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Differential Actions of d- and l-Amphetamine on the Metabolism of ^{3}H-Norepinephrine in Rat Brain[1]

DALE W. PETERSON[2] AND SHELDON B. SPARBER

Departments of Pharmacology and Psychiatry, University of Minnesota, Minneapolis MN 55455

(Received 9 July 1975)

PETERSON, D. W. AND S. B. SPARBER. *Differential actions of d- and l-amphetamine on the metabolism of ^{3}H-norepinephrine in rat brain.* PHARMAC. BIOCHEM. BEHAV. 4(5) 545-549, 1976. – Approximately equieffective doses of d- and l-amphetamine, using suppression of operant fixed-ratio responding for food reinforcement as the determinant of potency, were compared for their ability to alter the disposition of the major and minor metabolites of NE in push-pull perfusates from rat brain lateral ventricle. While 3 mg d-amphetamine/kg and 6 mg l-amphetamine/kg both increased total ^{3}H and the relative amounts of the minor metabolites ^{3}H-normetanephrine and ^{3}H-dihydroxymandelic acid, only l-amphetamine caused a significant increase in the major ^{3}H-NE metabolite, methoxyhydroxyphenylethyleneglycol. The data is discussed in relation to the abilities of the isomers of amphetamine to stereoselectively interact with noradrenergic neurons at doses that produce similar effects upon operant behavior.

Operant behavior   Amphetamines   Brain perfusion   Norepinephrine

AS in the peripheral nervous system, amphetamine can be shown to alter central nervous system catecholamines (CA) by more than one mechanism. The amount of CA at the postsynaptic receptor is increased by amphetamine through its blockade of the reuptake system in the pre-synaptic membrane [11, 14, 16, 27, 34, 35], by its ability to release CA from the nerve terminals [1, 3, 9, 39] and at high concentrations, it may inhibit the enzyme(s) monoamine oxidase [15,21]. The relative importance of the first two mechanisms in the actions of amphetamine is in dispute [2, 10, 13, 17, 26], but some of these differences may be related to the level of neuronal activity, because amphetamine-induced release of CA can be shown to be superadditive with electrically stimulated release [10,38]. Most of the studies referred to above have been carried out under completely in vitro conditions or partially in vitro, after administration of drugs or isotopically labeled amines, followed by sacrifice of the experimental animals. Various brain perfusion techniques have demonstrated an in vivo release of NE, DA and some of their metabolites [5, 6, 7, 8, 22, 25, 30, 32, 36]. A more discriminating analysis of the metabolites of the CA released into these perfusates could provide more definitive information about the various actions of amphetamine previously alluded to because the localization of the enzymes responsible for the various metabolites is known. Additionally, this method should also be sensitive to any neurochemical differences in the actions of d- and l-amphetamine on catecholaminergic function, as has been suggested by other studies [3, 8, 17, 33, 34, 38].

We have previously shown what appears to be qualitatively differential effects of the d- and l-isomers on operant behavior maintained by two schedules of reinforcement [37]. Additionally, selective partial destruction of NE neurons with 6-hydroxydopamine, at a dose which left DA neurons relatively intact, resulted in attenuation of the behavioral suppressant action of l-amphetamine and not that of equieffective doses of d-amphetamine [24]. These data suggested that NE was of relatively greater importance in the mechanism of action of l-amphetamine, compared to behaviorally equieffective doses of d-amphetamine. It was therefore of interest to compare the action of the isomers of amphetamine upon the disposition of the metabolites of radiolabeled NE, injected into the lateral ventricle of the rat brain and collected in push–pull perfusates during the performance of, and subsequent drug effects upon an operant.

METHOD

The procedure employed was essentially that described by Sparber and Tilson [30]. A cannula aimed at the right lateral ventricle of a rat is used to perfuse the region while the rat is performing a conditioned lever press response for food as a reinforcer. The effects of peripherally administered d- and l-amphetamine on cerebral metabolism and release of radiolabeled NE was studied. Perfusions, at a rate of 15 μl/min, were carried out with saline, rather than artificial CSF, so that the pH of the medium could be held more constant and below 8.0 for the entire session. The

[1] Supported in part by U.S.P.H.S. Grants DA00532, MH08565 and GM01117. Send reprint requests to: S. B. Sparber, Department of Pharmacology, 105 Millard Hall, University of Minnesota, Minneapolis, MN 55455.

[2] Present address: Department of Pharmacology, University of Otago, Medical School, Dunedin, New Zealand.

animals were three rats trained on a fixed ratio-10 schedule of food reinforcement. During 3 separate sessions, each rat was injected IP, with saline, 3 mg d-amphetamine/kg or 6 mg l-amphetamine/kg. Each session was 30 min long and began 30 min after the intraventricular infusion of 5 μCi of ^{3}H-NE (1-NE-7-^{3}H, Sp. Act. 3.7 Ci/mMole, New England Nuclear). During the behavioral sessions six 5 min perfusion samples were collected into vials containing 10 μg each of NE and its metabolites (see Table 1) in 10 μl N formic acid. A 10 μl aliquot of these samples was spotted on a 20 x 20 cm microcrystalline cellulose thin layer chromatography (TLC) plate (Brinkman Instruments Inc., Westbury, N.Y.) for development in the two dimensional TLC system of Fleming and Clark [12]. The ^{3}H associated with each cold carrier metabolite was determined by oxidizing the cellulose that contained the spot, which was visualized by p-nitroanaline, in a Biological Material Oxidizer (Beckman, Fullerton, California) and counting the ^3H_2O formed. The scintillation counting (Beckman LS-150) in a 0.8% butyl PBD, 3.0% Biosolv BBS-3 toluene cocktail was at an efficiency of 55%, as determined by external standard ratio.

The 3 mg d-amphetamine/kg was compared with 6 mg l-amphetamine/kg because approximately this dose of d-amphetamine was shown to produce significant release of ^{3}H-NE and metabolites into the perfusate [36], and because the d to l ratio of 1 to 2 results in approximately the same rapid onset to and duration of disruption of the operant [24,37]. If anything, the ratio is a conservative estimate of behavioral equieffectiveness. The injections were made to correspond with the time between the collection of the third and fourth 5 min perfusion samples. Because the third sample was collected immediately before the injection, the total ^{3}H in subsequent samples was expressed as a percent of the ^{3}H in Sample 3. This allowed for the comparison of the different injections during the repeated perfusions of these rats, since the amount of ^{3}H in the samples would vary from perfusion to perfusion. The TLC analysis was likewise performed on the sample before the injection (Sample 3) and the two samples immediately after the injection (Samples 4 and 5) to determine the effect of the drugs on the individual metabolites released into the perfusate.

The statistical analysis of any change, after d- or l-amphetamine relative to saline controls, in total ^{3}H in the perfusates or the ^{3}H at any of the TLC spots, was determined as follows. For both, the total ^{3}H and the ^{3}H at each spot on the TLC plate corresponding to the cold carrier metabolite of interest, the disintegrations per min in Samples 4 and 5 were averaged as a percent of Sample 3. The effects of d- and l-amphetamine were determined by comparison with the corresponding percentages from the saline control perfusion for each rat and the statistical reliability determined by the correlated 2-tailed *t*-test, $p<0.05$ being used as the α level for significance.

RESULTS

After the injection of saline the responses during the two following 5 min periods did not change, but after d- and l-amphetamine responding was significantly decreased. Sample cumulative records of the effects of injections of saline or the amphetamines on the fixed ratio-10 performance are shown in Fig. 1. An immediate suppression in responding in the 5 min periods after d- or l-amphetamine is evident with these doses. In this group of rats, 6 mg/kg

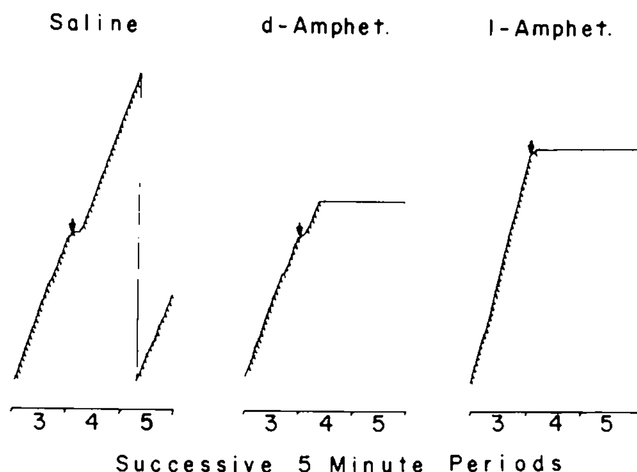

FIG. 1. Cumulative records of fixed ratio 10 performance for Rat J-2 after the injections of saline, d-amphetamine sulfate (3 mg base/kg) and l-amphetamine sulfate (6 mg base/kg). Arrows indicate the time of injections, which were made between the third and fourth 5 min periods (15 min into the 30 min session). Cumulative recorder pens reset after 550 responses.

l-amphetamine caused a slightly faster decrease in responding in the 5 min immediately after the injection than did 3 mg/kg d-amphetamine. This difference suggests a more rapid onset of behavioral disruption by the l-amphetamine, since both drugs at these doses caused a complete suppression of responding, which lasted for the remainder of the perfusion period. However, the differences were small and could be accounted for by differences in peripheral actions of the isomers, the larger dose of the l-isomer producing greater cardiovascular effects.

In the perfusion samples collected during the saline-injection behavioral sessions, the total ^{3}H in each successive 5 min sample always declined. The total ^{3}H in the samples immediately after the injections of either d- or l-amphetamine was in all cases greater than the individual saline controls for each rat (Fig. 2). If Samples 4 and 5 are averaged, the release of ^{3}H into the perfusate was slightly greater after l-amphetamine for Rat J-2; while Rat K-1 showed a greater release after d-amphetamine. The third rat, K-2, had the largest total increase of ^{3}H in the perfusates after the amphetamine injections, but there was little apparent difference in potency between the doses of isomers used. As a result, the mean ^{3}H as a percent of Sample 3, in the samples after d-amphetamine, or l-amphetamine was significantly greater than the saline controls (Table 1).

The TLC analysis of these perfusates indicated that the majority of the ^{3}H was associated with the authentic NE spot, but the increase in total ^{3}H in the perfusates after d- and l-amphetamine was not reflected by any significant increase in the amounts of ^{3}H-NE. While the parent compound was not altered by d- or l-amphetamine, its minor o-methylated metabolite, normetanephrine (NM), which represents only about 2% of the total ^{3}H on the TLC plate (Peterson and Sparber, unpublished observations), was increased by both isomers (Table 1). The mean level of this metabolite in Samples 4 and 5 was 83 ± 19% and 83 ± 21% (M ± SEM) of Sample 3 respectively, for d- and l-amphetamine, both of which were significantly greater than NM after saline injections (38 ± 7%). Unlike NM, the major NE

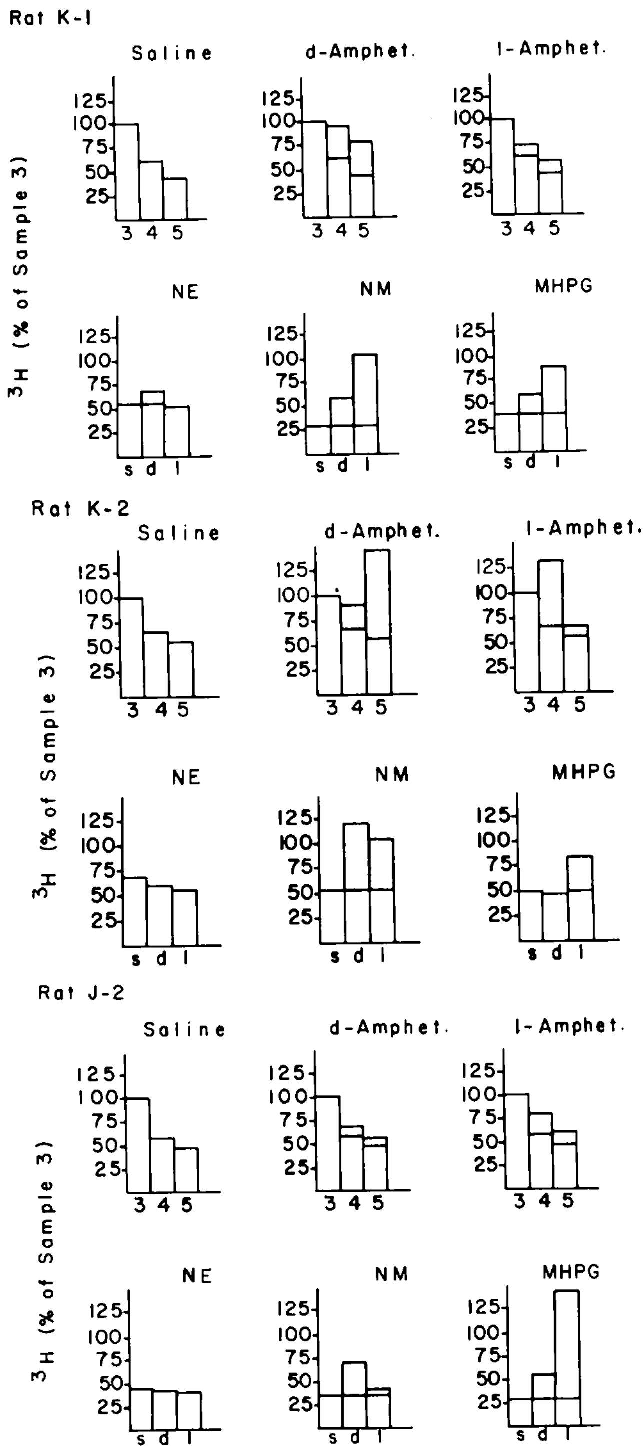

FIG. 2. Increases in total ^{3}H and ^{3}H-norepinephrine metabolism in the lateral ventricular perfusates after ^{3}H-norepinephrine infusions by d-amphetamine sulfate (3 mg base/kg) and l-amphetamine sulfate (6 mg base/kg). Saline, d- or l-amphetamine was injected between the collection of the third and fourth perfusion samples during a 30 min perfusion with sterile saline begun 30 min after the infusion of 5 μCi ^{3}H-norepinephrine. The top figures show the results of the injections on the total ^{3}H in Samples 4 and 5 as a percent of the ^{3}H in Sample 3. The lower 3 figures represent the average ^{3}H at norepinephrine (NE), normetanephrine (NM) and 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) on the thin layer chromatographic analysis of Samples 4 and 5 as a percent of the ^{3}H at the corresponding metabolite in Sample 3, after saline (s), d-amphetamine (d) or l-amphetamine (l). The shaded arease represent the increase above saline after d- or l-amphetamine.

metabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), which together with dihydroxyphenylethlene-glycol (DHPG) represents about 10% of the total ^{3}H in the TLC plate (Peterson and Sparber, unpublished observation), was altered by amphetamine in a stereospecific manner. For all 3 rats, l-amphetamine increased ^{3}H-MHPG to a greater extent than did d-amphetamine. In fact, Rat K-2 showed no increased ^{3}H-MHPG despite a large increase in total ^{3}H and ^{3}H-NM in the perfusate after d-amphetamine. The mean ^{3}H-MHPG after l-amphetamine, 106 ± 19% of Sample 3, was significantly higher than saline controls (40 ± 60%) but d-amphetamine (54 ± 4%) was not different from saline. The ^{3}H at the dihydroxymandelic acid (DHMA) spot while representing only 1% of the total ^{3}H on the plate, was significantly increased by d-amphetamine at 155 ± 62% and by l-amphetamine at 162 ± 53% relative to the saline control of 46 ± 16% of Sample 3. The ^{3}H found at the spots on the TLC plates not already mentioned were also increased by the d- and l-amphetamine injections relative to the saline controls (Table 1), but these increases were generally more variable or unidentifiable SO_4 conjugates near the origin of the plate.

DISCUSSION

The administration of d- and l-amphetamine, at doses that are relatively moderate but capable of totally suppressing the ongoing conditioned behavior, increased the amount of total ^{3}H in the perfusate and specific ^{3}H-NE metabolites, after the intraventricular administration of ^{3}H-NE. These results suggest that NE and/or its metabolites are readily released from the brain by the isomers of amphetamine. Other methods have demonstrated a release of CA by amphetamine in many in vitro preparations [1, 3, 17, 39] and by in vivo perfusions of the brain [4, 6, 7, 22, 25, 38]. The in vivo studies cited above differed from the method presented here in that the amphetamine was usually added to the perfusion fluid rather than administered peripherally, and the animals were anesthetized or immobilized while being perfused. The differences in the route of administration may result in a difference in the distribution of the amphetamine which could favor the release of CA after its intracerebral administration. That the behavioral (vis. central) mechanism of action of d-amphetamine, administered in equieffective dosages through a peripheral (IP) or central (intraventricular) route, is different has been suggested by a demonstration of a lack of cross-tolerance to the disruptive effects upon behavior by these two routes [31]. Additionally, if large amounts of the CA in the brain are involved in modulation of motor movements [18], an animal engaged in a high level of activity such as lever pressing on a fixed ratio schedule may have a greater turnover of CA than would an immobile animal. This greater utilization of CA might make it more difficult to effect and discriminate a change in the release of ^{3}H-CA or metabolites that could be detected in the perfusate.

The release of ^{3}H after intraventricular ^{3}H-NE was increased to the same extent by 3 mg of d- or 6 mg of

TABLE 1

EFFECTS OF D- AND L-AMPHETAMINE ON ^{3}H-NOREPINEPHRINE AND ITS METABOLITES AS MEASURED BY THIN LAYER CHROMATOGRAPHIC ANALYSIS OF BRAIN PERFUSATES

Source of ^{3}H*	Average ^{3}H in Samples 4 and 5 as a % of Sample 3		
	Saline	d-Amphetamine-SO_4 (3 mg base/kg)	l-Amphetamine-SO_4 (6 mg base/kg)
Total ^{3}H	55 ± 3†	89 ± 16‡	79 ± 11‡
Origin	71 ± 19	95 ± 16‡	119 ± 35
SO_4-conjugates	58 ± 4	109 ± 29	169 ± 87
NE	56 ± 7	56 ± 8	49 ± 5
NM	38 ± 7	83 ± 19‡	83 ± 21‡
DHMA	46 ± 16	155 ± 62‡	162 ± 53‡
VMA	63 ± 9	104 ± 46	169 ± 109
DHPG	25 ± 7	42 ± 6	104 ± 44
MHPG	40 ± 6	54 ± 4	106 ± 19‡

*Total ^{3}H refers to ^{3}H in aliquots of the perfusion samples, and the remaining sources of ^{3}H are those SO-chromatographed with the authentic compounds. The abbreviations used are described in the text.

†Mean ± S.E.M. of the average ^{3}H in samples 4 and 5 (samples collected immediately after the injection) as percent of sample 3 (sample immediately before the injection) for 3 paired observations with 3 rats.

‡Significantly increased above saline, correlated t-test, $p<0.05$, 2-tailed.

l-amphetamine/kg. This increased ^{3}H was not reflected by an increase of unchanged ^{3}H-NE in the perfusates, which may be due to a large percentage of the ^{3}H-NE in the perfusate having never been taken up by the brain and simply being washed out from the ventricle. In this situation a small increase in ^{3}H-NE released by amphetamine from the neurons could be masked. The ^{3}H-NM was increased by both isomers of amphetamine, which indicates that the ^{3}H-NE which did interact with the nervous tissue and/or was metabolized by the extraneuronal enzyme, COMT, was altered by the drug treatment.

A differential effect of d- and l-amphetamine occurred with the release, into the perfusate, of the major NE metabolite, MHPG. This metabolite is formed by the enzymatic action of both extraneuronal COMT and intraneuronal MAO, and it has been suggested that the normal route of this metabolism is for the released NE to be converted to NM which is then taken back into the NE neuron where it is deaminated to MHPG [19]. If amphetamines were to release NE and to block the reuptake mechanism, a greater increase of NM than deaminated metabolites would be expected, as is the case with d-amphetamine in this study and others [6,36]. The matabolites released after l-amphetamine suggest a difference in the actions of this isomer since both NM and MHPG were increased. This difference could be explained by a difference in the relative potencies of d- and l-amphetamine for the two mechanisms by which they may increase the metabolites in the perfusate. If both isomers were effectively increasing the release of ^{3}H-NE from the NE neuron, this would cause an increase in the total ^{3}H and ^{3}H-NM as was seen. If it were also the case that d-amphetamine were a more potent blocker of the uptake mechanism for NM and the NE neuron than l-amphetamine, the increase of MHPG only after l-amphetamine would be explained. However, d-amphetamine would have to be much more than two times as potent an inhibitor of reuptake than l-amphetamine to account for the differential effect on ^{3}H-MHPG, which is consistant with the results of Taylor and Snyder [34]. Alternatively, this isomeric difference on the metabolites of NE may be the result of a difference in the relative inhibition of MAO by amphetamines. This is unlikely because the decrease in deamination of NE by d-amphetamine is the result of the blockade of uptake, which decreases its access to MAO at doses that have little MAO inhibitory effects [20,28]. Regardless of the reason for the differences in metabolites, the major metabolite of NE, MHPG may be the best approximation of the action of the amphetamines on release mechanisms and function of noradrenergic neurons. The data suggest that with moderate doses of d- or l-amphetamine, that produce comparable behavioral effects, l-amphetamine is affecting noradrenergic function to a greater extent. This is in agreement with our previous report [24] where rats subjected to depletion of only NE by appropriate intraventricular injections of 6-OHDA showed significant attenuation of the behavioral suppressant action of l-amphetamine but not to (behaviorally) equieffective doses of d-amphetamine.

While there was this isomeric difference on the MHPG, both isomers of amphetamine caused the same increase of ^{3}H at a minor deaminated NE metabolite, DHMA. Since DHMA is not o-methylated, the explanation of the isomeric difference at the blockade of the reuptake of NM would not apply to this metabolite and may explain the lack of a stereospecific effect. It is also possible that since MHPG is generally thought to be the major NE metabolite, the ^{3}H-DHMA in the perfusate may have come from ^{3}H-NE that was taken up by DA neurons where an acid is the normal deaminated metabolite and where it could have been released equally by the doses of d- and l-amphetamine used. This implies a two-fold potency difference between d- and l-amphetamine upon dopaminergic function at the doses utilized. We are currently examining the effects upon the disposition of ^{3}H-DA and metabolites by doses of amphetamine isomers that induce overt stereotypy during the perfusion sessions, in order to verify the involvement of DA on the effects of higher doses of the stimulant.

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