and on the D lever during a D session. Responding on the inappropriate lever was counted and reset the response requirement on the appropriate lever. Gradually, the response requirement on either lever was increased to 30 responses per food pellet (Fixed-Ratio 30: FR 30).

The training sequence was continued until a rat emitted at least 80% of its responses before the first reinforcer and at least 90% of its responses for the entire session on the correct lever for at least seven of eight consecutive sessions. At this point the discrimination was considered to be acquired and test sessions were begun. Test sessions were identical to training sessions except that a novel solution or combination of solutions was injected before a test session and food was available for responding under a FR 30 schedule on either lever. In addition, responding on one lever did not reset the response requirement on the other lever. Test sessions were conducted on Tuesdays and Fridays with training sessions conducted on the remaining 3 experimental days of each week to maintain and affirm the discrimination. If responding fell below the training criteria for any rat, the rat was returned to the training sequence until it again achieved criterion performance.

Data analysis. For each test session, the per cent of the total responses that occurred on the drug lever (% DLR) as well as the overall response rate for both levers (responses/s) were calculated for each rat. The data from all animals tested were included in response rate analysis. However, the data from a given test dose were included in the analysis of per cent drug-lever responses only if the animal completed at least 30 responses on one or the other lever. The ED_{50} (the dose predicted to produce a 50% effect) and the 95% confidence limits (c.l.) were calculated from the linear portion of these dose-response functions by the method of least squares linear regression for both dependent measures. For response rate data the effect of each dose of drug was calculated individually as a percentage of rate following saline injection for use in the regression analyses. The per cent of rats selecting the drug lever (i.e., rats that emitted at least 80% of their responses on the drug lever) was considered a quantal measure of discrimination. Statistical significance of changes in the per cent of rats selecting the drug lever was evaluated using the chi-square test.

Drugs. d-Amphetamine sulfate (AMP) and morphine sulfate (National Institute on Drug Abuse) were dissolved in 0.9% saline. A stock solution of diazepam (Hoffman-La-Roche, Nutley, NJ), prepared in a concentration of 40 mg/ml in 1:1 ethanol and emulphor (GAF Corporation, Linden, NJ), was diluted with saline to the chosen concentration immediately preceding administration. Haloperidol was used in its injectable form (Haldol, McNeil Pharmaceuticals, Spring House, PA). Nimodipine (Miles Pharmaceuticals, West Haven, CT) was dissolved in ethanol and diluted with emulphor and water immediately before use (final ethanol concentration: 15%). Haloperidol was administered 60 min and nimodipine, morphine and diazepam 10 min before AMP. All injections were given IP, usually in a volume of 1.0 ml/kg.

Results

In increases in the dose of AMP induced dose-related increases in the per cent of responses that occurred on the drug lever and, at 2.0 mg/kg, a reduction in rate of responding (Fig. 1). The interval from principally saline lever responding (<20% drug-lever responses) to principally drug-lever responding (>80% drug-lever responses) was half of a log unit (from 0.20 to 0.25 mg/kg). Drug-lever responding occurred at doses approximately 10 times lower than those that reduced response rate. The ED_{50} for drug-lever responding was 0.14 mg/kg (c.l.: 0.09–0.27), whereas that for the reduction of response rate was 1.8 mg/kg (c.l.: 1.5–2.3).

Nimodipine alone did not engender drug-lever responding and reduced response rate in a dose-dependent way with an ED_{50} of 4.0 mg/kg (c.l.: 2.6–5.5) (Fig. 1). Administration of 2.0 mg/kg nimodipine in combination with AMP shifted the dose-response function for %DLR to the right and the effect of nimodipine was surmountable. Higher doses of nimodipine (4.0 and 5.6 mg/kg) also shifted the AMP dose-response function to the right but not to any greater extent than did 2.0 mg/kg. The ED_{50} of AMP was 0.23 mg/kg (c.l.: 0.1–0.42) in combination with 5.6 mg/kg nimodipine. Thus, nimodipine produced slightly less than a 2-fold shift in the AMP %DLR dose-response function. The group data for this effect accurately reflect the data