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BRIEF COMMUNICATION

Amphetamine Isomers: Influences on Locomotor and Stereotyped Behavior of Cats[1]

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NORTH, R. B., S. I. HARIK AND S. H. SNYDER. *Amphetamine isomers: influences on locomotor and stereotyped behavior of cats.* PHARMAC. BIOCHEM. BEHAV. 2(1) 115–118, 1974. – Catecholamine release and reuptake are considerably more stereoselective at norepinephrine than at dopamine nerve terminals, suggesting that pronounced differences in the influence of amphetamine isomers on particular behaviors favors norepinephrine mediation while similar actions of these isomers indicates a predominant role for dopamine. (+)-Amphetamine is markedly more potent than its (–)-isomer in stimulating locomotor activity of the cat while the two isomers differ less in provoking stereotyped behavior. These findings support a major role for brain norepinephrine in mediating amphetamine-induced locomotor enhancement, while dopamine may be more important in facilitating stereotyped behavior. Besides inducing stereotyped behavior, L-Dopa greatly enhances locomotor activity, which suggests an important role for dopamine in mediating locomotor activation.

Amphetamine Norepinephrine Dopamine Locomotor activity Stereotyped behavior

BECAUSE of chemical similarities, the behavioral effects of amphetamines are generally thought to involve the brain catecholamines, norepinephrine (NE) and dopamine (DA). One approach to differentiating whether a particular behavioral effect of amphetamine is mediated by NE or DA employs specific lesions of particular DA or NE pathways [4,24]. Another line of investigation has made use of steric differences – the asymmetry of the NE molecule contrasted with DA's molecular symmetry – which are recognized differentially by NE and DA neurons. Synaptically released catecholamines are primarily inactivated by reuptake into nerve terminals. The uptake process has been reported to display more affinity for (–)-NE and (+)-amphetamine than for the opposite isomers [3,12], though discrepant findings have been reported [7, 9, 23] for amphetamine isomers. By contrast, catecholamine uptake by DA neurons in the corpus striatum [3] or retina [10] is affected similarly by both isomers of NE. Ephedrine isomers also differentiate NE and DA in a pattern confirming results with NE and amphetamine isomers [3, 11, 12]. In the intact rat [21,22] and mouse [15], (+)-amphetamine is considerably more potent than (–)-amphetamine in depleting NE levels in the brain.

Because amphetamines are thought to act by release of catecholamines or blockade of their reuptake inactivation, both of which processes are affected differentially by amphetamine isomers in DA and NE neurons, several investigations have employed amphetamine isomers to determine whether NE or DA were primarily involved in a given behavioral effect. Behaviors mediated predominantly by NE should be influenced much more by (+)- than by (–)-amphetamine, while DA mediated behaviors should be affected similarly by the two isomers. Self-stimulation in the area of the medial forebrain bundle in the lateral hypothalamus, an area rich in NE axons and terminals, is enhanced 7–9 times more by (+)- than by (–)-amphetamine [16,20]. By contrast, self-stimulation in the area of the substantia nigra, which contains dopamine call bodies, is affected similarly by the two amphetamine isomers [16]. Turning behavior by rats after unilateral lesions of the substantia nigra, a behavior which is definitely dopamine mediated, is elicited to the same

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extent by (+)- and (−)-amphetamine [1].

In rats (+)-amphetamine is 10 times as potent as (−)-amphetamine in stimulating locomotor activity [18, 21, 22], suggesting a major role for NE in this behavior, while (+)-amphetamine is only about twice as potent (−)-amphetamine in enhancing stereotyped behavior in rats [21,22] dogs [25], and cats [26], indicating a greater importance for DA. Stereotyped behavior is elicited by amphetamine in a variety of mammalian species [17] and is thought to mimic such behavior observed in amphetamine addicts undergoing psychosis [14,19]. The exact pattern varies with species. In rats, sniffing, licking and gnawing predominate, and are graded on an all-or-none scale [21,22]. Cats exhibit side-to-side head movements with staring which has been likened to hallucinatory and stereotyped behavior of human amphetamine addicts [5], and which can be evaluated in a more quantitative fashion. In the present study, we have compared the influence of several doses of (+)- and (−)-amphetamine on locomotor activity and on stereotyped behavior of cats and contrasted these effects with those elicited by L-dihydroxyphenylalanine (L-Dopa), the metabolic precursor of NE and DA.

METHOD

Locomotor and stereotyped behavior of unrestrained adult cats (2.4 − 4 kg) was monitored in Lucite cages (90 × 60 × 54 cm). Locomotor activity was quantitated as total interruptions of 3 horizontal red light beams (2 traversing the cage's width and one its length, at a height of 20 cm), detected by photoelectric relays triggering electromechanical counters. Activity score was expressed as the ratio of locomotor activity under the influence of a given drug to activity during the two hours placebo period preceding such drug administration. Stereotyped behavior was simultaneously graded on a scale from 0 to +4; zero represents a normal absence of stereotyped behavior, while +4 is equivalent to the stereotyped behavior induced in preliminary examinations by supramaximal doses of intravenously-administered L-Dopa (100 mg/kg) or (+)-amphetamine (10 mg/kg).

L-Dopa was dissolved in 0.5 N HCl which was titrated with 10 N NaOH to a pH of 1.5−2. Amphetamine sulfate isomers were dissolved in 0.9% NaCl. Drugs were injected into the saphenous vein in amount of 1 ml/kg over a 15 sec period. Prior to administration of drug, animals were observed for 2 hr and activity and stereotypy scored, after injection of 1 ml/kg of the appropriate vehicle for each drug.

The effects of 3 doses of the 3 drugs were monitored in each of 15 cats. Each cat received the 9 drug treatments at weekly intervals and in a random sequence. Observers were unaware of the drug or dose administered. Scores of stereotyped behavior were kept independently by two observers in early trials and agreed closely.

RESULTS

L-Dopa and the 2 amphetamine isomers all enhance locomotor activity and induce stereotyped behavior; however, the dose-response characteristics vary with the different drugs. (Fig. 1) At all three doses (+)−amphetamine is markedly more effective than (−)−amphetamine in enhancing locomotor activity. At 1, 4 and 10 mg/kg, (+)−amphetamine produces 2, 4 and 12 times as much activity, respectively, as the vehicle. By contrast at 1 and at 5 mg/kg (−)−amphetamine elicits no more activity than vehicle alone, and at 10 mg/kg enhances locomotion only twice vehicle levels. Since 10 mg/kg of (−)−amphetamine is required to elicit the same amount of locomotor stimulation as 1 mg/kg of (+)−amphetamine appears to be about 10 times as potent as (−)−amphetamine in stimulating locomotor activity in cats, although precise comparisons of potency are not feasible.

By contrast amphetamine isomers differ much less in stimulating stereotyped behavior. Both produce stereotyped activity at the three doses studied. At 1 mg/kg mean stereotypy scores are 2.5 and 1.3 for (+)− and (−)−amphetamine respectively. At 5 mg/kg, the isomers differ less with scores of 3.5 for (+)− and 2.8 for (−)−amphetamine; and at 10 mg/kg there is very little difference between the effects of the two isomers. It is difficult to quantitate the isomeric variations in potencies for eliciting stereotyped behavior. The stereotypy score obtained with 10 mg/kg of (−)−amphetamine is the same as that obtained with 5 mg/kg of (+)−amphetamine, suggesting a 2-fold difference in potency, while the stereotypy value at 5 mg/kg of (−)−amphetamine is not markedly greater than that produced by 1 mg/kg of (+)−amphetamine. Thus, the potencies of the isomers for producing stereotyped behavior vary about 2−4 fold.

L-Dopa enhances locomotor activity and elicits stereotypy at all doses. For both locomotor activity and stereotypy, the effects of L-Dopa at 25, 50 and 100 mg/kg are the same as those of 1, 5 and 10 mg/kg of (+)−amphetamine, respectively. Thus the relative proportions of locomotor activity and stereotypy at all doses are similar for L-Dopa and (+)−amphetamine. The patterns for L-Dopa and (+)−amphetamine are unlike results with (−)−amphetamine, which produces much less locomotor stimulation at all doses than either of the other two drugs.

The qualitative features of locomotor stimulation and stereotyped behavior are similar for all three drugs. Locomotor activity that interrupts the photoelectric beams involves rapid pacing and occasional jumping around the cage. Stereotyped behavior consists of side-to-side head and neck searching movements and repetitive sniffing and licking of the walls of the cage, and does not interrupt the light beams.

The time course for stereotypy and locomotor activity are similar for all three drugs and all three doses. Stereotyped behavior initially appears at 5−15 min, is most intense at about 30 min and largely subsides at the end of the 2 hr observation period. Locomotor stimulation is first apparent 15−30 min after drug administration and peaks at 60 min, when stereotyped behavior is already decreasing. Locomotor activity then declines by 2 hr to about half of peak activity.

DISCUSSION

The approximately 10-fold difference in the potency of amphetamine isomers in stimulating locomotor activity of cats resembles previous observations in rats [18, 21, 22]. Their much greater similarity in inducing stereotyped behavior accords with previous observations in cats [26], dogs [25], and rats [21,22]. According to biochemical models predicting that NE mediated behavior should be affected much more by (+)− than by (−)−amphetamine whereas DA mediated behavior should be affected similarly by the

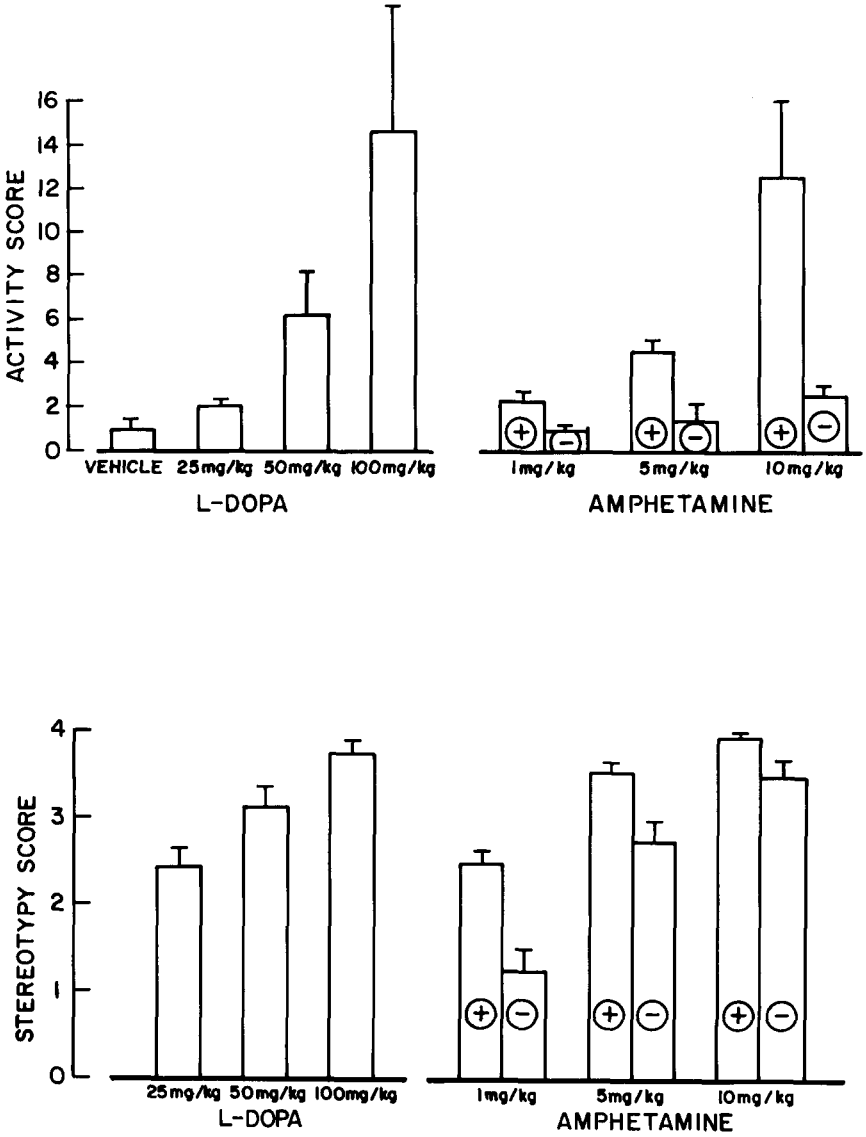

FIG. 1. Effects of L-Dopa, (+)–amphetamine and (−)–amphetamine on locomotor activity (UPPER) and stereotyped behavior (LOWER) of cats. Locomotor activity scores are expressed as the ratio of activity (measured by light beam interruption) under the influence of drug to activity during a two hr placebo administration preceding drug administration. Stereotyped behavior was graded by observers on a scale from 0 to 4+. Data presented are the mean values ± S.E.M. for 15 cats.

two isomers, our findings are consistent with previous suggestions that locomotor stimulation primarily involves brain NE and stereotyped behavior is principally associated with brain DA [19, 21, 22]. The 2–4 fold difference in potency of amphetamine isomers in eliciting stereotyped behavior in several species may be related to recent observations that dopamine neuronal uptake shows some differential response to amphetamine isomers [7, 9, 23]. Studies with different approaches support these conclusions. DA microinjection into selective areas of DA terminals elicits stereotyped behavior [6,8] and selective destruction of DA pathways abolishes amphetamine induced stereotypy [4,13]. While our observations suggest a major role for NE in locomotor stimulation, the correlation of increased DA turnover with amphetamine induced locomotor stimulation suggests a role for DA [2]. Our findings with L-Dopa might be consistent with a role for DA in locomotor stimulation. L-Dopa administration is followed by the formation in the brain of a large amount of DA but considerably less NE [27]. Thus, the close correspondence of L-Dopa with (+)–amphetamine but not (−)–amphetamine in augmenting locomotor activity suggests that L-Dopa might act via DA in enhancing locomotor activity.

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