COMPARISON OF EXCITATORY ACTION OF AMPHETAMINE AND METHYLAMPHETAMINE WHEN ADMINISTERED IN CONJUNCTION WITH A DONOR AND ACCEPTOR OF METHYL GROUPS

V. M. Avakumov and K. S. Raevskii

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Most investigators comparing the pharmacological activity of amphetamine and of its methyl analogue methylamphetamine consider that the latter is a more active stimulator of the central nervous system [1, 2, 7, 11].

During its conversion, methylamphetamine has been shown to undergo demethylation at the nitrogen atom at the end of the alkyl chain, thereby changing into amphetamine [4, 8]. Hydroxylation of the aromatic ring then takes place, with the formation of p-hydroxyamphetamine. Axelrod has postulated that the difference between the pharmacological activity of amphetamine and methylamphetamine may depend on the rate of N-demthylation of the latter.

Bearing in mind that the N-methylation of certain phenylalkylamines, notably noradrenalin, may take place in vivo with the aid of methionine [5, 9, 10], and reports that sodium tellurite as an acceptor of free methyl groups is capable of inhibiting the N-methylation of noradrenalin, the authors have postulated that the methods of obtaining an excess or deficiency of free methyl groups described above, by analogy with noradrenalin, may also be applicable to amphetamine and methylamphetamine, which are similar to it in structure.

In this connection it was interesting to determine how an artificially produced deficiency or excess of methyl groups would be reflected in the stimulant action of amphetamine and methylamphetamine. For this purpose it was necessary first of all to compare the stimulant action of amphetamine and methylamphetamine, with a view to the subsequent study of the effect of a donor and acceptor of methyl groups on the activity of these substances. The strength of the stimulant action of the substances was judged from the motor excitation they produced.

EXPERIMENTAL METHOD

Experiments were carried out on male albino mice weighing 20-26 g. Amphetamine and methylamphetamine were injected intraperitoneally 15 min before measurement of the motor activity began. Each of the 20 mice used in the experiment was placed in a separate recording compartment, so that its motor activity could be assessed individually. The motor activity was recorded for a period of 1 h by means of a multichannel actometer [3].

EXPERIMENTAL RESULTS AND DISCUSSION

Effect of Amphetamine and Methylamphetamine. Amphetamine causes a definite increase of motor activity in mice (amphetamine hyperactivity). An appreciable increase in the number of journeys made by the mice was observed after administration of amphetamine in a dose of 2.5 mg/kg. Methylamphetamine gave a definite stimulant effect starting with a dose of 2.5 mg/kg. An increase in the doses of amphetamine and methylamphetamine was accompanied by an increase in the stimulant effect, but this was observed only within certain limits (see figure).

Laboratory of Pharmacology of the Nervous System and Laboratory of Psychopharmacology, Institute of Pharmacology and Chemotherapy, Academy of Medical Sciences of the USSR, Moscow (Presented by Active Member of the Academy of the Medical Sciences of the USSR V. V. Zakusov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 64, No. 10, pp. 54-57, October, 1967. Original article submitted May 9, 1964.

TABLE 1. Effect of Methyl Group Donor and Acceptor on Stimulant Effect of Amphetamine

Substance	Dose (in mg/kg)	Motor activity (mean value with confidence limits at P = 0.05)	Significance of difference between means (P) compared with results when methylamphetamine was given
Methylamphetamine	2.5	557 (456-658)	
Methionine +	100		
methylamphetamine	2.5	701 (605-797)	<0.02
Sodium tellurite +	0.625		
methylamphetamine	2.5	595 (500-690)	>0.1
Methionine +	100		
sodium tellurite +	0.625		
methylamphetamine	2.5	650 (550-770)	>0.05

TABLE 2. Effect of Methyl Group Donor and Acceptor on Stimulant Effect of Methylamphetamine

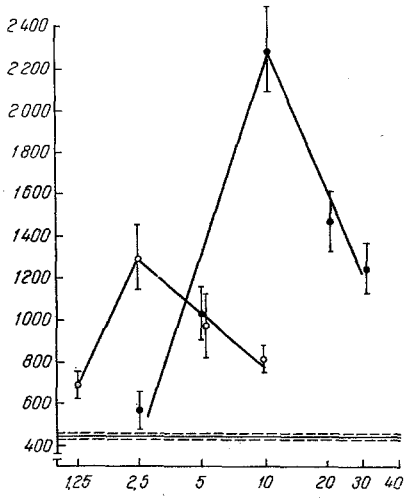
Substance	Dose (in mg/kg)	Motor activity (mean value with confidence limits at P = 0.05)	Significance of difference between means (P) compared with results when methylamphetamine was given
Methylamphetamine	1.25	694 (170-818)	
Methionine +	100		
methylamphetamine	1.25	1006 (815-1197)	<0.002
Sodium tellurite +	0.625	649 (543-755)	>0.1
methylamphetamine	1.25		
Methionine +	100		
sodium tellurite +	0.625		
methylamphetamine	1.25	852 (745-959)	>0.05

As the figure shows, the hyperactivity for amphetamine reached a maximum with a dose of 10 mg/kg, and increasing the dose of 20 mg/kg led to marked weakening of the excitatory effect. When methylamphetamine was given the stimulant effect was greatest with a dose of 2.5 mg/kg, but in absolute values the hyperactivity following administration of methylamphetamine was much less than that after administration of amphetamine.

Hence, comparison of the two stimulants showed that methylamphetamine is approximately twice as active as amphetamine. At the same time, by using methylamphetamine the spontaneous motor activity could be increased by not more than 2.7 times, whereas with amphetamine the mean number of journeys made by the mice could be increased 5 times.

Effect of Methionine and Sodium Tellurite. Before using methionine and sodium tellurite as donor and acceptor of methyl groups, it was necessary to discover how these substances influence the magnitude of the spontaneous motor activity. When given by intraperitoneal injection in a dose of 100 mg/kg, methionine had practically no effect on the motor activity of the mice. When given in larger doses, the motor activity was reduced. After administration of methionine in a dose of 500 mg/kg, for instance, the number of journeys was 214 (168-260), whereas with a dose of 1000 mg/kg the number was 77 (44-110). A similar picture was observed after injection of sodium tellurite solutions. With a dose of 2.5 mg/kg, for instance, the number of movements was 141 (90-192), while with a dose of 1.25 mg/kg the number of 270 (242-316). Injection of the preparation in a dose of 0.625 mg/kg was accompanied by only a very slight decrease in motor activity.

Combined Administration of Amphetamine or Methylamphetamine with Methionine or Sodium Tellurite. In these experiments methionine and sodium tellurite were injected into mice in doses of 100 and 0.625 mg/kg respectively. Solutions of amphetamine (2.5 mg/kg) and methylamphetamine (1.25 mg/kg) were injected 45 min after administration of these substances. When methionine was given with sodium tellurite and



Excitatory effect of amphetamine in relation to dose. Ordinate) Magnitude of motor activity, abscissa) dose of stimulant (in mg/kg; logarithmic scale). Clear circle) effects of methylamphetamine, black circles) effects of amphetamine. Verticle lines denote the standard error of the means, horizontal lines in the lower part of the figure represent the mean value (with standard error) of motor activity of normal mice.

amphetamine or methylamphetamine, the sodium tellurite was injected 15 min after the methionine, and the amphetamine (or methylamphetamine) was given 30 min after the injection of sodium tellurite.

When methionine and amphetamine were given together the motor activity of the mice was greater than when amphetamine alone was injected (Table 1).

Sodium tellurite had practically no effect on the hyperactivity resulting from administration of amphetamine. When all three substances (amphetamine, methionine, sodium tellurite) were used together, the motor activity was slightly increased, although the effect in this case was less than when methionine was given with amphetamine. Similar results were obtained with methylamphetamine, when in 3 series of experiments the following combinations of substances were studied: methionine and methylamphetamine, sodium tellurite and methylamphetamine, and methionine, sodium tellurite, and methylamphetamine (Table 2).

Against the background of the preliminary administration of methionine, methylamphetamine produced a marked increase in the excitatory effect. The preliminary administration of sodium tellurite slightly reduced the excitatory effect of methylamphetamine, but the difference was not statistically significant. Following the combined use of methione, sodium tellurite, and methylamphetamine,the hyperactivity was less than that observed when methylamphetamine was given together with methionine, although in this case the movements were greater than in the experiments when methylamphetamine was given alone.

The results suggest that the increase in excitatory effect of amphetamine observed in the presence of an excess of free methyl groups is probably associated with methylation of amphetamine at the nitrogen atom, i.e., with its partial conversion into methylamphetamine. In turn, potentiation of the methylamphetamine effect when given in conjunction with methionine may be explained by interference with the process of demethylation of methylamphetamine, for a marked excess of free methyl groups, arising as the result of administration of methionine, partially blocks methylferase.

Sodium tellurite undergoes methylation in the body, being converted into dimethyltelluride [12]. On this basis it may be postulated that when methionine, sodium tellurite, and amphetamine or methylamphetamine are given together, the total number of free methyl groups is reduced. However, the excess of methyl groups cannot be completely blocked, because administration of larger doses of tellurite would be associated with the appearance of a nonspecific toxic effect.

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