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Self-Administration of Central Stimulants by Rats: A Comparison of the Effects of d-Amphetamine, Methylphenidate and McNeil 4612

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NIELSEN, J. A., N. J. DUDA, D. J. MOKLER AND K. E. MOORE. *Self-administration of central stimulants by rats: A comparison of the effects of d-amphetamine, methylphenidate and McNeil 4612.* PHARMACOL BIOCHEM BEHAV 20(2) 227–232, 1984.—Rats were trained to press a lever for the intravenous administration of d-amphetamine. The rate of responding was decreased in a dose-dependent and time-related manner by non-contingent injections of d-amphetamine, methylphenidate or McNeil 4612. Methylphenidate and McNeil 4612 also maintained self-administration behavior when they were substituted for d-amphetamine, whereas substitution of saline for d-amphetamine resulted in extinction of the self-administration behavior. These data suggest that methylphenidate and McNeil 4612, like d-amphetamine, can act as reinforcers in rats.

Self-administration d-Amphetamine Methylphenidate Rats

RATS will lever press for intravenous self-injections of d-amphetamine [10,17]. Dopaminergic neurons appear to be criticially involved in mediating this behavior [23]. For example, non-contingent injections of dopaminergic agonists (apomorphine, piribedil) reduced the lever pressing for d-amphetamine [24], whereas dopaminergic antagonists (pimozide, d-butaclamol) increase the rate of self-injections of d-amphetamine [26].

Many of the central stimulant actions of amphetamine-like drugs result from their ability to facilitate the release or inhibit the uptake of dopamine (DA) [9]. Methylphenidate has central stimulant properties which are similar in many respects to those of d-amphetamine. Like d-amphetamine, methylphenidate blocks the neuronal uptake [5] and facilitates the release of DA [4], although the mechanism by which it does this is not identical to that of d-amphetamine. For example, the central stimulant actions of d-amphetamine are blocked by α-methyltyrosine, which disrupts DA synthesis [21], but not by reserpine, which depletes stores of DA [1]; while the central stimulant actions of methylphenidate are reduced by reserpine but not by α-methyltyrosine [15, 16, 18]. d-Amphetamine and methylphenidate can also be differentiated by the way they influence the rate of DA synthesis in the brain. Methylphenidate decreases in *in vivo* rate of DA synthesis in the striatum, nucleus accumbens and olfactory tubercle, while d-amphetamine increases DA synthesis in the striatum but is without effect in the other two regions [7].

McN 4612 ([6 β, 10bα]-1,2,3,5,6,10b-hexahydro-6-phenylpyrrolo[2,1-a] isoquinoline) is an experimental drug with central stimulant and possibly antidepressant properties. It resembles the actions of d-amphetamine and methylphenidate in several respects (Moore, Nielsen and Demarest, unpublished). In rodents it increases locomotor activity, causes ipsilateral turning in rats with unilaterally destroyed nigrostriatal DA neurons, and blocks the uptake of DA into striatal synaptosomes. It resembles methylphenidate, but not d-amphetamine, in that it reduces the rate of DA synthesis is selected regions of the rat forebrain.

Results of studies to date suggest that methylphenidate and McN 4612 mimic d-amphetamine in that they exert at least some of their characteristic central stimulant effects by facilitating the release and/or by blocking the reuptake of DA at terminals of neurons in the forebrain, albeit by different

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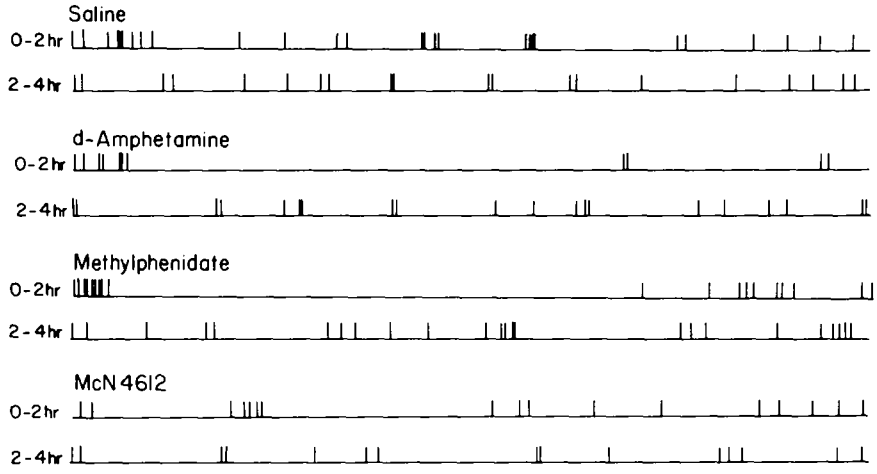

FIG. 1. Disruption of d-amphetamine self-administration by non-contingent injections of d-amphetamine, methylphenidate and McN 4612. On separate days rat number 32 was given a subcutaneous injection of saline, d-amphetamine (2 mg/kg), methylphenidate (8 mg/kg) or McN 4612 (1 mg/kg) and then allowed to self-inject d-amphetamine (0.06 mg/kg/injection) for 4 hr. Each vertical line represents one self-injection.

mechanisms. The purpose of the present study was to determine if methylphenidate and McN 4612 influence d-amphetamine self-administration, and if substitution of these drugs for d-amphetamine maintains self-administration behavior in rats accustomed to self-injecting d-amphetamine.

METHOD

Male Sprague-Dawley rats (225–250 g) were purchased from Spartan Farms, Haslett, MI, and individually caged in an animal room where they were allowed access to food and water ad lib. Each animal was anesthetized with Equithesin (3 ml/kg) and a silastic catheter was surgically implanted into the jugular vein [19]. After a 5–7 day period for recovery from surgery self-administration training was begun.

Animals were placed in self-administration cages (18×20×26 cm) equipped with a partially shielded operant lever activating a pneumatic pump which delivered predetermined volumes (0.2 ml/kg) of saline or drug solution via the jugular catheter [8,20]. Initial training sessions were for approximately 8 hr (0900–1700 hr) or 16 hr (1700–0900 hr) during which time one lever press delivered one drug injection of 0.12 mg d-amphetamine sulfate/kg in sterile 0.9% saline. Rats were given 3 "free" injections at the beginning of the first few training sessions so as to facilitate self-administration behavior. By the end of 7 sessions this behavior had stabilized (less than 20% variation in the number of self-injections over three testing days). In all subsequent sessions the dose of d-amphetamine sulfate was lowered to 0.06 mg/kg/injection in order to increase the basal rate of responding.

Influence of Non-Contingent Injections of d-Amphetamine, Methylphenidate and McN 4612 on the Intravenous Self-Administration of d-Amphetamine

Seven rats were placed in the self-administration cages every second day from 0900–1300 hr and allowed to self-inject d-amphetamine (0.06 mg/kg/injection) until their rate of responding had stabilized. Then, in random order, the animals were injected subcutaneously with d-amphetamine (1 or 2 mg/kg), methylphenidate (4 or 8 mg/kg) or McN 4612 (0.5 or 1 mg/kg) immediately before they were placed in the self-administration cages. Between drug testing sessions each rat was allowed to self-administer d-amphetamine following the subcutaneous injection of saline (1 ml/kg) to insure that self-administration behavior was maintained; the responses during these sessions are subsequently referred to as "control responding".

Self-Administration of Methylphenidate and McN 4612 by Rats Accustomed to Self-Administering d-Amphetamine

Four rats were placed in the self-administration cages every second day from 1600–0800 hr and allowed to self-inject d-amphetamine (0.06 mg/kg/injection) until their rate of responding had stabilized. Then, in random order, the drug solution in the injection reservoir was changed to saline (0.9%), methylphenidate (0.2 or 0.4 mg/kg/injection) or McN 4612 (0.05 or 0.1 mg/kg/injection). Between these sessions animals were allowed to self-administer d-amphetamine to insure that control responding was maintained.

In all experimental sessions the number of lever presses per hour is expressed as a percentage of the lever presses in the corresponding period of the immediately preceeding control session. The doses of drugs are expressed as their respective water soluble salts which were d-amphetamine sulfate (Sigma, St. Louis, MO), methylphenidate hydrochloride (Ciba-Geigy, Summit, NJ), and McN 4612 butenedioate (McNeil Pharmaceutical, Spring House, PA).

RESULTS

Influence of Non-Contingent Injections of d-Amphetamine, Methylphenidate and McN 4612 on the Intravenous Self-Administration of d-Amphetamine

There was some variability in the rate of lever pressing for d-amphetamine among animals, but once the responding had stabilized, the number and pattern of lever presses by each animal remained fairly constant from control session to control session. An example of control responding can be seen

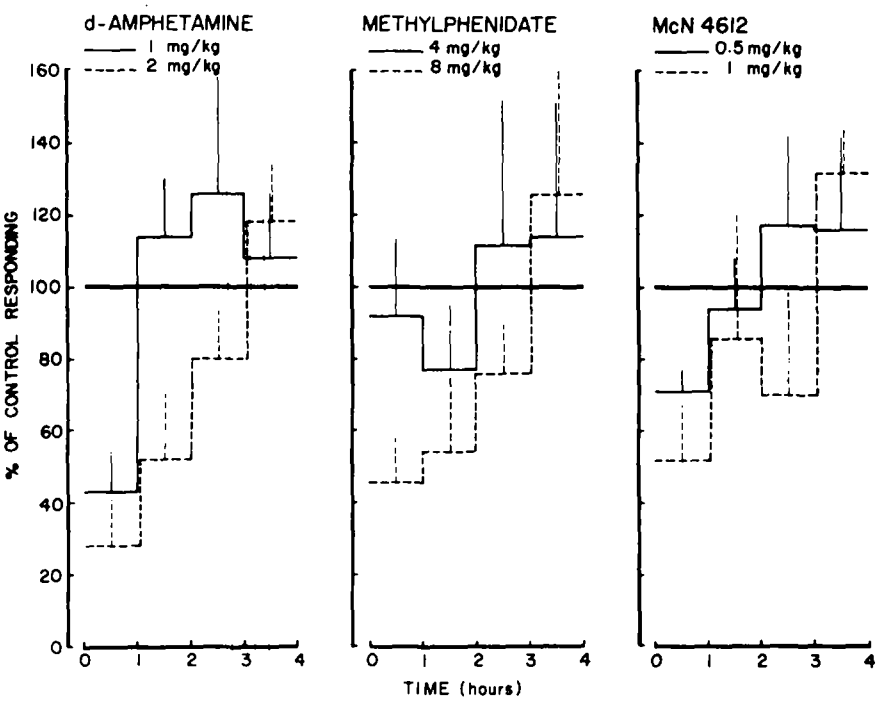

FIG. 2. Time and dose characteristics of non-contingent injections of d-amphetamine, methylphenidate and McN 4612 on the self-administration of d-amphetamine. Immediately after subcutaneous injections of saline, d-amphetamine (1 or 2 mg/kg), methylphenidate (4 or 8 mg/kg) or McN 4612 (0.5 or 1 mg/kg) rats were allowed to self-inject d-amphetamine (0.06 mg/kg/injection) for 4 hr. Responding after each non-contingent injection of drug was calculated as a percentage of responding in the preceeding session in which the animal was administered a non-contingent injection of saline and made 28±3, 16±3, 13±1, 13±2 (mean±1 S.E., N=5–7) self-injections per hour during the 4 consecutive hours.

at the top of Fig. 1. In this example a rat had been injected with saline immediately prior to being placed in the self-administration cage. When the same animal was injected subcutaneously with d-amphetamine (2 mg/kg), methylphenidate (8 mg/kg) or McN 4612 (1 mg/kg) there was, after a short latency, a period of at least an hour when the rate of responding for d-amphetamine was reduced.

A summary of the effects of non-contingent injections of d-amphetamine, methylphenidate and McN 4612 on d-amphetamine self-injection behavior is presented in Fig. 2. An injection of 1 mg/kg d-amphetamine reduced responding for the first hour while a higher dose (2 mg/kg) was effective for about 2 hours. The lower of two doses of methylphenidate (4 mg/kg) was without effect while the higher dose (8 mg/kg) reduced lever pressing for at least 2 hours. McN 4612 caused a dose-related decrease in responding during the first hour after it was injected. In all cases, lever pressing returned to approximately 100% of control responding by the fourth hour. Thus, non-contingent injections of all three central nervous system stimulants caused a dose-related and time-dependent reduction in the self-administration of d-amphetamine.

Self-Administration of Saline, Methylphenidate and McN 4612 by Rats Accustomed to Self-Administering d-Amphetamine

The pattern of lever pressing for injections of d-amphetamine in an animal previously experienced in self-administering this drug is depicted in Fig. 3. The animal exhibited fairly frequent lever pressing during the first hour, and maintained a slower, but fairly constant rate of pressing thereafter. When the d-amphetamine solution in the injection reservoir was replaced with saline the animals repeatedly pressed the lever during the first hour, often at a rate greater than that seen when the animal was pressing for injections of d-amphetamine. Thereafter, however, the number of self-injections of saline declined, although occasional bursts of responding were observed. On the other hand, when the d-amphetamine solution was switched to methylphenidate (0.4 mg/kg/injection) or to McN 4612 (0.1 mg/kg/injection) the rat maintained a fairly consistent rate of lever pressing throughout the 8-hour period.

The mean responses of 4 animals subjected to these changes in the injection solution are summarized in Fig. 4. Although quite variable, the number of lever presses for saline increased during the first hour. During the remainder of the session the number of responses declined, but there was still great variability because of intermittent bursts of responding. When the injection fluid contained methylphenidate (0.4 mg/kg/injection) or McN 4612 (0.1 mg/kg/injection) there was less variation in the number of lever presses made, and the rate did not differ appreciably from the rate of responding for d-amphetamine. Furthermore, as depicted in Fig. 5, when the concentration of methylphenidate and McN 4612 in the injection solution was reduced by half (to 0.2 and 0.05 mg/kg/injection, respectively) the rate of responding throughout the 8 hour period was approximately doubled.

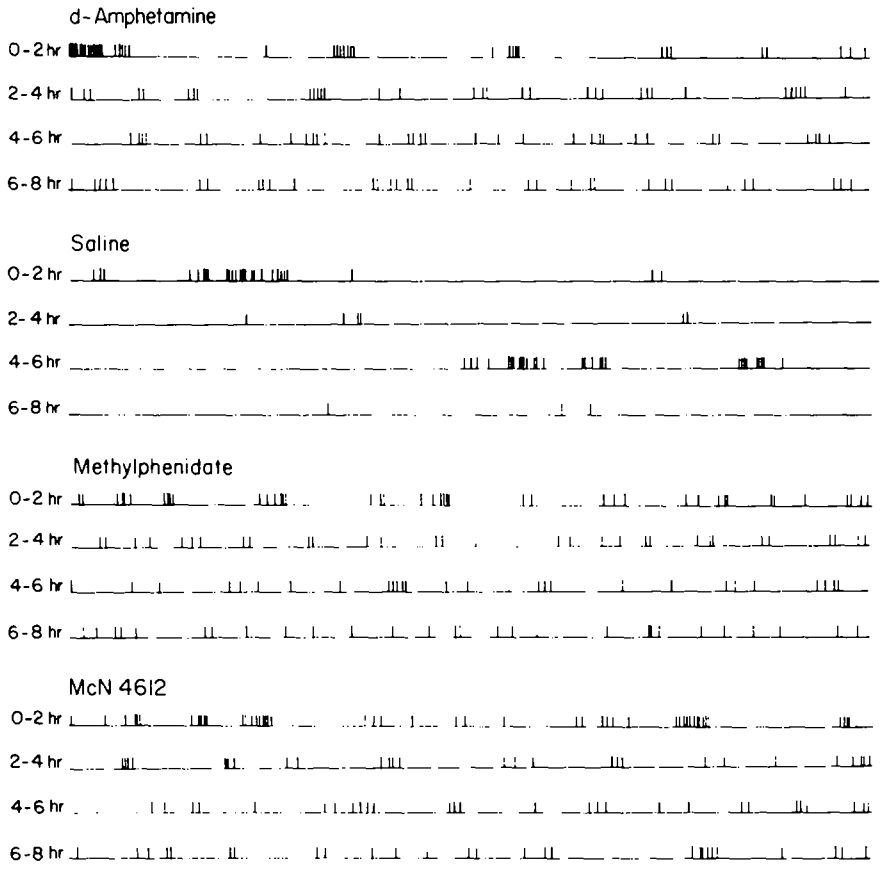

FIG. 3. Self-injections of saline, d-amphetamine, methylphenidate and McN 4612 by a rat previously trained to self-administer d-amphetamine. On separate days the d-amphetamine solution (0.06 mg/kg/injection) in the injection reservoir of rat number 56 was filled with saline, methylphenidate (0.4 mg/kg/injection) or McN 4612 (0.1 mg/kg/injection). Each vertical line represents one self-injection.

DISCUSSION

Although neurochemical profiles of methylphenidate and McN 4612 differ in some respects from those of d-amphetamine, all three compounds appear to exert at least part of their central stimulant properties as a result of their ability to indirectly activate DA receptors in the forebrain; they all either facilitate the release and/or block the reuptake of released DA (see Introduction). The results of the present study suggest that methylphenidate and McN 4612 resemble d-amphetamine with regard to their behavioral reinforcing properties in the rat. First, non-contigent injections of methylphenidate and McN 4612 cause a dose-related and time-dependent suppression of d-amphetamine self-administration. It is likely that this effect results from the ability of these drugs to increase the concentration of DA at postsynaptic receptor sites (possibly in the nucleus accumbens, see [8, 13, 14]). Non-contigent injections of direct DA receptor agonists (apomorphine and piribedil) also suppress self-injection of d-amphetamine [27]. Secondly, methylphenidate and McN 4612, unlike saline, will substitute for d-amphetamine in maintaining self-administration behavior. Rats accustomed to self-administering d-amphetamine will temporarily increase their rate of responding prior to extinction when the amphetamine-containing solution is replaced by saline ([24–27]; see also Fig. 3 and 4). On the other hand, if these animals are permitted to self-inject a drug which mimics d-amphetamine, an extinction response is not obtained and the animals continue to lever-press for the drug. For example, when the d-amphetamine solution is replaced with one containing apomorphine, piribedil, phenmetrazine or diethylpropion the animals continue to self-administer these drugs [6,27]. The results of the present study suggest that both methylphenidate and McN 4612 are also capable of maintaining self-injection behavior in animals trained to self-administer d-amphetamine. Furthermore, the rate at which they respond is dependent upon the self-injection dose. This is consistent with previous reports that the rate of self-administration of direct or indirect acting DA receptor agonists (d-amphetamine, cocaine, methamphetamine, pipradrol, and apomorphine) is inversely related to the dose of drug [2, 3, 10–12, 22].

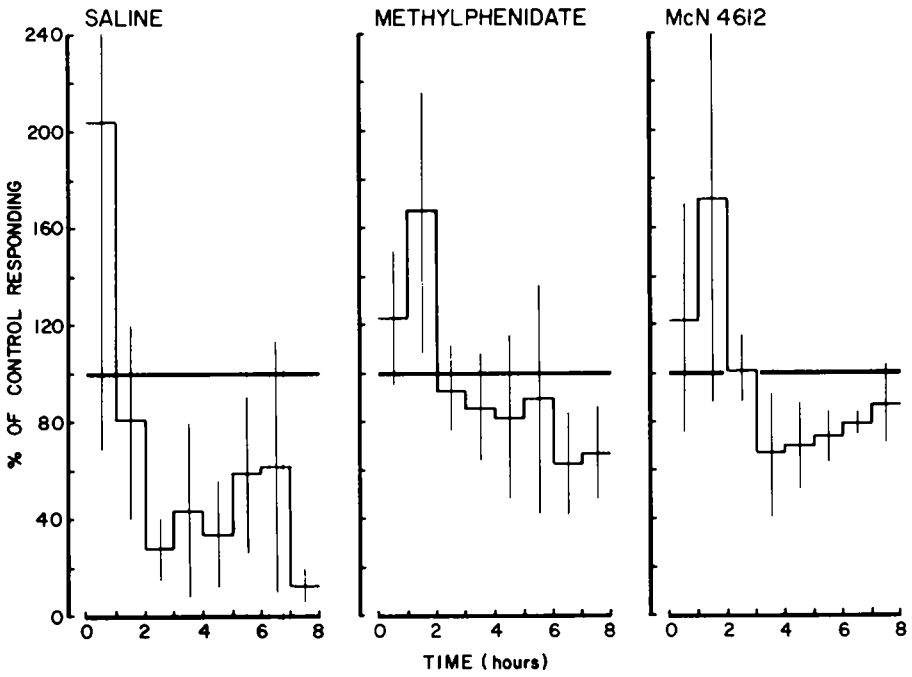

FIG. 4. Time course of self-administration of saline, methylphenidate and McN 4612 by rats previously trained to self-administer d-amphetamine. Rats lever-pressed for d-amphetamine (0.06 mg/kg/injection) at a rate of 24±6, 14±6, 17±4, 16±4, 16±1, 18±1, 19±2 and 17±4 injections/hour (mean±1 S.E., N=4) during 8 consecutive hours. The rate of responding of these rats for injections of saline, methylphenidate (0.4 mg/kg/injection) and McN 4612 (0.1 mg/kg/injection) is expressed as a percentage of their responding for d-amphetamine. Values represent means and vertical lines±1 S.E. calculated from 3–4 rats.

In summary, methylphenidate and McN 4612 act like d-amphetamine in suppressing, in a dose-related and time-dependent fashion, the response rate for d-amphetamine self-injections. They are also similar to d-amphetamine in that they are able to maintain self-administration behavior. The similarity of the three drugs suggests that they may have a common mechanism of action, namely indirect stimulation of postsynaptic DA receptors.

ACKNOWLEDGEMENTS

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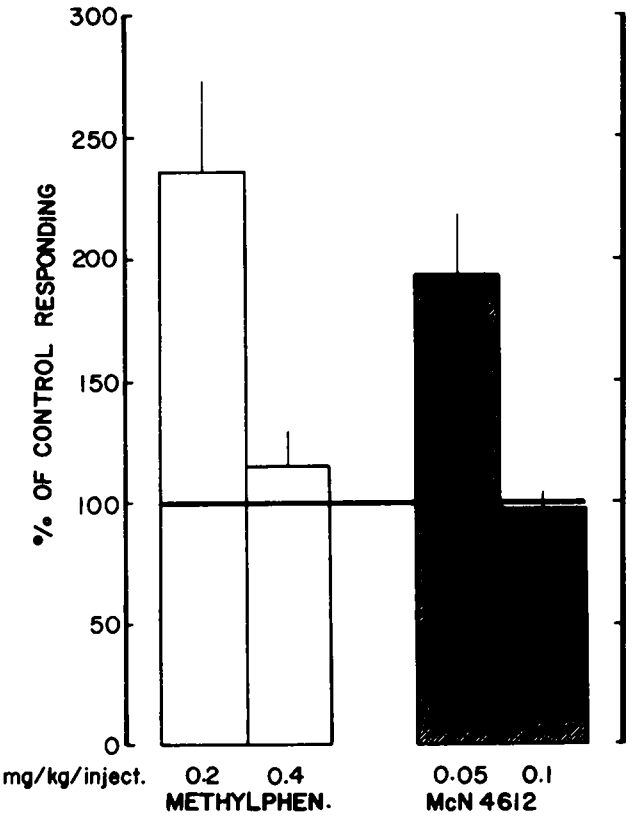

FIG. 5. Dose-related changes in the number of self-injections of methylphenidate and McN 4612 in rats trained to self-administer d-amphetamine. Rats self-injected d-amphetamine (0.06 mg/kg/injection) 145±10 (mean±S.E., N=4) times during an 8 hour session (100%). The responding of these rats for methylphenidate (0.2 or 0.4 mg/kg/injection) or McN 4612 (0.05 or 0.1 mg/kg/injection) is expressed as a percentage of their responding for d-amphetamine. Values represent means and vertical lines±1 S.E. calculated from 3–4 rats.

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