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EFFECTS OF THE *d*- AND *l*-ISOMERS OF AMPHETAMINE ON UPTAKE, RELEASE AND CATABOLISM OF NOREPINEPHRINE, DOPAMINE AND 5-HYDROXYTRYPTAMINE IN SEVERAL REGIONS OF RAT BRAIN*

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Abstract—The stereoselectivity of *d*- and *l*-amphetamine for uptake, release and catabolism of biogenic amines was studied *in vitro* in three regions of rat brain. The *d*-isomer was about two times more potent than the *l*-isomer in inhibiting uptake and releasing biogenic amines from chopped cerebral cortex labeled with norepinephrine and midbrain labeled with 5-hydroxytryptamine. On the other hand, the *d*-isomer was five times more potent than the *l*-isomer in inhibiting the uptake and releasing [^{3}H]dopamine from nerve terminals of corpus striatum. When the relative potencies of amphetamine on uptake and release were compared, it was found that approximately 11-fold higher concentrations of both isomers were required to release dopamine compared to their ability to inhibit neuronal uptake. Only 4-fold higher concentrations of both isomers of amphetamine were required to release [^{3}H]norepinephrine compared to their ability to inhibit neuronal uptake. Approximately equal concentrations of the two isomers released and inhibited neuronal uptake of 5-hydroxytryptamine. With high concentrations (10^{-3} M), the *d*-isomer of amphetamine was more effective than the *l*-isomer in inhibiting monoamine oxidase activity in synaptosome-free homogenates of cerebral cortex tissue. These results indicate that the dopamine nerve terminals of the corpus striatum possess greater stereoselectivity toward amphetamine than either the norepinephrine nerve terminals of cerebral cortex or 5-hydroxytryptamine neurons of midbrain.

Amphetamine is thought to produce its behavioral effects by interactions with central neurons containing the putative neurotransmitters, norepinephrine, dopamine and 5-hydroxytryptamine [1,2]. The effects of amphetamine on these neurons include: release of the amine from the nerve terminal [3–6], inhibition of neuronal uptake of the amine [3,7–9] and, in high concentrations, inhibition of oxidative deamination of the amine by monoamine oxidase [10–12]. These actions tend to increase the concentration of the putative neurotransmitter in the vicinity of the post-synaptic receptor. It is the enhanced activation of the post-synaptic receptor by the neurotransmitter which presumably leads to behavioral changes.

Numerous studies have indicated that inhibition of neuronal uptake of norepinephrine and dopamine by *d*- and *l*-amphetamine is stereoselective and that the stereoselectivity varies with different regions of the brain [13–17]. Since neurons containing dopamine and norepinephrine have different regional distributions in the brain, this difference in stereoselectivity has been attributed to differences between these two types of neurons. The differences in the potencies of *d*- and *l*-amphetamine on neuronal uptake into dopamine- and norepinephrine-containing nerve terminals have been used as a means for determining the role of these two groups of neurons in mediating specific behavioral effects of amphetamine [18,19]. Much less is known about the stereoselectivity of amphetamine for: (1) uptake of amines into 5-hydroxytryptamine nerve terminals, (2) release of amines from all three groups of nerve terminals, and (3) oxidative deamination of the three amines in tissues containing the three types of neurons. Since it is probable that these actions are also involved in mediating the behavioral effects of amphetamine, the present study was designed to compare the effects of *d*- and *l*-amphetamine on inhibition of neuronal uptake to their effects on release and catabolism in three brain regions, each with different distribution of norepinephrine, dopamine and 5-hydroxytryptamine nerve terminals. The aim will be to examine whether the effects of amphetamine on these three processes can be distinguished in the three types of neurons, using stereoselectivity of the amphetamine isomers as the experimental tool.

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METHODS

Release of biogenic amines by d- *and* l-*amphetamine.* The procedure for studying release of biogenic amines has been previously described [5,6]. The method involved incubating chopped brain tissue with 10^{-6} M of either [^{3}H-*dl*]-norepinephrine (8 μCi), [^{3}H]dopamine (1·0 μCi) or [^{3}H-5]hydroxytryptamine (12 μCi). The ^{3}H-amine was accumulated within the nerve endings, the unbound and nonspecifically bound ^{3}H-amine was washed from the tissue and the ^{3}H-amine was released into the incubation medium after incubation with *d*- and *l*-amphetamine. ^{3}H-catecholamines in the tissue and medium fractions were separated from ^{3}H-deaminated metabolites by cation-exchange chro-

matography on Dowex 50, Na^+ [20]. [^{3}H-5]hydroxytryptamine was separated from its principal ^{3}H-deaminated metabolite, [^{3}H-5]-hydroxyindoleacetic acid, by extraction of the metabolite into ether from acidified samples [2,21].

The protein content per sample was determined by the Biuret method [22] and both medium and tissue radioactivities were based on the amount of tissue (mg protein) present in the sample. The results were generally expressed as a percentage of ^{3}H-amine in the incubation medium calculated as:

$$\frac{^3\text{H-amine in medium} \times 100}{(^3\text{H-amine in medium}) + (^3\text{H-amine in tissue})}.$$

The EC_{50} (median effective concentration) for release was estimated as the concentration of drug which gave half the maximal response (adjusted for "spontaneous release"). Statistical comparisons were made by Student's *t*-test.

Monoamine oxidase activity. The method of Waymire *et al.* [23], as modified by Wenger and Rutledge [24], was used. This involves incubation of 1:5 homogenates of rat cerebral cortex with [^{14}C]tryptamine (5×10^{-4} M) and measurement of the formation of [^{14}C]indoleacetic acid, the deaminated product of [^{14}C]tryptamine. After the initial incubation, [^{14}C]indoleacetic acid was extracted from acidified tissue extracts into toluene, and the radioactivity in the toluene phase was determined by liquid scintillation spectrometry.

Inhibition of uptake of biogenic amines by d- *and* l-*amphetamine.* Uptake and accumulation of biogenic amines into chopped brain tissue were measured by a method described by Ziance *et al.* [5]. The chopped tissue was washed and suspended in the physiological medium and an aliquot of this suspension was incubated with various concentrations of *d*- and *l*-amphetamine for 10 min. Either [^{3}H]norepinephrine (0·76 μCi), [^{3}H]dopamine (0·1 μCi) or [^{3}H-5]hydroxytryptamine (1·7 μCi) was added to the incubation medium to attain a final concentration of 10^{-7} M. The incubation was continued for 5 min and the uptake and accumulation of the ^{3}H-amine were terminated by centrifugation at 4°. The radioactivity in tissue and medium extracts was determined by liquid scintillation spectrometry. Uptake was calculated by determining the tissue/medium (T/M) ratio [(dis./min/g of tissue)/(dis./min/ml of medium)].

Substances. The *d*- and *l*-amphetamine sulfate were obtained from Smith, Kline & French Lab., Philadelphia, Pa. The optical rotations of *d*- and *l*-amphetamine were determined to be as specified using a Cary model 60 spectropolarimeter. [^{3}H-*d,l*]norepinephrine-[7-^{3}H]hydrochloride (7·7 to 13 Ci/m-mole), [^{3}H]dopamine hydrochloride (0·5 Ci/m-mole) and [^{3}H-5]hydroxytryptamine creatinine sulfate monohydrate (8·5 Ci/m-mole) were obtained from Amersham/Searle Corp., Arlington Heights, Ill. [^{3}H-*d,l*]-norepinephrine-[7-^{3}H]bitartrate (4·2 to 9·1 Ci/m-mole) and β-indoleacetic acid-[5-^{3}H] (29 Ci/m-mole) were obtained from New England Nuclear Corp., Boston, Mass. 5-Hydroxytryptamine creatinine sulfate complex was obtained from Sigma Chemical Co., St. Louis, Mo. *d,l*-Arterenol (norepinephrine) hydrochloride and 3-hydroxytyramine (dopamine) hydrochloride were obtained from Calbiochem, Los Angeles, Calif.

RESULTS

Release of biogenic amines by d- *and* l-*amphetamine.* [^{3}H]norepinephrine was released by both isomers of amphetamine from chopped cerebral cortex which had previously accumulated the ^{3}H-amine (Fig. 1). The concentration effect curves for *d*- and *l*-amphetamine differed only at 10^{-6} M, where the *d*-isomer released a greater proportion of [^{3}H]norepinephrine. The EC_{50} for *d*-amphetamine ($8·0 \pm 1·0 \times 10^{-7}$ M) was not statistically different ($P > 0·05$) from the EC_{50} of *l*-amphetamine ($1·7 \pm 0·5 \times 10^{-6}$ M). In contrast, *d*-amphetamine was considerably more potent than the *l*-isomer in releasing [^{3}H]dopamine from dopamine neurons of the corpus striatum (Fig. 2). The EC_{50} for *d*-amphetamine ($1·1 \pm 0·3 \times 10^{-5}$ M) was significantly lower ($P < 0·05$) than that of *l*-amphetamine

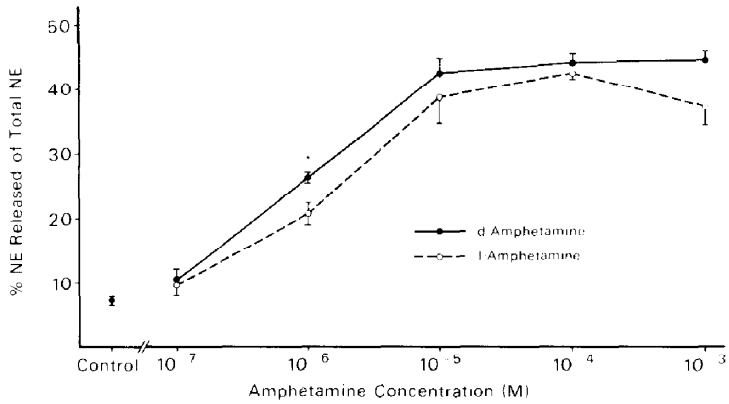

Fig. 1. Relase of [^{3}H]norepinephrine from chopped rat cerebral cortex by *d*- and *l*-amphetamine. Neurons were labeled by incubation of the tissue with [^{3}H]norepinephrine. The tissue was washed and incubated for 30 min in the presence or absence of *d*- or *l*-amphetamine. The deaminated metabolites were separated from the amines by cation-exchange chromatography. The proportion of norepinephrine released into the incubation medium was calculated as norepinephrine in the medium (100)/total norepinephrine. Tritium in tissue and medium fractions represents $54·8 \pm 1·0 \times 10^3$ dis./min/mg of protein. The values represent the mean ± S.E.M. of three experiments. The asterisk indicates *d*-am-phetamine different from *l*-amphetamine, $P < 0·05$.

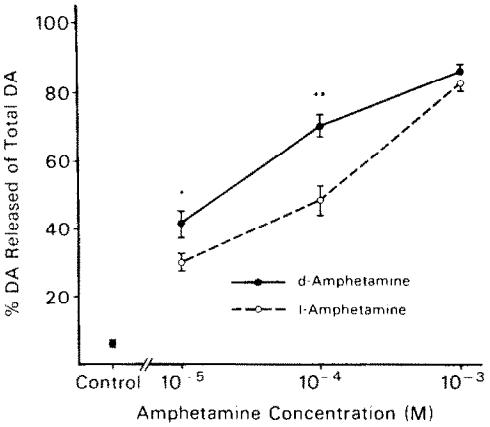

Fig. 2. Release of [^{3}H]dopamine from chopped rat corpus striatum by *d*- or *l*-amphetamine. Neurons were labeled by incubating the tissue with [^{3}H]dopamine. The tissue was washed and incubated for 30 min in the presence or absence of *d*- or *l*-amphetamine. The deaminated metabolites were separated from the amines by cation-exchange chromatography. The proportion of dopamine released into the incubation medium was calculated as dopamine in the medium × 100/total doapmine. Tritium in tissue and medium fractions represents $29{\cdot}3 \pm 1{\cdot}5 \times 10^3$ dis./min/mg of protein. The values represent the mean ± S.E.M. of four experiments. The asterisk indicates *d*-amphetamine significantly different from *l*-amphetamine, $P < 0{\cdot}05$; the double asterisk indicates *d*-amphetamine significantly different from *l*-amphetamine, $P < 0{\cdot}01$.

($6{\cdot}1 \pm 2{\cdot}2 \times 10^{-5}$ M). Higher concentrations of both isomers were required to release [^{3}H]dopamine than were required for release of [^{3}H]norepinephrine. Another difference between the two types of experiments is that the maximum release of [^{3}H]dopamine was considerably greater than the maximum release of [^{3}H]norepinephrine. High concentrations of both isomers of amphetamine also released [^{3}H-5]hydroxytryptamine from midbrain tissue in a concentration-related manner (Fig. 3). The IC_{50} for the *d*-isomer ($2{\cdot}6 \pm 0{\cdot}5 \times 10^{-5}$ M) was significantly lower ($P < 0{\cdot}05$) than that of the *l*-isomer ($7{\cdot}1 \pm 2{\cdot}3 \times 10^{-5}$ M).

Effect of d- *and* l-*amphetamine on monoamine oxidase activity.* In experiments on the release of ^{3}H-amines from chopped brain tissue, the formation of ^{3}H-deaminated metabolites of each of the three ^{3}H-amines was reduced by high concentrations (10^{-3} M) of amphetamine. To evaluate further the effect of high concentrations of both isomers of amphetamine on monoamine oxidase, enzyme activity was measured in homogenates of cerebral cortex free of synaptosomes (nerve endings). When [^{14}C]tryptamine was used as a substrate for monoamine oxidase, *d*-amphetamine was much more potent (IC_{50}, $4{\cdot}6 \pm 0{\cdot}2 \times 10^{-4}$ M) than the *l*-isomer (IC_{50}, $4{\cdot}0 \pm 0{\cdot}2 \times 10^{-3}$ M) in inhibiting oxidative deamination (not shown). The IC_{50} values were significantly different at $P < 0{\cdot}01$. It should be noted that very high concentrations (0·1 to 10 mM) of both isomers were required to inhibit monoamine oxidase.

Inhibition of neuronal uptake by d- *and* l-*amphetamine.* Both *d*- and *l*-amphetamine inhibited neuronal uptake of [^{3}H]norepinephrine into neurons of cerebral cortex with *d*-amphetamine having a greater effect only at 10^{-6} M (not shown). The IC_{50} for *d*-amphetamine ($1{\cdot}7 \pm 0{\cdot}5 \times 10^{-7}$ M) was significantly lower ($P < 0{\cdot}05$) than that of *l*-amphetamine ($4{\cdot}6 \pm 0{\cdot}7 \times 10^{-7}$ M).

The differences between the two isomers in inhibiting the uptake of [^{3}H]dopamine into dopamine nerve terminals of the corpus striatum (not shown) were greater than those observed for [^{3}H]norepinephrine and norepinephrine nerve terminals. *d*-Amphetamine (IC_{50}, $1{\cdot}0 \pm 0{\cdot}2 \times 10^{-6}$ M) was greater than five times more potent ($P < 0{\cdot}01$) than the *l*-isomer (IC_{50}, $5{\cdot}4 \pm 0{\cdot}8 \times 10^{-6}$ M) in inhibiting uptake into dopamine neurons. Higher concentrations of both isomers also inhibit uptake of [^{3}H-5]hydroxytryptamine into neurons of the midbrain (not shown). Although the *d*-isomer was more potent than the *l*-isomer in this system, the differences were not as great as those seen in the dopamine system. The IC_{50} for *d*-amphetamine ($2{\cdot}8 \pm 0{\cdot}2 \times 10^{-5}$ M) was significantly lower ($P < 0{\cdot}05$) than that of *l*-amphetamine ($6{\cdot}6 \pm 1{\cdot}2 \times 10^{-5}$ M.

A summary of the potencies of *d*- and *l*-amphetamine on uptake and release can be seen in Table 1. The ratio of the potencies of *d*- to *l*-amphetamine on both uptake and release are 2·1 to 2·7 in norepinephrine nerve terminals of the cerebral cortex and 5-hydroxytryptamine nerve terminals of the midbrain. The ratio of the potencies of the two isomers on uptake and release in dopamine nerve terminals of corpus striatum is 5·4 to 5·5. The relative effects on uptake versus release can also be seen in Table 1. In norepinephrine nerve terminals, approximately 4-fold higher concentrations are required for release as compared to inhibition of uptake. In dopamine nerve terminals, the ratios are 11-fold, while in 5-hydroxytryp-

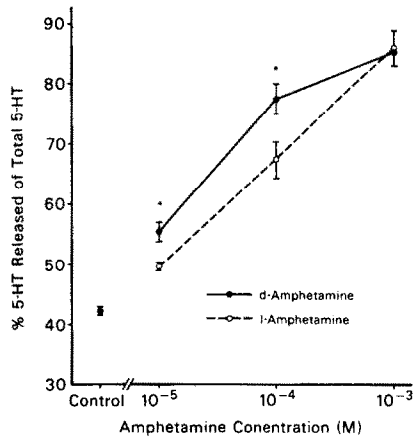

Fig. 3. Release of [^{3}H-5]hydroxytryptamine from chopped rat midbrain by *d*- or *l*-amphetamine. Neurons were labeled by incubating the tissues with [^{3}H-5]hydroxytryptamine. The tissue was washed and incubated for 30 min in the presence or absence of *d*- or *l*-amphetamine. The deaminated metabolites were separated from the amines in the tissue and medium fractions by extraction of the metabolites into ether. The proportion of 5-hydroxytryptamine released into the incubation medium was calculated as 5-hydroxytryptamine in the medium × 100/total 5-hydroxytryptamine. Tritium in tissue and medium fractions represents $157{\cdot}5 \pm 5{\cdot}3 \times 10^3$ dis./min/mg of protein. The values represent the mean ± S.E.M. of five experiments.

Table 1. Effects of *d*- and *l*-amphetamine on uptake and release of biogenic amines from isolated brain tissue*

Tissue	Uptake IC_{50} *d*-Amp	Uptake IC_{50} *l*-Amp	Uptake Ratio of potencies *d*:*l*	Release IC_{50} *d*-Amp	Release IC_{50} *l*-Amp	Release Ratio of potencies *d*:*l*	Ratio of potencies Uptake:Release *d*-Amp	Ratio of potencies Uptake:Release *l*-Amp
^{3}H-NE								
Cerebral cortex	0·17 ± 0·05	0·46 ± 0·07	2·7	0·8 ± 0·1	1·7 ± 0·5	2·1	4·7	3·7
^{3}H-DA								
Corpus striatum	1·0 ± 0·2	5·4 ± 0·8	5·4	11 ± 3	61 ± 22	5·5	11	11
^{3}H-5-HT								
Midbrain	28 ± 2	66 ± 12	2·4	26 ± 5	71 ± 23	2·7	0·93	1·1

* Amp, amphetamine; NE, norepinephrine; DA, dopamine; 5-HT, 5-hydroxytryptamine. The IC_{50} and IC_{50} values are expressed as μM concentrations. Each value represents the mean ± S.E.M. of three to five values. Ratios of potencies *d*:*l* were calculated as: [IC_{50} or IC_{50} of the *l*-isomer IC_{50} or IC_{50} of the *d*-isomer] since the the potency is related to the reciprocal of the IC_{50} or IC_{50}.

tamine nerve terminals, approximately equal concentrations are required for uptake and release. These ratios were observed for both the *d*- and *l*-isomers.

DISCUSSION

The experiments on uptake and release of the three amines into the three tissues assume selectivity of uptake of each amine into neurons containing the respective endogenous amine. Snyder and Coyle [25] observed that [^{3}H]norepinephrine was selectively accumulated in regions of the brain containing predominantly norepinephrine neurons rather than dopamine neurons, while dopamine was selectively accumulated in the corpus striatum with a K_m which was one-fifth of that for [^{3}H]norepinephrine in this tissue. Shaskan and Snyder [26] observed the accumulation of [^{3}H]norepinephrine and [^{3}H-5]hydroxytryptamine in six regions of rat brain and found that the difference in the accumulation of the two amines was most striking for midbrain. In a previous study from this laboratory [6], selectively of uptake and release was examined by the addition of unlabeled biogenic amine during either the uptake or release phase of the experiment. The results indicated selectivity in release as well as in uptake for each of the three amines, although there was some overlap between norepinephrine and dopamine neurons.

Dopamine nerve terminals of the corpus striatum appear to have stereoselective characteristics which differ from those of norepinephrine and 5-hydroxytryptamine neurons. The *d*-isomer of amphetamine was about five times more potent than the *l*-isomer in releasing [^{3}H]dopamine as well as in inhibiting neuronal uptake. The differences between the two isomers in norepinephrine and 5-hydroxytryptamine nerve terminals were only 2-fold. The relative potencies of the two amphetamine isomers on release in norepinephrine and dopamine nerve terminals are consistent with those obtained in previous studies on release of exogenous [^{3}H]norepinephrine and [^{3}H]dopamine in various regions of brain [5,14]. The results on inhibition of uptake into dopamine and norepinephrine nerve terminals are also consistent with those of several other investigators [14–17]; however, the results differ from those of Coyle and Snyder [13] and Taylor and Snyder [18], who found in kinetic studies that the two isomers were equipotent in dopamine nerve terminals, but that there was a 10-fold greater effect of the *d*-isomer in norepinephrine nerve terminals. The differences between the two observations have been ascribed [16] to the difficulty in performing kinetic experiments in systems where uptake and accumulation are relatively low, such as the uptake of norepinephrine into cerebral cortex tissue from reserpine-treated animals.

It is possible that release was primarily due to inhibition of neuronal uptake of spontaneously released amines, since the ratios of potencies of the two isomers on uptake paralleled those on release. However, this does not appear to be the case for norepinephrine neurons of cerebral cortex, since in a previous study [27] desipramine and cocaine were much more effective as inhibitors of neuronal uptake than in releasing [^{3}H]norepinephrine from the tissue. In 5-hydroxytryptamine neurons, the concentrations of both isomers which are required for release are approximately the same as those for inhibition of uptake. In this system, it is possible that the apparent inhibition of neuronal uptake is due to release of recently accumulated [^{3}H-5]hydroxytryptamine.

It is also possible that the stereospecificity of amphetamine for uptake and release is conferred by the stereoselective uptake of amphetamine into the neuron. That is, amphetamine could be accumulated into the neuron by the same mechanism that transports the biogenic amine into the neuron. If this were the case, then the affinity of *d*- and *l*-amphetamine for the amine uptake site might determine the stereospecificity of amphetamine for release of ^{3}H-amines. The neuronal uptake of amphetamine into nerve endings of brain tissue slices and homogenates has been difficult to demonstrate, presumably because of nonspecific tissue binding of amphetamine which could mask specific neuronal uptake [27 30]. However, using a more purified preparation of nerve endings (synaptosomes), it has been possible to show that neuronal uptake of [^{3}H]amphetamine is temperature sensitive and that the uptake of [^{3}H]amphetamine can be antagonized by selective inhibitors of neuronal uptake such as desipramine and cocaine [27,31]. Cocaine and desipramine also decrease the potency of *d*-amphetamine as a releasing agent [27]. It was suggested [27] therefore that antagonists of norepinephrine uptake decrease the potency of amphetamine in releasing norepinephrine by inhibiting the uptake of amphetamine into the neuron.

The effect of amphetamine to inhibit oxidative deamination could be due to inhibition of the neuronal uptake transport system, which could reduce the concentration of the biogenic amine in the vicinity of intraneuronal monoamine oxidase. This has been

shown to occur with low concentrations of amphetamine in uptake experiments [12]. However, the reduction in oxidative deamination in the release experiments occurred with concentrations of amphetamine which were much higher than those which released biogenic amines or those in which uptake was inhibited. Furthermore, inhibition of oxidative deamination of tryptamine in synaptosome-free homogenates suggests that the stereoselectivity of high concentrations of amphetamine is directly on the enzyme, monoamine oxidase. Since the stereoselectivity occurred with all three biogenic amines as well as with tryptamine, it is not likely that the stereoselectivity is confined to one of the several forms of monoamine oxidase [32,33].

Although it is difficult to extrapolate from data *in vitro* on release and neuronal uptake to changes in behavior, it has been argued that the effect of amphetamine on locomotor activity is due to activation of norepinephrine neuronal systems, since the ratios of the potencies of *d*- and *l*-amphetamine on both neuronal uptake and locomotor activity were 10-fold, while those on stereotyped behavior and uptake into dopamine neurons were only 2- to 5-fold [18]. The results of the present study as well as those of others [34–37] suggest, however, that both dopamine and norepinephrine neurons are probably involved in the increase in locomotor activity produced by amphetamine.

The hypothesis that dopamine neurons rather than norephinephrine neurons mediate the amphetamine-induced stereotyped behavior is consistent with the data of this study [38–41]. We found *d*-amphetamine to be 5·4 times more potent than *l*-amphetamine in inhibiting the accumulation of [^{3}H]dopamine into corpus striatum. In addition, Scheel-Kruger [38] showed that *d*-amphetamine is six times more potent than *l*-amphetamine in inducing stereotyped behavior in rats not pretreated with a monoamine oxidase inhibitor. Because of this correlation, it is possible that amphetamine induces stereotyped behavior by activating dopamine neurons.

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