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Drug Interactions with Brain Biogenic Amines and the Effects of Amphetamine Isomers on Locomotor Activity[1]

JOSEPH E. ZABIK, RICHARD M. LEVINE AND ROGER P. MAICKEL

Department of Pharmacology, Medical Sciences Program, Indiana University, Bloomington, IN 47401

Department of Pharmacology and Toxicology, School of Pharmacy and Pharmacal Sciences Purdue University, West Lafayette, IN 47907

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ZABIK, J. E., R. M. LEVINE AND R. P. MAICKEL. *Drug interactions with brain biogenic amines and the effects of amphetamine isomers on locomotor activity.* PHARMAC. BIOCHEM. BEHAV. 8(4) 429–435, 1978. – Administration of single IP doses of 1.0 or 4.0 mg/kg of d-amphetamine evoked an increase in mouse spontaneous motor activity (SMA); in contrast, 1.0 mg/kg of l-amphetamine had no significant effect, while 4.0 mg/kg caused a decreased SMA. Pretreatment with αMT or pargyline had little effect on the actions of the l-isomer, but reduced the magnitude and duration of the stimulatory effect of d-amphetamine. Pretreatment with p-chlorophenylalanine had little effect on the actions of d-amphetamine but completely abolished the depressant actions of the l-isomer. Reserpine pretreatment markedly reduced basal SMA levels; such pretreatment caused both d- and l-amphetamine to act as stimulants of SMA.

d–Amphetamine l–Amphetamine Amphetamine isomers Locomotor activity Drug interactions

THE methyl group attached to the α-carbon of amphetamine confers on the molecule the property of stereoisomerism, giving rise to two enantiomers, both of which have significant pharmacological activity [1]. For a number of years, the belief was generally held that d-amphetamine was 3 to 5 times more potent than the l-isomer as a stimulant of the central nervous system, while l-amphetamine was slightly more potent than the d-isomer as a peripheral pressor agent [7]. However, studies reported in the past fifteen years give support to the hypothesis that the two isomers may have actions on various behavioral test systems that differ in both qualitative and quantitative aspects. For example, Moore [15] has shown that the d-isomer is more toxic than the l-isomer in both isolated and aggregated mice; this toxicity difference paralleled the potency of the isomers in reducing brain norepinephrine (NE). Several laboratories, in studying the actions of amphetamine isomers on locomotor activity, have concluded that the d-isomer is merely more potent than the l-isomer [17, 21, 23–25]. It should be noted that some of these studies are confounded by the fact that animals were pretreated with a monoamine oxidase inhibitor (MAOI). Studies of the effects of the isomers on stereotyped behavior suggested that the effects of d-amphetamine could be correlated with actions on NE systems while those of l-amphetamine correlated better with actions on dopamine (DA) systems [5, 23, 24]. Sparber and coworkers [18,27] have reported differential actions of the amphetamine isomers in operant behavioral systems such as fixed-interval and fixed-ratio responding.

In addition to these behavioral studies, a number of reports have demonstrated differential actions of the amphetamine isomers on brain catecholamine uptake, release, and metabolism; these actions show both qualitative and quantitative differences in the isomers [4, 19, 26]. Finally, several studies have suggested that a catecholamine-serotonin interaction may exist in the control of locomotor activity in the rat [11,16], although this hypothesis has recently been challenged by Jacobs *et al.* [8].

In terms of the effects of amphetamine isomers on spontaneous motor activity in mice, Bainbridge [2] found that d,l-amphetamine had a dose-dependent effect on SMA; doses<5 mg/kg were depressant, while doses>10 mg/kg were stimulatory. A previous publication from this laboratory [12] demonstrated that at low (0.5 mg/kg) and high (8.0 mg/kg) doses, both isomers were stimulants of SMA in mice, while at intermediate doses (1.0–4.0 mg/kg), the d-isomer was stimulatory while the l-isomer caused a significant depression.

The present paper examines the actions of d- and l-amphetamines on SMA in mice pretreated with agents

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known to cause alterations in brain biogenic amines: α-methyltyrosine (αMT), p-chlorophenylalanine (PCPA), pargyline, and reserpine.

METHOD

Adult, male, Swiss-Webster mice, weighing 25–30 g were obtained from Murphy Breeding Laboratories, Plainfield, IN. The animals were maintained on ad lib diet of Wayne Lab Blox and tap water for 7–10 days prior to experimental use in an animal room with controlled temperature and a 14:10 light-dark cycle. All testing was done between 1000 and 1600 hr, midway in the light cycle. Drugs were administered by IP injection as aqueous solutions (d-amphetamine, l-amphetamine, pargyline, reserpine) or peanut oil suspensions (αMT, PCPA) in a volume of 0.1 ml/10 g body weight. All dosages were given and are reported as base weight.

αMT and PCPA were purchased from Regis Chemical Company and Pierce Chemical Company, respectively. d–Amphetamine sulfate was kindly supplied by Smith-Kline and French; l-amphetamine phosphate was kindly supplied by Pennwalt Corporation; pargyline hydrochloride was kindly supplied by Abbott Laboratories; and lyophylized reserpine phosphate was kindly supplied by CIBA-Geigy Corporation.

SMA activity was measured, using groups of 3 mice, in Woodward actophotometers; the procedure was basically that described in a previous paper from the laboratory [12]. The system as utilized has been considered as a standardized measurement of psychogenic spontaneous locomotion [9]. It is especially reliable for stimulant drugs such as d-amphetamine, yielding inverted U dose-response curves similar to those obtained with continuous avoidance responding. Brain levels of 5HT and NE were determined by the method of Maickel *et al.* [13].

Statistical comparisons were made in two steps. Initial comparisons of each group to the corresponding control group were made by one way ANOVA. If group significance was achieved ($p<0.05$), individual time points were compared to the corresponding control groups by two-tailed *t*-test.

RESULTS

Standardization of the SMA Test System. Effects of Single Doses of Amphetamine Isomers

In order to restandardize the test system and provide baseline data for interaction experiments, the experiments reported by Maickel *et al.* [12] were repeated, using doses of 1.0 or 4.0 mg/kg of d-amphetamine or l-amphetamine. The data obtained are presented in Table 1. As can be seen, both doses of d-amphetamine caused a significant increase in SMA activity at all time points. The lower dose of l-amphetamine (1.0 mg/kg) caused a decrease in activity only in the first 10 min, while the higher dose significantly decreased SMA activity in the first three 10 min periods and caused an increase in the final period.

Effects of Drug Treatments and Pretreatments on Brain Levels of 5HT and NE

In order to have some information on the effects of the various compounds studies on brain levels of 5HT and NE, assays for these amines were performed. The data are presented in Table 2. As can be seen, αMT reduced brain NE levels by 64% with no change in 5HT, while PCPA reduced 5HT levels by 67% with no significant change in NE. Pargyline increased 5HT levels by 89% and NE levels by 81%, while reserpine reduced 5HT levels by 82% and NE levels by 81%. Neither of the amphetamine isomers had any significant effect on either amine.

Effects of αMT Pretreatment on Actions of Amphetamine Isomers

The data in Table 3 demonstrate the effects of αMT pretreatment on the actions of d- and l-amphetamine no mouse SMA activity. The αMT pretreatment itself caused a slight, but not significant, reduction in SMA at all four time intervals. Both doses of d-amphetamine caused an increase in SMA in the αMT pretreated mice, although the characteristics of the effect differed from that seen in control animals. Thus, the stimulatory effect of both doses in the first activity interval of αMT pretreated mice was similar to

TABLE 1

EFFECTS OF SINGLE DOSES OF AMPHETAMINE ISOMERS ON MOUSE SMA

Isomer	Dose mg/kg	N	Counts per Interval ± SEM* 0–10 min	11–20 min	21–30 min	31–40 min	$p^{\dagger}$
–	–	15	818 ± 25	558 ± 16	393 ± 12	297 ± 10	–
d	1.0	12	1266 ± 46^{I}	1290 ± 42^{I}	1270 ± 31^{I}	1257 ± 45^{I}	<0.001
d	4.0	12	1498 ± 43^{I}	1697 ± 47^{I}	1209 ± 37^{I}	1508 ± 41^{I}	<0.001
l	1.0	12	690 ± 22	565 ± 14	460 ± 17	385 ± 16	NS
l	4.0	12	675 ± 19^{D}	303 ± 14^{D}	483 ± 15^{D}	409 ± 19^{I}	<0.01

Data were obtained as described in Materials and Methods; each N representa a run of 3 mice.

*Superscript letters refer to individual comparisons of each interval to corresponding control interval by two-tailed *t*-test: I = increased counts ($p<0.001$); D = decreased counts ($p<0.001$); NS = non-significant.

†One way analysis of variance for drug effect; *p* values are given for comparison of drug group to non-drug control group.

TABLE 2

EFFECTS OF DRUG TREATMENTS ON LEVELS OF 5HT AND NE IN MOUSE BRAIN

Drug Treatment	N	Brain Levels (μg/g ± SEM) 5HT	NE
None	12	0.73 ± 0.02	0.59 ± 0.02
αMT	8	0.77 ± 0.02	0.21 ± 0.01^{D}
PCPA	8	0.24 ± 0.02^{D}	0.51 ± 0.02
Pargyline	8	1.38 ± 0.05^{I}	1.07 ± 0.05^{I}
Reserpine	8	0.13 ± 0.01^{D}	0.11 ± 0.01^{D}
d-Amphetamine	6	0.71 ± 0.02	0.58 ± 0.02
l-Amphetamine	6	0.73 ± 0.03	0.59 ± 0.02

Each N value represents a pool of brains from 2 mice. Pretreatment schedules were as follows: αMT – 150 mg/kg, IP (peanut oil suspension) at 24 hr and 4 hr prior to sacrifice. PCPA – 400 mg/kg, IP (peanut oil suspension) at 48 hr prior to sacrifice. Pargyline – 40 mg/kg, IP (aqueous solution) at 24 hr and 4 hr prior to sacrifice. Reserpine – 10 mg/kg, IP (aqueous solution) at 24 hr prior to sacrifice. d- or l-Amphetamine – 4 mg/kg, IP (aqueous solution) at 30 min prior to sacrifice.

Values differing significantly from control (two-tailed t-test, $p<0.05$) are indicated by D = decrease or I = increase.

that seen in control mice; however, in the final two intervals, the αMT pretreatment virtually absolished the stimulatory effect of d-amphetamine. With the 1.0 mg/kg dose of the l-isomer, a slight increase in SMA (as compared to αMT alone) was observed in the first interval, followed by a modest decrease in the second interval. The overall effect was nonsignificant. The 4.0 mg/kg dose of l-amphetamine in αMT pretreated mice showed a significant overall depression of SMA counts.

Effects of PCPA Pretreatment of Actions of Amphetamine Isomers

These data are presented in Table 4. Pretreatment with PCPA had no significant effects on SMA, while doses of d-amphetamine increased SMA significantly at all intervals as compared to PCPA pretreatment alone. The magnitude of stimulation evoked by the lower dose of d-amphetamine appeared somewhat reduced by the PCPA pretreatment, while the higher dose of d-amphetamine was slightly more effective in the animals pretreated with PCPA.

The lower dose of l-amphetamine acted as a stimulant in PCPA pretreated animals with an effect greater than that of the same dose in control animals. The higher dose of l-amphetamine (4.0 mg/kg) had no significant effect on SMA in PCPA pretreated mice.

Effects of pargyline Pretreatment on Actions of Amphetamine Isomers

The data, as presented in Table 5, show that the pargyline pretreatment itself caused a small, but non-significant decrease in SMA over the last three intervals. When compared to these values, both doses of d-amphetamine caused increased SMA at all intervals; only the first interval with the lower dose was not statistically significant. However, in comparison to the effects in control animals, the pargyline-pretreated animals were less responsive to the stimulatory action of d-amphetamine at both doses.

l-Amphetamine had no significant actions at either dose when compared to pargyline pretreatment alone. At the higher dose (4.0 mg/kg), a complex pattern was seen, with slightly decreased SMA in the first and fourth intervals, and a marked increase in the second, when compared to pargyline pretreatment alone.

TABLE 3

EFFECTS OF αMT PRETREATMENT ON ACTIONS OF AMPHETAMINE ISOMERS

Isomer	Dose mg/kg	N	Counts per Interval ± SEM* 0–10 min	11–20 min	21–30 min	31–40 min	$p^{\dagger}$
–	–	8	708 ± 39	429 ± 22	297 ± 17	237 ± 16	NS
d	1.0	4	1157 ± 61^{I}	850 ± 55^{I}	408 ± 43^{NS}	317 ± 23^{I}	<0.05
d	4.0	4	2062 ± 119^{I}	1239 ± 86^{I}	309 ± 24^{NS}	301 ± 26^{NS}	<0.05
l	1.0	4	856 ± 43	283 ± 23	296 ± 20	276 ± 28	NS
l	4.0	4	628 ± 41^{NS}	329 ± 24^{D}	254 ± 27^{NS}	160 ± 16^{D}	<0.05

Animals were treated with αMT as described in Table 2; each N represents a run of 3 mice.

*Superscript letters refer to individual comparisons of each interval to the corresponding control (for αMT alone) or αMT interval by two-tailed t-test: I = increased counts ($p<0.05$); D = decreased counts ($p<0.05$); NS = non-significant.

†One way analysis of variance for αMT effect as compared to control data (Table 1) and for each drug effect as compared to αMT alone.

TABLE 4

EFFECTS OF PCPA PRETREATMENT ON ACTIONS OF AMPHETAMINE ISOMERS

Isomer	Dose mg/kg	N	Counts per Interval ± SEM* 0–10 min	11–20 min	21–30 min	31–40 min	p†
–	–	16	832 ± 24	559 ± 23	427 ± 16	310 ± 15	NS
d	1.0	4	1167 ± 66^{I}	927 ± 52^{I}	867 ± 36^{I}	1008 ± 35^{I}	<0.001
d	4.0	4	1742 ± 69^{I}	1724 ± 96^{I}	1824 ± 74^{I}	1883 ± 98^{I}	<0.001
l	1.0	4	898 ± 39^{NS}	764 ± 46^{I}	767 ± 36^{I}	726 ± 48^{I}	<0.005
l	4.0	4	809 ± 49	497 ± 45	392 ± 49	357 ± 34	NS

Animals were treated with PCPA as described in Table 2; each N represents a run of 3 mice.

*Superscript letters refer to individual comparisons of each interval to the corresponding control (for PCPA alone) or PCPA interval by the two-tailed *t*-test: I = increased counts ($p<0.001$); D = decreased counts ($p<0.001$); NS = non-significant.

†One way analysis of variance for PCPA effect as compared to control data (Table 1) and for each drug effect as compared to PCPA alone.

TABLE 5

EFFECTS OF PARGYLINE PRETREATMENT ON ACTIONS OF AMPHETAMINE ISOMERS

Isomer	Dose mg/kg	N	Counts per Interval ± SEM* 0–10 min	11–20 min	21–30 min	31–40 min	p†
–	–	6	901 ± 32	483 ± 24	340 ± 15	250 ± 11	NS
d	1.0	3	972 ± 27^{NS}	1075 ± 58^{I}	657 ± 54^{I}	599 ± 55^{I}	<0.001
d	4.0	3	1257 ± 105^{I}	1099 ± 59^{I}	697 ± 62^{I}	797 ± 38^{I}	<0.001
l	1.0	3	797 ± 44	483 ± 46	241 ± 53	209 ± 42	NS
l	4.0	3	722 ± 48	748 ± 73	357 ± 43	128 ± 21	NS

Animals were treated with pargyline as described in Table 2; each N represents a run of 3 mice.

*Superscript letters refer to individual comparisons of each interval to the corresponding control (for pargyline alone) or pargyline interval by the two-tailed *t*-test: I = increased counts ($p<0.02$); D = decreased counts ($p<0.02$); N = non-significant.

†One way analysis of variance for pargyline effect as compared to control data (Table 1) and for each drug effect as compared to pargyline alone.

Effects of Reserpine Pretreatment on Actions of Amphetamine Isomers

Table 6 shows that mice treated with a single dose of reserpine (10 mg/kg, IP) 24 hr prior to testing obviously displayed the typical sedation syndrome with a virtual absence of SMA. Administration of the low dose (1.0 mg/kg) of d-amphetamine evoked a small but significant increase in SMA, far less than that produced by a similar dose in control animals. However, the larger dose of the d-isomer, when given to reserpine-pretreated mice, produced counts that were greater, at each interval, than those seen in control animals given the same dose.

Administration of the low dose (1 mg/kg) of l-amphetamine to mice pretreated with reserpine resulted in a brief stimulatory response followed by negligible activity over the last two intervals. At the higher dosage, the l-isomer was slightly stimulatory in all time intervals.

DISCUSSION

The effects of amphetamine on various aspects of animal behavior have been the subject of literally thousands of experiments. Until about twelve years ago, most reports concluded that the two isomers of amphetamine differed only in terms of quantitative potency. This was especially true in terms of behavioral tests in which the drug effect was manifested as a central stimulatory activity, that is, one

TABLE 6

EFFECTS OF RESERPINE PRETREATMENT ON ACTIONS OF AMPHETAMINE ISOMERS

Isomer	Dose mg/kg	N	Counts per Interval ± SEM* 0–10 min	11–20 min	21–30 min	31–40 min	p†
–	–	6	6 ± 1^{D}	5 ± 1^{D}	11 ± 2^{D}	12 ± 4^{D}	<0.001
d	1.0	3	191 ± 16^{I}	300 ± 28^{I}	354 ± 26^{I}	189 ± 20^{I}	<0.001
d	4.0	3	1631 ± 191^{I}	1799 ± 94^{I}	1838 ± 114^{I}	1930 ± 59^{I}	<0.001
l	1.0	3	68 ± 10^{I}	50 ± 12^{I}	18 ± 6^{NS}	8 ± 3^{NS}	<0.01
l	4.0	3	485 ± 46^{I}	464 ± 58^{I}	330 ± 28^{I}	162 ± 24^{I}	<0.001

Animals were treated with reserpine as described in Table 2; each N represents a run of 3 mice.

*Superscript letters refer to individual comparisons of each interval to the corresponding control (for reserpine alone) or reserpine interval by the two-tailed t-test: I = increased counts ($p<0.01$); D = decreased counts ($p<0.01$); NS = non-significant.

†One way analysis of variance for reserpine effects as compared to control data (Table 1) and for each drug effect as compared to reserpine alone.

resulting in increases in rates of activity or responding. More recently, a variety of reports [18,27], including one from this laboratory [12], have suggested that some basic qualitative differences may exist in the actions of the amphetamine isomers on animal behavior. In extending our previous work, the use of the simple actophotometer, with groups of 3 mice per unit, was continued as a measure of spontaneous motor activity. The use of naive mice in each test run insured a high component of exploratory activity in the overall SMA measurement; the use of 10 min counting intervals permitted evaluation of varying duration of drug effects as well as enhancing the magnitude of specific phenomena of brief duration [9].

The data obtained in control (nonpretreated) animals, as presented in Table 1, were basically similar to those previously reported by this laboratory [12]. Thus, d-amphetamine, at both dosages (1.0 and 4.0 mg/kg), caused a marked increase in SMA over control values. The decrease in SMA during the third interval at the higher dose of d-amphetamine was seen consistently and may reflect a temporary fatigue. In contrast to the d-isomer, l-amphetamine showed markedly differing dosage effects. At the lower dose (1.0 mg/kg), a modest decrease in SMA in the first interval was followed by no effect in the second test interval, and a slight stimulatory action in the remaining two intervals. In contrast, the higher dose of l-amphetamine (4.0 mg/kg) caused a significant reduction in SMA activity over the first 3 test intervals, reverting to stimulatory actions only in the last ten min.

The first pretreatment studied was that of αMT which produced a 64% decrease in whole brain NE at the time of starting the test period with no significant alteration in brain 5HT (Table 2). Since αMT depletes NE by inhibition of tyrosine hydroxylase, it may be assumed that some reduction in brain dopamine levels also occurred under these conditions [22]. With this pretreatment, the stimulatory effects of the low dose of d-amphetamine were markedly reduced both in magnitude and duration (Table 3), while the higher dose had an initial stimulatory effect greater than that seen in controls, followed by a rapid abatement of stimulatory activity. These results confirm the observations made by Miller *et al.* [14] that αMT pretreatment had a marked initial effect on the ability of d-amphetamine to increase continuous avoidance responding in rats. Thus, the stimulatory actions of d-amphetamine may be dependent upon the presence of a labile or newly synthesized catecholamine pool. In contrast to the actions on d-amphetamine, the αMT pretreatment generally had little effect on the actions of the l-isomer. This would agree with the hypothesis that this depressant action may involve systems that are functionally antagonistic in terms of controlling SMA; one involving catecholamines, and the other involving some other biogenic amine.

Pretreatment with PCPA, at a dosage regimen that reduced brain 5HT by 67% with only a slight and nonsignificant action on brain NE (Table 2), had no significant effect on the SMA (Table 4). PCPA treatment caused only a small reduction in the SMA stimulation evoked by the lower dose of d-amphetamine. The action of PCPA pretreatment, with its concomitant reduction of brain 5HT, was most dramatic on the effects of l-amphetamine. The depressant effects of both doses of the l-isomer was completely blocked; indeed the lower dose even showed a modest stimulatory effect on SMA. These results lend support to the hypothesis that the depressant actions of the l-isomer on SMA may involve action on a serotonergic system.

Pargyline pretreatment, elevating brain levels of 5HT by 110% and NE by 81% (Table 2), caused a modest, but nonsignificant, decrease in SMA (Table 5). The stimulatory effects of both doses of d-amphetamine were reduced at all intervals; the most dramatic reductions were seen in the periods beyond 20 min, where the 3- to 5-fold increase in counts seen in control animals was reduced to 2- to 3-fold increases by the pargyline pretreatment. In contrast to these observations, both doses of l-amphetamine were without significant effect on SMA.

Reserpine pretreatment, on the other hand, reduced

TABLE 7

EFFECTS OF VARIOUS PRETREATMENTS ON SMA ACTIONS OF AMPHETAMINE ISOMERS

Pretreatment	Isomer	Dose mg/kg	Percent Control Counts 0–10 min	11–20 min	21–30 min	31–40 min
None	d	1.0	155	231	323	423
		4.0	183	304	308	508
αMT	d	1.0	163	198	137	134
		4.0	291	289	104	127
PCPA	d	1.0	139	165	203	325
		4.0	208	308	427	607
Pargyline	d	1.0	108	223	193	240
		4.0	140	228	205	319
Reserpine	d	1.0	3183	6000	3218	1575
		4.0	27183	35980	16709	16083
None	l	1.0	84	101	117	130
		4.0	83	54	72	138
αMT	l	1.0	121	66	100	116
		4.0	89	77	86	68
PCPA	l	1.0	107	137	180	234
		4.0	96	89	92	115
Pargyline	l	1.0	88	100	71	84
		4.0	80	155	105	51
Reserpine	l	1.0	1133	1000	164	67
		4.0	8083	9280	3000	1350

brain 5HT levels by 82% and brain NE levels by 80% (Table 2); under these conditions, SMA was virtually abolished (Table 6). Both doses of d-amphetamine had stimulatory activity in reserpine pretreated animals (Table 6). In fact, the effects of the 4.0 mg/kg dose were similar to or greater than the actions of the drug in nontreated controls. This may reflect a central nervous system version of Supersensitivity [28] or it may reflect a direct stimulatory action of d-amphetamine as proposed by Rech [20]. At the lower dose, l-amphetamine had a very small stimulant effect in reserpine-pretreated animals, while at the higher dose the l-isomer had a stimulant action approximately one-fourth as potent as that of the d-isomer. Of course, since the SMA after reserpine pretreatment was so low, it was impossible to elicit any further depression with l-amphetamine. Nevertheless, it was of interest to discover that the mixed activity of the l-isomer could be so easily converted to purely stimulatory action by virtue of reserpine pretreatment.

When the various results presented in this paper are recomputed in terms of percent control as described by Jacobs *et al.* [8], a most interesting set of numbers are generated; these are presented as Table 7. In no instance did any dose or count interval in animals treated with d-amphetamine show a decrease in SMA; in contrast, with the exception of the animals pretreated with reserpine or PCPA, the preponderant response to l-amphetamine was a decreased SMA.

An overview of these results leads to the conclusion that the d-isomer of amphetamine, at doses of 1.0 and 4.0 mg/kg, IP in mice, has a net stimulant action as reflected by increased SMA, and, that this effect is mediated by catecholamine release from freshly synthesized or labile pools.

In contrast, the l-isomer of amphetamine appears to have a dual nature. In addition to possessing a modicum of catecholamine releasing activity, it also has an ability to interact with serotonergic systems, perhaps by the very nature of its β-phenylethylamine structure. Thus, if one assumes that SMA reflects a net activity controlled by a balance of 5HT and catecholamine functions [3,6], d-amphetamine will increase SMA by shifting the balance to the catecholamine side, while l-amphetamine will decrease SMA by shifting the balance in favor of the serotonin side. The possible role of other biogenic amine systems (such as dopamine) cannot be eliminated, although in the present work, the levels of amphetamines used may not have had a significant action on dopaminergic systems [10].

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