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Effect of reserpine on accumulation and removal of *d*-amphetamine-^{3}H*

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PREVIOUS work has indicated that both acute[1, 2] and chronic reserpine pretreatments[3] enhance the locomotor stimulant effects of *d*-amphetamine. Many drugs, notably chlorpromazine[4] and the tricyclic antidepressants,[5, 6] have been shown to alter the metabolism and removal of amphetamine in tissues. We have investigated the accumulation and elimination of *d*-amphetamine-^{3}H from brain and plasma in rats pretreated with reserpine.

Female Sprague–Dawley rats, 150–180 g, were injected intraperitoneally with saline or 2 mg/kg of reserpine 24 hr before receiving 2 mg/kg of *d*-amphetamine-^{3}H sulfate (universally labeled, 8·9 c/mmole; New England Nuclear Corp.). These animals are referred to as acutely pretreated rats. The chronic pretreatment groups received 0·9% saline or 0·5 mg/kg of reserpine (i.p.) daily for 14 consecutive days. These chronic pretreatment groups were challenged with 1 mg/kg of *d*-amphetamine-^{3}H 24 hr after the last pretreatment injection. All doses of amphetamine were injected intraperitoneally.

Amphetamine was measured by the method of Axelrod,[7] as modified for liquid scintillation spectrophotometry.[5] Rats were killed by decapitation at specified intervals after amphetamine injection. Aliquots of plasma and whole brain homogenates were analyzed for unmetabolized *d*-amphetamine-^{3}H sulfate. Rate constants for drug removal were calculated by the method of least-squares fit with the use of a computer.

There were no significant differences in the amphetamine levels from tissues of either acute pretreatment group at any time after 2 mg/kg of the labeled stimulant (Fig. 1). The rates of drug removal from plasma and brain in these rats were nearly identical (Table 1).

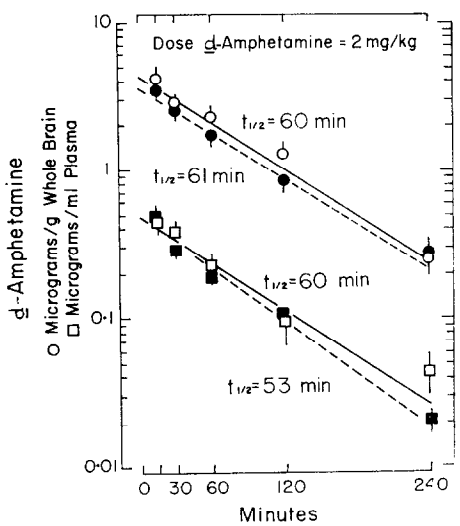

FIG. 1. Brain (circles) and plasma (squares) drug levels in acute saline-treated (open symbols, solid lines) and acute reserpine-treated rats (solid symbols, broken lines) after injection of 2 mg/kg of *d*-amphetamine-^{3}H sulfate. Each point represents the mean amphetamine level (± S.E.M.) at the indicated time after injection. The brain or plasma half-life of amphetamine is depicted adjacent to the appropriate curve.

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TABLE 1. RATE CONSTANTS FOR THE REMOVAL OF *d*-AMPHETAMINE-^{3}H SULFATE FROM BRAIN AND PLASMA IN RATS PRETREATED WITH SALINE OR RESERPINE

Pretreatment	Dose *d*-amphetamine (mg/kg)	N	Mean k (min^{-1}) ± S.E.M. Brain	Plasma
Saline (24 hr)	2	30	− 0·0121 ± 0·0017	− 0·0121 ± 0·0013
Reserpine (2 mg/kg; 24 hr)	2	24	− 0·0117 ± 0·0010	− 0·0135 ± 0·0008
Chronic saline	1	15*	− 0·0148 ± 0·0028	− 0·0150 ± 0·0019
Chronic reserpine	1	15*	− 0·0061 ± 0·0022†	− 0·0081 ± 0·0024†

* N = 12 for brain samples (see text).
†$P < 0·05$ compared to values obtained in chronic saline rats.

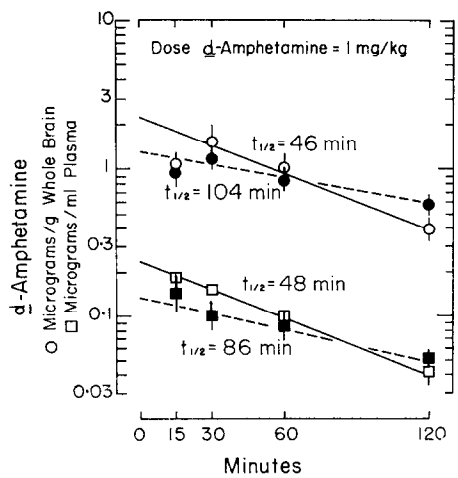

FIG. 2. Brain (circles) and plasma (squares) drug levels in chronic saline treated (open symbols, solid lines) and chronic reserpine-treated rats (solid symbols, broken lines) after injection of 1 mg/kg of *d*-amphetamine-^{3}H sulfate. Each point represents the mean amphetamine level (± S.E.M.) at the indicated time after injection. The brain or plasma half-life of amphetamine is depicted adjacent to the appropriate curve.

Tissue drug levels after 1 mg/kg *d*-amphetamine-^{3}H in the chronic pretreatment groups are shown in Fig. 2. In contrast to the larger dose of the stimulant used in acutely pretreated rats, brain amphetamine levels in the chronic pretreatment groups were not maximal until 30 min after the drug. Accordingly, the 15-min drug levels were not utilized in the calculation of the rate constant for the decline of drug levels from brain in the chronic pretreatment groups (Table 1). The rates of removal of amphetamine from tissues obtained in chronic reserpine-pretreated rats were significantly lower than values obtained in the chronic saline group. At no time, however, were the absolute tissue levels of amphetamine significantly different in the two chronic groups.

These data demonstrate that the enhanced locomotor stimulation effects of amphetamine in either the acute[1] or the chronic reserpine[3] pretreatment groups cannot be attributed to increased drug levels in

brain or plasma. An increase in the duration of stimulation to 1 mg/kg of the stimulant was reported previously for the chronic reserpine-pretreated rats.[3] This increased duration may be related to the slower rate of removal of the drug reported here (Table 1). Whether or not altered catabolism of amphetamine can explain the results obtained in the chronic reserpine-pretreated rats is currently under study.

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