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BRIEF COMMUNICATION

Apomorphine Self-Injection is Not Affected by Alpha-methylparatyrosine Treatment: Support for Dopaminergic Reward

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Pretreatment with AMPT at doses which markedly altered the self-injection of amphetamine did not affect the self-injection of apomorphine. These data support the idea that the self-injection of apomorphine is produced via the direct activation of dopamine receptors rather than by the release of either norepinephrine or dopamine.

Apomorphine Reward Reinforcement Dopamine Catecholamines Self-injection Drug abuse

WE reported recently that rats will self-inject the dopamine receptor stimulant apomorphine [1]. This discovery strongly supports the idea that the activation of certain dopaminergic receptors in the brain can produce reinforcement. But, it has been suggested that dopamine receptor stimulation also produces activation of noradrenergic neurons [6]; that central levels of norepinephrine are affected by high doses of apomorphine [5,6]; and that both noradrenergic and dopaminergic neurons are involved in the stimulation of motility by apomorphine [4]. Thus it appeared possible that the reinforcing activity of apomorphine was mediated via the release of norepinephrine.

In order to test this proposition we decided to examine the self-injection (S.I.) pattern of apomorphine during the lowered brain levels of norepinephrine (and dopamine) produced by parenteral treatment with the tyrosine hydroxylase inhibitor alpha-methylparatyrosine (AMPT). Our assumption was that if the reinforcing property of apomorphine is due to the direct stimulation of dopaminergic receptors, AMPT treatment would have no effect; but if the release of norepinephrine (or of dopamine) is involved, AMPT treatment would alter the self-injection pattern of apomorphine.

Since we performed no brain chemistry we also examined the effect of AMPT treatment on the S.I. of amphetamine, in order to indirectly indicate whether or not our AMPT regimen was effective in altering brain catecholamine levels. It has previously been demonstrated that AMPT treatment reduces the reinforcing effect of methamphetamine [7] and of d-amphetamine [2] and markedly reduces the reinforcing property of electrical self-stimulation [8].

METHOD

Female rats weighing 230–250 g had a Weeks cannula [11], fabricated from a combination of silastic and polyethylene tubing, implanted into the right external jugular vein and then brought around the body subcutaneously to an exit from the back of the neck. At least 14 days were allowed for recovery from surgery. Test cages contained a standard rodent operant lever. Solutions were delivered to the jugular cannula by a motor driven pump connected to a feed-thru swivel (BRS/LVE, No. 191 03). Each lever press produced one injection (FR-1) of 0.08 ml during a 2.5 sec infusion period. All animals injecting apomorphine received 0.125 mg/kg per lever press. Animals injecting d-amphetamine received 0.25 mg/kg per press. Food and water were available ad lib.

Apomorphine hydrochloride (Merck) was dissolved in physiological saline which contained 0.025% ascorbic acid. D-amphetamine sulphate (Smith-Kline) was dissovled in physiological saline. AMPT (DL-alpha-methyltyrosine methylester hydrochloride, Aldrich) was dissolved in water. Doses of these drugs were calculated as mg salt per kg. Both the d-amphetamine S.I. and apomorphine S.I. groups consisted of 4 rats. All animals were placed in their test

chambers and allowed to self-inject for 5 hr per day (11:00 a.m. to 4:00 p.m.). All had been self-injecting drug (d-amphetamine or apomorphine) for at least 10 days prior to the AMPT treatment day. On a treatment day each rat received 150 mg/kg total dose of AMPT IP given in injections of 50 mg/kg at 1:00 a.m., 5:00 a.m. and 9:00 a.m.

RESULTS AND DISCUSSION

The pattern of apomorphine S.I. was undisturbed by treatment with AMPT and no significant differences in the number of injections taken on the days before treatment versus the day of AMPT treatment were observed. ($p<0.05$ using analysis of variance with a split-block design). The results are summarized in Fig. 1, which shows the mean injections taken per hour on the 3 days preceding AMPT and on the day of AMPT treatment.

On the contrary, AMPT treatment dramatically altered the pattern of d-amphetamine S.I. (see Fig. 1). After AMPT the number of injections taken increased, particularly during the first hour of S.I. An analysis of variance using a split-block design showed that the increase in injections of d-amphetamine taken during the first hour on the AMPT day was significantly different from the number of injections taken during the first hour of the control days at the 0.005 level. The overall increase during the entire 5 hr period was significant at the 0.05 level of confidence.

We used the AMPT doses and schedule established by Reck *et al.* [9] who showed that this treatment reduces brain levels of both norepinephrine and dopamine by more than 70%. Although we did not perform any brain chemistry we showed that the S.I. pattern of d-amphetamine was dramatically altered by our AMPT treatment. The change produced, particularly the much higher level taken during the first hour, resembles that which we have observed when saline is substituted for a reinforcing drug: i.e., the pattern of d-amphetamine S.I. after AMPT resembles that observed during the first day of extinction [1]. We regard this as an indirect indication that our AMPT treatment regimen was effective in reducing brain catecholamine levels.

In the experiment reported here AMPT produced no effect on the self-administration of apomorphine. Only if one argues that the reinforcing activity of apomorphine is based exclusively on release of catecholamines from the reserve pool, or that the same level of reinforcement can be maintained by a given level of apomorphine (post AMPT) via a shift from functional pool release to reserve pool release, can it be maintained that the release of catecholamines is involved. These possibilities appear unlikely at the present time.

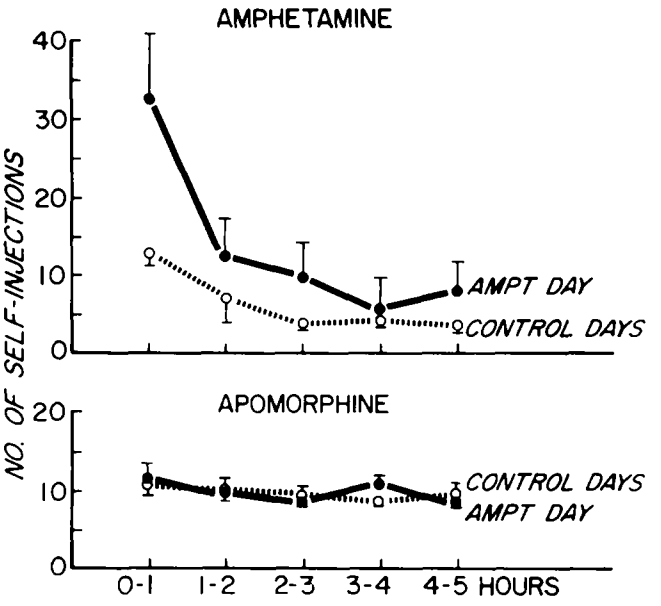

FIG. 1. Effect of AMPT on the self-injection of d-amphetamine and of apomorphine (4 rats per group). Data shown are means and standard errors for injections taken on the 3 days preceding, and on the day of, AMPT treatment hour by hour for the 5 hour self-injection period. AMPT treatment produced no alteration in the S.I. of apomorphine but produced a statistically significant increase in the intake of d-amphetamine (see text).

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