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BRIEF COMMUNICATION

Differential Effects of d- and l-Amphetamine on Mouse-Killing Behavior in Rats

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MALICK, J. B. *Differential effects of d- and l-amphetamine on mouse-killing behavior in rats.* PHARMAC. BIOCHEM. BEHAV. 3(4) 697–699, 1975. – Muricidal behavior in rats was selectively antagonized by both the d- and the l-isomer of amphetamine. However, d-amphetamine was approximately 8 times as potent as l-amphetamine as an inhibitor of mouse killing. The results of this study suggest that amphetamine antagonizes muricidal behavior in rats primarily via noradrenergic mechanisms. In addition, these results, as well as those in previous reports, imply that agents which modify the level of activity at central noradrenergic receptors may significantly alter the mouse-killing response of rats.

Muricidal (mouse-killing) rats Amphetamine isomers Norepinephrine Dopamine

STIMULANT drugs have been shown to be antagonists of the muricide (mouse-killing) response in rats [6]. Both d-amphetamine [2, 6, 8, 12] and methamphetaime [12] have been shown to be potent, selective (i.e., they do not produce neurological impairment at effective doses) inhibitors of muricidal behavior.

The behavioral effects of amphetamine are generally believed to involve the brain catecholamines, dopamine (DA) and norepinephrine (NE); amphetamine is thought to act via release of catecholamines or by blockade of their reuptake inactivation processes or a combination of both [11]. The two steric isomers of amphetamine have been shown to differentiate DA and NE in the brain since d-amphetamine was much more potent as a releaser of NE than was l-amphetamine in both mice [9] and rats [13, 14, 16]. In addition, d-amphetamine was approximately 10 times as potent as its l-isomer as an inhibitor of the reuptake inactivation process in NE neurons in the brain whereas the two isomers had similar potencies in DA neurons [3].

Taylor and Snyder [14] have proposed that, when the two isomers of amphetamine are studied, the ratio of their activities can be used to determine whether the effects are predominantly noradrenergic or dopaminergic. They state that, if d-amphetamine is approximately 10 times as potent as l-amphetamine, the effect is primarily NE-mediated; however, if the d/l ratio is only two or less, the effect is primarily DA-mediated. Many investigators have utilized this technique in rats and, as a result, it was concluded that amphetamine-induced anorexia [1] and stereotypy [13,14] were primarily mediated by DA whereas amphetamine-induced increases in locomotor activity [13,14] and lateral hypothalamic self-stimulatory behavior [10] were primarily mediated by NE.

The primary goal of this study was to determine the relative activities of d-amphetamine and l-amphetamine as inhibitors of muricidal behavior in rats. The effect of l-amphetamine on mouse-killing has not been reported previously.

METHOD

Male Long-Evans hooded rats (Blue Spruce Farms, Altamont, New York), weighing 200–250 g at the beginning of screening for muricidal response, were used in these studies. After selection, all rats were isolated one per cage and maintained on ad lib food and water. Only rats that consistently killed mice within the 5 min test period were used in this study. When utilized for drug testing, the rats were tested in the morning (same day control) and then given test drug or

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TABLE 1

INHIBITION OF MOUSE-KILLING BY AMPHETAMINE ISOMERS

Treatment*	Dose (mg/kg IP)	No. of Rats Inhibited / No. of Rats Tested	ED_{50} (mg/kg IP) for Inhibition of Mouse-Killing (95% Fiducial Limits)†
d-amphetamine sulfate	0.125	3/10	0.18
	0.25	7/9	(0.05–0.27)‡
	0.5	8/10	
	1.0	5/5	
l-amphetamine sulfate	0.3	0/10	1.47
	0.6	2/15	(1.07–2.22)
	1.0	9/20	
	2.0	6/10	
	3.0	11/15	

*Rats tested for muricidal behavior 60 min post drug administration.

†ED_{50} and 95% fiducial limits were calculated by Probit Maximum Likelihood Analysis [5].

‡The potency ratio and 95% fiducial limits comparing d-amphetamine to l-amphetamine was 8.3 (4.9–17.0), calculated by Maximum Likelihood Potency Probit Analysis [5].

placebo in the afternoon and retested for killing one hour after drug administration. Immediately following the mouse killing test, all rats were tested for neurological impairment (ataxia) on a 45° inclined screen. Subsequent drug administrations were at least one week apart. The ED_{50}, that dose of drug which inhibited muricidal behavior in 50% of the rats tested, and 95% fiducial limits were calculated by Probit Maximum Likelihood Analysis [5].

The drugs used in this study were l-amphetamine sulfate and d-amphetamine sulfate. Drug doses are expressed in terms of mg/kg of free base. All drugs were dissolved in distilled water and administered intraperitoneally (IP) in volumes of 1 ml/kg.

RESULTS

d-Amphetamine was found to be a potent inhibitor of mouse-killing in rats. The ED_{50} value for d-amphetamine was found to be 0.18 mg/kg, i.p. (Table 1). The effect was selective in that, at the ED_{50} dose, no other overt changes in behavior were observed (e.g., motor stimulation, neurological impairment or stereotypy).

l-Amphetamine also produced a dose-related inhibition of muricide with an ED_{50} value of 1.47 mg/kg, i.p. (Table 1). The l-isomer was 8.3 times less potent than the d-isomer of amphetamine as an antagonist of mouse-killing by rats (Maximum Likelihood Potency Probit Analysis).

DISCUSSION

The selective antagonism by d-amphetamine of muricidal behavior in this study confirms the results of previous investigations [2, 6, 8, 12]. In addition, l-amphetamine was also found to be a potent, selective antagonist of this response; the effect of the l-isomer on mouse-killing has not been reported in prior publications. Since the d-isomer was approximately 8 times as potent as the l-isomer as an inhibitor of mouse killing, the Taylor and Snyder hypothesis [14] would predict that the effect of amphetamine on this behavior was primarily mediated by NE.

Previous studies [4,7] have demonstrated that the lateral hypothalamus, an area rich in NE axons and terminals, plays an important role in the mediation of predatory aggression (muricide). In addition to amphetamine, other drugs which augment the action of NE at adrenoceptive sites, the monoamine oxidase inhibitors (e.g., iproniazid and phenelzine), and the reuptake inhibitors (e.g., imipramine and amitriptyline), also demonstrate selective antimuricidal activity [6]. In another study, Vogel and Haubrich [15] observed that a significant number of muricidal rats stopped killing following a series of 20 electroconvulsive shock treatments that resulted in significantly elevated brain levels of NE without significant changes in DA or 5-HT levels. The results of this study suggest that amphetamine antagonized muricidal behavior in the rat primarily via noradrenergic mechanisms.

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