Psychopharmacology (1982) 78:204–209

Psychopharmacology

Heroin and Cocaine Intravenous Self-Administration in Rats: Mediation by Separate Neural Systems

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Abstract. The hypothesis that separate neural systems mediate the reinforcing properties of opiate and psychomotor stimulant drugs was tested in rats trained to lever-press for IV injections of either cocaine or heroin during daily 3-h sessions. Pretreatment with the opiate receptor antagonist drug naltrexone produced dose-dependent increases in heroin self-administration, but had no effect on the rate or pattern of cocaine self-administration. Similarly, pretreatment with low doses of the dopamine antagonist drug alpha-flupenthixol produced dose-dependent increases in cocaine but not heroin self-administration. High doses of alpha-flupenthixol eliminated all responding for cocaine and slightly reduced heroin self-administration. The specificity with which the two antagonist drugs exerted their behavioral effects strongly suggests that independent neural substrates are responsible for the reinforcing actions of heroind and cocaine.

Key words: Cocaine – Heroin – Opiate – Dopamine – Alpha-flupenthixol – Psychomotor-stimulant – Naltrexone – Receptor antagonists – Self-administration – Reinforcement

The reinforcing properties of both opiate and psychomotor stimulant drugs have been demonstrated in animal studies where subjects make an operant response that results in the intravenous administration of drug (e.g. Pickens and Harris 1968; Woods and Schuster 1969; Deneau et al. 1969; Thompson and Pickens 1970; Yokel and Pickens 1973; Werner et al. 1976; Pickens et al. 1978). In such situations, positively reinforcing drugs possess characteristics similar to those of other natural reinforcers by strengthening and maintaining the operant behavior, e.g., drug self-administration (Schuster and Thompson 1969; Pickens et al. 1978). However, a unique property of drug self-administration, is that animals maintain a relatively stable level of drug intake over time (Yokel and Pickens 1974; Pickens et al. 1978). For example, animals respond to changes in the injection dose by increasing their self-administration behavior following decreases in dose and decreasing self-administration following increases in the injection dose (e.g. Pickens and Thompson 1968; Yokel and Pickens 1973, 1974; Glick et al. 1975). It is generally assumed, therefore, that unlike other positive reinforcers such as food, water or rewarding brain stimulation, as one decreases the reinforcement strength of the drug (by reducing the dose administered after each response) subjects increase their response rate, thereby returning net drug intake back to preferred levels. During extinction conditions, when drug reinforcement is not presented, animals react initially with relatively high rates of responding followed, eventually, by response cessation (Pickens and Thompson 1968; Yokel and Pickens 1976; De Wit and Wise 1977; Pickens et al. 1978).

Administration of the opiate receptor antagonist naloxone produces an increase in morphine self-administration (e.g. Goldberg et al. 1971; Weeks and Collins 1976) similar to that observed following a reduction in the injection dose (e.g., Glick et al. 1975). Several studies have similarly reported this effect in animals self-administering psychomotor stimulants (e.g. cocaine or amphetamine) when challenged with the dopamine (DA) receptor antagonists butaclamol or pimozide (Yokel and Wise 1975, 1976; De Wit and Wise 1977). Demonstrations that receptor antagonists can produce behavioral results analogous to those observed with decreases in the injection dose of self-administered drugs have led to the suggestion that such receptor antagonists are competing with the reinforcing drugs at their pharmacological sites of action, thereby reducing their reinforcing properties (Thompson et al. 1973; Pickens et al. 1978; Wise 1978). Thus DA receptors appear to be implicated in the neural mediation of the reinforcing effects of psychomotor stimulants and opiate receptors in the mediation of opiate drug reinforcement. This is supported by reports of extinction-like responding for cocaine following destruction of the DA terminals in the nucleus accumbens (Roberts et al. 1977, 1980), by reports that in humans the euphoric properties of amphetamine are greatly attenuated during DA receptor blockade (Gunne et al. 1972), and by the observation that the physiological and affective consequences of morphine self-administration can be prevented by opiate receptor blockade (Jaffe 1980).

However, crucial to the notion of two separate neural systems mediating the reinforcing properties of stimulants and opiates, is the demonstration that manipulations that affect the self-administration of one do not similarly affect the other. The present study, therefore, was devised to examine the specificity with which DA and opiate receptor antagonists alter the self-administration of either heroin or cocaine in rats.

Materials and Methods

Subjects and Apparatus. Twenty five male Wistar rats, weighing 300–350 g at the start of the experiment, served as

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0033-3158/82/0078/0204/$01.20

subjects. Each animal was surgically implanted with a chronic silastic jugular cannula under 50 mg/kg sodium pentobarbital anesthesia. The cannula was passed subcutaneously to a polyethylene assembly mounted on the animals back and was permanently connected to a harness/swivel system which was in turn connected to a syringe pump as described by Roberts et al. (1977, 1980). The animals lived for the duration of the experiment inside individual standard operant-conditioning cages where they were provided with free access to food and water. The cages themselves were housed inside sound attenuating chambers and maintained on a 12-h reversed light-dark cycle (lights off from 1:00 p.m. to 1:00 a.m.).

Procedure. Starting 3 days after surgery, each rat was allowed 3 h access every day (commencing in the first hour after lights out) to a metal lever mounted on the front wall of its cage. A lever-press resulted in an IV injection of either 0.1 ml of cocaine hydrochloride (0.75 mg/kg/injection) or heroin (0.06 mg/kg/injection) dissolved in 0.9% physiological saline and administered over a period of 4 s. A signal light mounted above the lever indicated the onset of an injection and remained lit for 20 s, during which time the lever was inactive. Lever-presses during the period when the signal light was not lit were reinforced on a schedule of continuous reinforcement. Only animals that demonstrated stable drug intake for 4 consecutive days were employed in the study.

Test days consisted of pretreating animals with IP injections of either naltrexone (0.01, 0.05, 0.1, 0.2, 1.0 or 10.0 mg/kg), alpha-flupenthixol (0.01, 0.05, 0.1, 0.2, or 0.4 mg/kg) or saline. Each dose of antagonist was tested once for each animal. Naltrexone is a potent opiate receptor antagonist (Martin et al. 1973; Braude et al. 1974; Blumberg and Dayton 1974; Verebey et al. 1976) while alpha-flupenthixol is a potent and highly specific DA receptor antagonist (Møller-Nielsen et al. 1973; Creese et al. 1976; Leysen et al. 1978; Magistretti and Schordest 1979). The antagonist drugs were both prepared in a vehicle solution of 0.9% physiological saline and injected in a volume of 1.0 mg/kg of body weight either 30 min (naltrexone) or 2.5 h (alpha-flupenthixol) before the daily 3-h reinforcement session. A minimum of 3 no-pretreatment days separated each antagonist test day. Animals self-administering heroin were tested on the full range of naltrexone doses and on three doses of alpha-flupenthixol (0.1, 0.2, and 0.4 mg/kg). Cocaine self-administering rats were challenged with each of the alpha-flupenthixol doses and with three doses of naltrexone (0.1, 1.0 and 10.0 mg/kg). The order in which the drugs and doses were administered was randomly determined for each animal. Saline pretreatment was administered on different test days either 2.5 h or 15 min prior to the 3-h test session. There were no differences in the pattern or rate of responding between the two saline conditions and the mean performance during these two sessions was used for statistical analyses.

Eleven animals made up of the heroin self-administration group and 14 rats made up the cocaine group. Because of the length of time required to complete the experiment, animals did not always maintain stable baseline self-administration (due to cannula leaks or blockages) and had to be dropped from the study before having completed the entire test regimen. As a result statistical analyses were computed as for independent rather than correlated samples. Each treatment cell, however, contained a minimum of six subjects and all subjects completed over 60% of the treatment regimen.

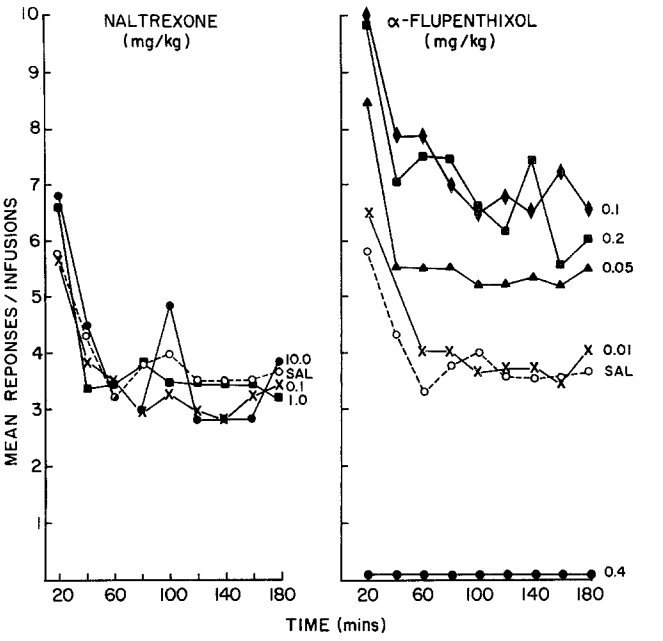

Fig. 1. The effects of the opiate receptor antagonist, naltrexone, and the dopamine receptor antagonist, alpha-flupenthixol, on intravenous cocaine self-administration. Alpha-flupenthixol (except at the highest dose) produced a dose-dependent increase in cocaine-reinforced responding while naltrexone had no effect.

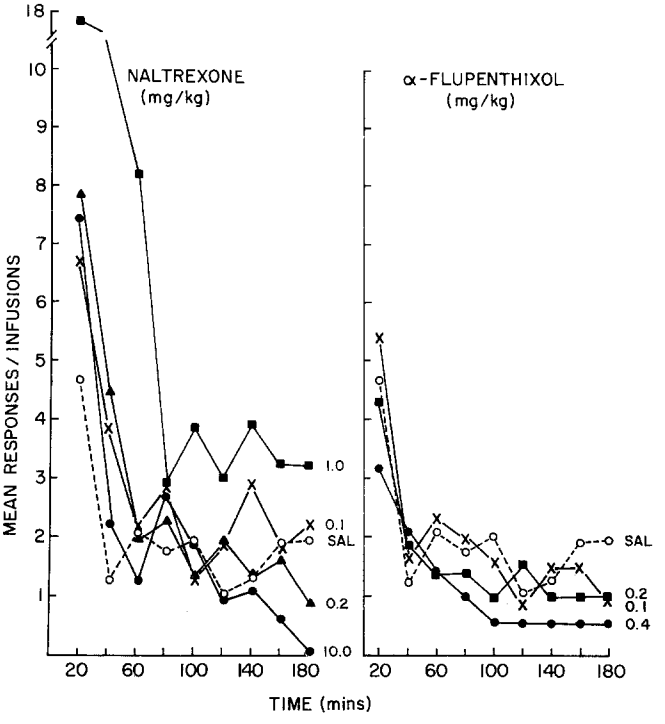

Fig. 2. The effects of naltrexone and alpha-flupenthixol on intravenous heroin self-administration. For clarity, two doses of naltrexone (0.01 and 0.05 mg/kg) were omitted from the figure; these doses were not reliably different from saline pretreatment. Naltrexone produced an increase in heroin self-administration while alpha-flupenthixol only produced a slight decrease in responding.

Results

The effects of alpha-flupenthixol and naltrexone on heroin and cocaine self-administration are shown in Figs. 1 and 2.

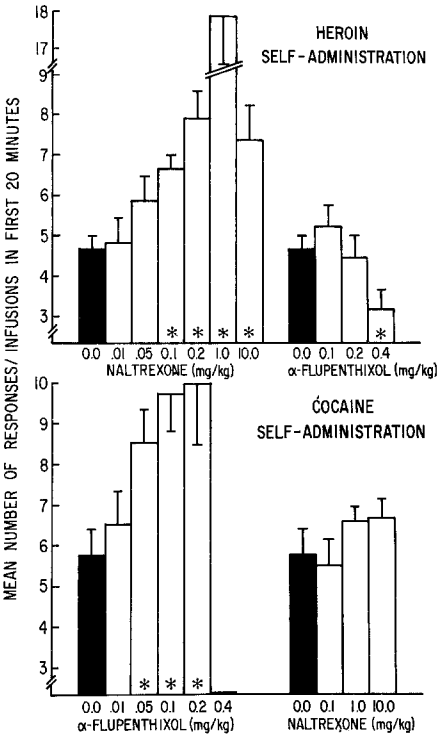

Fig. 3. The effects of naltrexone and alpha-flupenthixol on the loading dose (infusions in the first 20 min of the 3-h test sessions) in both heroin and cocaine self-administering animals. Increases in responding were only observed in cocaine animals pretreated with dopamine receptor antagonist and in heroin animals pretreated with opiate receptor antagonist. A posteriori Newman-Keuls tests compared each treatment dose with the appropirate no-drug control. An asterisk in the base of a histogram indicates that the treatment dose was reliably different from the no drug/saline condition ($P < 0.05$)

Two-way analyses of variance with repeated measures on one factor were computed on the data presented in these two figures. It was revealed that DA receptor antagonism produced by low doses of alpha-flupenthixol, resulted in a dose-dependent increase in responding for IV cocaine [$F(4,41) = 18.7$, $P < 0.001$] but not heroin. In fact, alpha-flupenthixol slightly decreased heroin self-administration [$F(3,25) = 3.58$, $P < 0.05$]. Conversely, opiate receptor blockade increased responding for heroin [$F(4,31 = 5,61$, $P < 0.01$] but had no effect on cocaine-reinforced responding [$F(3,28) = 0.51$, n.s.].

These results can also be observed in Fig. 3 which depicts the "loading dose" of cocaine or heroin under the different antagonist conditions. In self-administration paradigms where animals are allowed only limited access to the drug reinforcement (3 h/day in the present study), the animals respond at relatively high rates during the initial few minutes of the session, apparently to increase blood levels quickly to preferred values (Pickens et al. 1978). The subjects then maintain a relatively stable response rate/drug intake for the remainder of the session (as observed in Figs. 1 and 2). Reducing the injection dose per response (i.e. reinforcement magnitude) produces a corresponding increase in this intitial responding. Similarly, in the present study, pretreating rats with a selective DA or opiate receptor antagonist also produced a dose-dependent increase in the "loading dose" of cocaine or heroin, but not both (see Fig. 3). Thus naltrexone (0.01 – 1.0 mg/kg) respectively produced a 2%, 23%, 43%, 66%, and 278% increase in initial heroin-reinforced responding over saline performance. The highest naltrexone dose (10 mg/kg) produced a 57% increase in responding during the first 20 min of the session. However, naltrexone did not produce any reliable increase in cocaine self-administration. Compared to saline pre-treatment, low to moderate doses of alpha-flupenthixol (0.01 – 0.2 mg/kg produced increases in cocaine-reinforced responding of 14%, 49%, 72%, and 75% respectively. Once again these effects were extremely selective, since no dose of alpha-flupenthixol produced a reliable increase in heroin-reinforced responding. At its highest dose (0.4 mg/kg) alpha-flupenthixol eliminated all cocaine self-administration and reliably attenuated even heroin self-administration (see Fig. 3).

One-way ANOVAs for independent groups confirmed that pretreatment with the opiate antagonist naltrexone, resulted in reliable increases in the "loading dose" (infusions during the first 20 min) of heroin [$F(6,41) = 15.6$, $P < 0.001$] but not of cocaine [$F(3,28) = 0.91$, n.s.]. On the other hand the DA antagonist alpha-fluphenthixol increased only the number of cocaine infusions [$F(4,41) = 8.58$, $P < 0.001$] while slightly decreasing the number of heroin infusions [$F(3,25) = 3.12$, $P < 0.05$].

Examples of characteristic 3 h response records are shown for two rats, one self-administering heroin and the other cocaine, in Fig. 4A and B respectively. Each mark represents a single response/infusion. Note that animals tend to maintain responding at equal time intervals throughout the session. As the challenging dose of antagonist is increased this regular pattern of responding is generally maintained, but with shorter inter-response intervals. Reducing the injection dose of the reinforcing drug similarly increases the response rate by shortening the time between responses/infusion (Pickens and Thompson 1968; De Wit and Wise 1977; Pickens et al. 1978). The extinction data in each case shows the response patterns generated when the reinforcing drug is replaced with nonreinforcing IV saline. No such patterns were produced by any dose of the DA receptor antagonist in any rat. High doses of alpha-flupenthixol (0.2 – 0.4 mg/kg) either completely eliminated responding for cocaine or greatly attenuated it. The same doses slightly reduced (but never increased) heroin self-administration. Challenging heroin self-administration with 1.0 – 10.0 mg/kg of naltrexone did produce patterns somewhat similar to those observed during real extinction. However, the duration of action of opiate antagonists, even relatively long-acting ones like naltrexone, are far less than the test session duration. The same high doses of naltrexone did not alter responding for cocaine reinforcement.

Discussion

Naltrexone produced a dose-dependent increase in the IV self-administration of heroin. Similarly, alpha-flupenthixol produced a dose-dependent increase (at all but the highest dose) in IV cocaine self-administration. These results confirm those reported by others (Goldberg et al. 1971; Yokel and Wise 1975, 1976; Weeks and Collins 1976; De Wit and Wise 1977). It is assumed that, in each case, the increased responding occurs because the reinforcing and antagonist drugs are competing at the same synaptic sites. Heroin, for example, is assumed to bind to central opiate receptors (Way and Adler 1960; Misra 1978; Jaffe and Martin 1980) which are blocked by the receptor antagonist naltrexone (Martin et al. 1973; Braude et al. 1974; Verebey et al. 1976). Cocaine is believed to enhance dopaminergic neurotransmission by reducing the

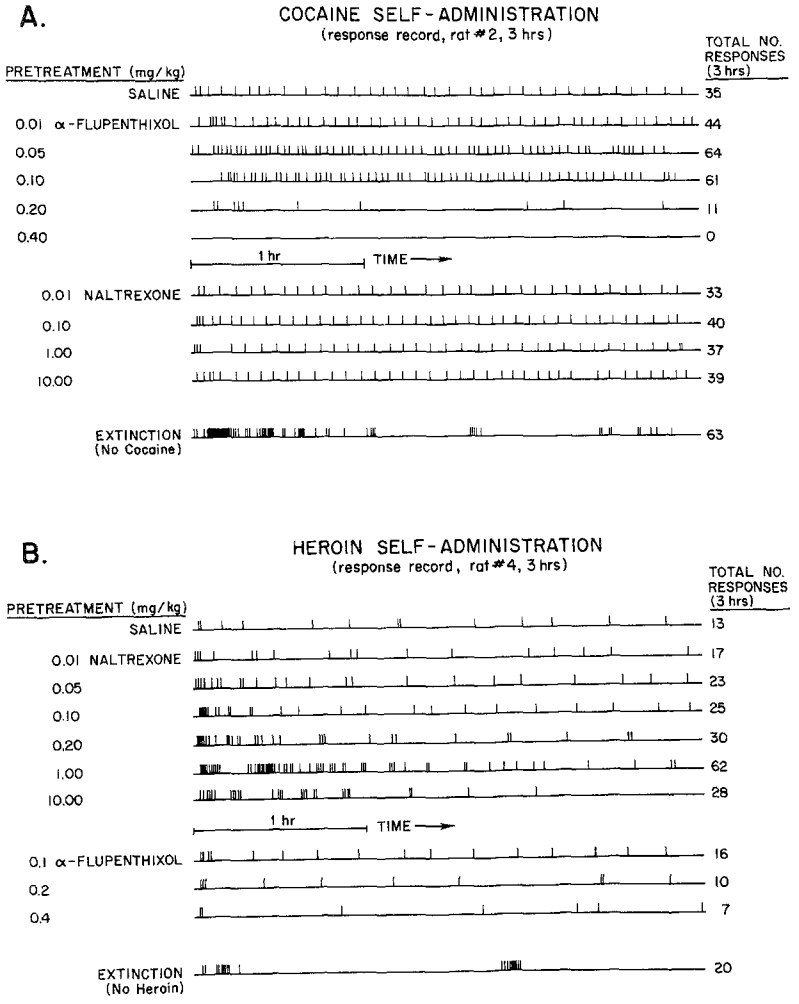

Fig. 4 A and B
Representative response records for two self-administering animals. **A** A rat self-administering cocaine, and **B** a heroin self-administering rat. Test sessions were 3 h in duration. Each mark represents a response/infusion of intravenous drug. Extinction data represent the effects of replacing the reinforcing drugs with intravenous saline. These extinction tests were conducted after all the antagonist treatments were completed

presynaptic uptake of DA (Ross and Renyi 1967; Patrick et al. 1975; Heikkila et al. 1975) the effects of whch can be attenuated by a post-synaptic receptor antagonist, such as alpha-flupenthixol (Møller-Nielsen et al. 1973; Creese et al. 1976; Leysen et al. 1978; Magistretti and Schordest 1979). Therefore theoretically, the net reinforcement produced by combining these drugs is equivalent to their net effect on synaptic neurotransmission, and animals respond to increasing doses of antagonist drugs by increasing their intake of the reinforcing drug. In such situations, the regularly spaced pattern of responding remains (see Fig. 4), while the interval between responses is shortened. This result is also characteristic of reductions in the reinforcement strength of the self-administered drug (i.e. reducing the injection dose per response) and, therefore, supports the notion that heroin reinforcement is mediated by an interaction with central opiate receptors and cocaine reinforcement by DA receptors.

If this was correct, then one might expect that with sufficiently high doses of antagonist, all of the reinforcing properties of the self-administered drugs would be blocked. Indeed, high doses of naltrexone did produce extinction-like patterns of heroin-reinforced behavior but had not effect on cocaine self-administration. The heroin self-administration did not cease entirely, probably because the antagonist action of naltrexone had weakened by the end of the 3-h test session (Martin et al. 1973; Braude et al. 1974; Blumberg and Dayton 1974; Verebey et al. 1976). However, no extinction curves were observed during high doses of alpha-flupenthixol in either self-administration group. Cocaine-reinforced responding, for example, was completely eliminated by the 0.4 mg/kg dose of alpha-flupenthixol while heroin self-administration was maintained at lower but constant rates throughout the course of the test session. This result is, however, consistent with numerous demonstrations that high doses of various DA receptor antagonists produce deficits in the animal's ability to initiate and maintain responding (e.g. Beninger et al. 1980; Ettenberg et al. 1981; Fibiger et al. 1975; Posluns 1962). An attenuation in response capability would, of course, be expected to reduce both heroin- and cocaine-reinforced responding. However, combining such a response deficit with an apparently selective decrease in cocaine but not heroin reinforcement, might completely eliminate cocaine self-administration while leaving heroin self-administration at a reduced but constant rate.

Perhaps of greater significance, was the observation that low doses of alpha-flupenthixol did not increase responding for heroin, nor did naltrexone increase cocaine-reinforced responding. The specificity with which these antagonists exerted their behavioral effects again strongly suggests that separate neural substrates are responsible for the reinforcing actions of heroin and cocaine. This conclusion is further supported by the observation that haloperidol (another DA receptor antagonist) does not block morphine-induced conditioned reinforcement (Smith and Davis 1973). These data

are, of course, contrary to suggestions that the DA system mediates (in whole or in part) the reinforcing properties of both cocaine and heroin (e.g. Phillips and Le Paine 1980: Bozarth and Wise 1981a). This latter hypothesis is based on the demonstration that conditioned place preferences, produced by pairing a distinctive environment with opiate agonists, can be blocked by pretreatment with haloperidol (Schwartz and Marchok 1974) or pimozide (Bozarth and Wise 1981a). The observation that rats will acquire and maintain responding for morphine applied directly into the brain region containing mesolimbic DA cell bodies (the ventral tegmental area) is also suggestive of a dopamine involvement in opiate reinforcement (Bozarth and Wise 1981b; Phillips and Le Paine 1980).

While we cannot as yet offer a firm explanation that will resolve this contradiction, it is conceivable that the presence of numerous procedural differences may account for the discrepancy in the findings from the two experimental approaches. For example, the self-administration paradigm employs an active drug-seeking behavior while the place preference employs passive injections of the reinforcing drug. The doses and routes of administration are very different in the two paradigms: small IV injections in one and large IP injections in the other. In the self-administration paradigm, animals regulate the amount and frequency of the reinforcement and, indeed, administer a relatively large quantity of drug during each test session. The place preference procedure, however, employs a single injection of the reinforcer on each drug/place pairing day. How one or more of these procedural differences might act to produce the discrepant results from the two paradigms is, of course, a matter of conjecture. In any event it should be noted that the self-administration paradigm is, of course, more comparable to the human condition where both heroin and cocaine represent serious drug abuse problems (Jaffe 1980).

In summary, the present data, derived from an animal model of drug self-administration, demonstrate that DA and opiate receptor blockers differentially alter cocaine and heroin self-administration in a pharmacologically distinct way. Such results do not support the notion that activation of brain DA systems is necessary for opiate reinforcement. Rather, the present results suggest that independent substrates mediate the positive reinforcing properties of opiates and psychomotor stimulants.

Acknowledgements. We gratefully acknowledge Ralph Jacobson of Endo Laboratories (Garden City, N.Y.) and Ove Svendsen of H. Lundbeck and Company (Copenhagen, Denmark) for respectively providing us with generous amounts of naltrexone and alpha-flupenthixol. This work was supported in part by grants-in-aid from a series of U.S. corporations and foundations consisting of: Allied Chemical Foundation, Amco Foundation, Arthur Vining Davis Foundation, Conrad N. Hilton Foundation, Metropolitan Life Foundation, Occidental Research Corporation, Phillip Morris Inc., Phillips Petroleum Foundation, PPG Industries and Sun Company. Support was also provided by NIDA grant No. 01785 and NIAAA grant No. 03504. AE holds a J. Aron Foundation Fellowship and is a Medical Research Council of Canada Postdoctoral Fellow.

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Received January 14, 1982; Final version May 3, 1982