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Research report

N-Methylation dissociates methamphetamine's neurotoxic and behavioral pharmacologic effects

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Abstract

The present studies further examined the effect of *N*-methylation on the behavioral and neurotoxic effects of methamphetamine. Drug discrimination studies employing a training dose of 1 mg/kg of methamphetamine were used to confirm and extend previous behavioral studies indicating that *N*-methylation reduced the behavioral activity of methamphetamine 5- to 10-fold. In subsequent neurotoxicity studies, rats received doses of methamphetamine (10 mg/kg, s.c., every 6 h $\times 5$) or its *N*-methylated derivative, *N*,*N*-dimethylamphetamine (100 mg/kg, s.c., every 6 h $\times 5$) that, based on the results of the behavioral studies, would be expected to produce behaviorally equivalent effects. Saline-treated rats served as controls. Two weeks after treatment, the status of brain dopamine (DA) and serotonin (5-HT) neurons was assessed by measuring DA and 5-HT axon terminal markers. As anticipated, methamphetamine produced neurochemical deficits indicative of DA and 5-HT axon terminal damage. By contrast, despite the fact that it was given at a dose behaviorally equivalent to methamphetamine, *N*-*N*-dimethylamphetamine failed to produce signs of DA or 5-HT neurotoxicity. These results indicate that *N*-methylation dissociates methamphetamine's neurotoxic and behavioral pharmacologic effects, and suggest that it may be possible to separate the neurotoxic and pharmacologic effects of other substituted amphetamine derivatives with potentially useful clinical activity (e.g. fenfluramine and methylenedioxymethamphetamine). © 1997 Elsevier Science B.V.

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1. Introduction

N,*N*-Dimethylamphetamine is an analog of methamphetamine that surfaced in the illicit drug market in the late 1980s [2,38]. In a previous study, *N*,*N*-dimethylamphetamine was found to have less neurotoxic activity than methamphetamine [25]. However, in that study, it was not possible to compare behaviorally equivalent doses of *N*,*N*-dimethylamphetamine and methamphetamine for two reasons. First, behavioral data on relative potency of the two drugs was not available at the time. Second, attempts to test higher doses of *N*,*N*-dimethylamphetamine did not prove feasible because the animals did not tolerate the higher doses when these were given according to a schedule commonly used to study the neurotoxic effects of amphetamine derivatives (twice daily for four consecutive days) [28,32,40].

Subsequently, Witkin et al. [41], using a variety of behavioral measures, established that *N*,*N*-dimethylamphetamine is approximately one-tenth as potent as methamphetamine. Furthermore, in additional preliminary studies, we have determined that rats can tolerate 10-fold higher doses of *N*,*N*-dimethylamphetamine, if these are given subcutaneously every 6 h for 30 h. The purpose of the present study was to compare the neurotoxic potential of behaviorally equivalent doses of *N*,*N*-dimethylamphetamine and methamphetamine in order to establish whether *N*-methylation selectively attenuates the neurotoxic effects of methamphetamine.

We now report that, even when given at a behaviorally equivalent dose as methamphetamine, *N*,*N*-dimethylamphetamine lacks both DA and 5-HT neurotoxic activity. These findings strongly suggest that the neurotoxic and

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pharmacologic effects of methamphetamine and related drugs are separable.

2. Materials and methods

2.1. Subjects

Male albino Sprague–Dawley rats (Harlan, Madison, WI) served as subjects. Rats used in behavioral studies were maintained at 350 g body weight through restricted feeding; rats used in neurotoxicity studies weighed 240–260 g at the time of drug treatment. The animals were housed individually in either acrylic cages (behavioral studies) or suspended wire mesh cages (neurotoxicity studies) in temperature-controlled rooms (22 ± 1°C) on a 12:12 h light/dark cycle (light from 06.00 to 18.00 h), with free access to water. Rats in the neurotoxicity studies also had free access to food (Purina rat chow).

2.2. Behavioral studies

For behavioral studies, individually housed rats were studied in operant conditioning chambers (BRS/LVE, Model RTC-022, Laurel, MD) which contained two response levers (17 cm apart), centered on either side of a tray for delivery of food pellets (45 mg, BioServ, Inc., Frenchtown, NJ). White and red stimulus lamps above the right and left levers, respectively, and a white lamp at the top center of the front wall were used as discriminative stimuli. Chambers were enclosed within sound- and light-attenuating cubicles and supplied with white noise to mask extraneous sounds. Responses were recorded and produced an audible click if a downward force exceeding 0.2 N was made on either lever. Before daily sessions, subjects received either saline or 1.0 mg/kg methamphetamine in a mixed sequence. Twenty consecutive responses on only one of the response levers produced food which was followed by a 20-s timeout during which all stimulus lights were out and responses had no scheduled consequences. When subjects received methamphetamine, responses on one of the levers produced food, and on the alternate lever after saline (methamphetamine levers were counterbalanced across subjects). Sessions started with a 5-min timeout period and ended after 20 food presentations or 20 min, whichever occurred first. Test sessions were conducted if subjects met criteria of emitting greater than 85% correct responses in the entire session, and before the first reinforcement for two consecutive sessions. Test sessions were identical to training sessions with the exception that 20 consecutive responses on one of either of the response levers produced food. Subjects ($n = 7$ per group) were injected i.p. with one of several doses of methamphetamine or *N,N*-dimethylamphetamine. Each dose was typically examined once in each subject. The percentage of responses on the drug-appropriate lever, as well as the rate of responding during test sessions was recorded. Dose–effect functions and relative potency estimates were analyzed using data from the linear portion of the curves using standard bioassay analysis of variance techniques [11,34].

2.3. Neurotoxicity studies

For neurotoxicity studies, rats received drugs (or saline) s.c. every 6 h over a 30-h period, such that five injections of each drug (or saline) were given. Three treatment groups were used in these studies: (1) methamphetamine ($n = 10$); (2) *N,N*-dimethylamphetamine ($n = 10$); and (3) saline ($n = 10$). Methamphetamine, as the hydrochloride salt, was tested at a dose of 10 mg/kg, since this dose is known to produce marked deficits in rat brain DA and 5-HT axonal markers when given according to the aforementioned schedule of drug administration [13,14,30]. *N,N*-Dimethylamphetamine, also as the hydrochloride salt, was tested at a dose of 100 mg/kg, since pilot studies indicated that 50–60% of rats could tolerate this dosage regimen, and since we wished to test behaviorally equivalent doses of methamphetamine and *N,N*-dimethylamphetamine. In the present study, 6 of 10 rats survived the *N,N*-dimethylamphetamine regimen, and 7 of 10 rats survived the methamphetamine regimen. The latter survival rate is in keeping with previous experience using the same methamphetamine regimen [26]. It is to be noted that the s.c. route of administration was used in these studies, whereas the i.p. route was used in the behavioral studies. The s.c. route was selected for the toxicity studies since this route is the one most often used to induce methamphetamine neurotoxicity. The *S*(+)-enantiomer of each drug was used, as this is the more active enantiomer [17]. Two weeks after drug treatment, rats were sacrificed and regional brain levels of DA and 5-HT axonal markers were measured as previously described [27]. Regional brain monoamine data were analyzed by analysis of variance (ANOVA), with post-hoc Duncan's multiple range tests.

2.4. Drugs and chemicals

Samples of *S*(+)-methamphetamine and *S*(+)-*N,N*-dimethylamphetamine were obtained from the National Institute on Drug Abuse. Serotonin creatine sulfate, 5-hydroxyindoleacetic acid, and dopamine hydrochloride were purchased from the Sigma Chemical Company (St. Louis, MO).

3. Results

3.1. Behavioral

As in other behavioral paradigms [41], *N,N*-dimethylamphetamine was found to be less potent than, but as efficacious as, methamphetamine when the two drugs were

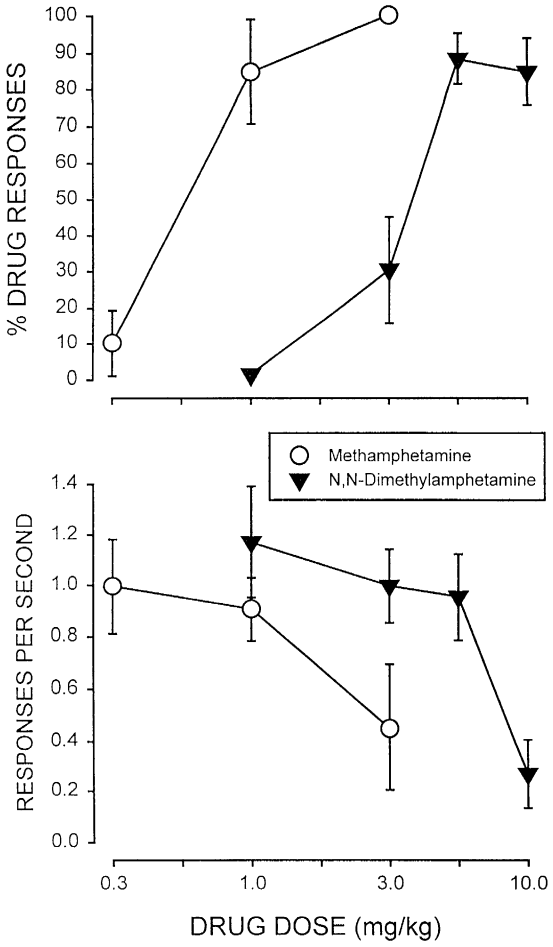

Fig. 1. Effects of methamphetamine and *N,N*-dimethylamphetamine in rats trained to discriminate methamphetamine from saline. Top panel: the percentages of responses on the methamphetamine-appropriate lever. Bottom panel: rates of responding expressed as responses per second. Each point represents performance in seven rats with the exception of the highest doses of each drug at which not all rats were able to respond, so values for the percentage of responses on the methamphetamine lever are averages of less than seven subjects. The vertical bars show ±1 S.E.M.

compared in a drug discrimination procedure in which methamphetamine was used as the training drug (Fig. 1). As shown in Fig. 1, *N,N*-dimethylamphetamine was less potent than methamphetamine, with a relative potency ratio calculated at 5.4 (Table 1). This value is less than that found previously in rats trained on 10 mg/kg cocaine [41]. A similar relative potency (4.8) was evident when examining the effects of *N,N*-dimethylamphetamine and methamphetamine on response rate (Table 1).

3.2. Neurochemical

In accordance with previous findings [13,14], rats treated with methamphetamine (10 mg/kg, s.c., every 6 h ×5) had marked decreases in regional brain DA and 5-HT axonal markers when examined two weeks after drug treatment (Table 2). By contrast, rats treated with behaviorally equivalent (or higher) doses of *N,N*-dimethylamphetamine (100 mg/kg., s.c., every 6 h ×5) showed no evidence of either DA (Table 2) or 5-HT (Table 2) deficits in brain regions where methamphetamine-treated rats showed profound deficits. For example, methamphetamine-treated rats had 49 and 53% depletions of DA and DOPAC, respectively, in the striatum, whereas rats treated with 10-fold higher doses of *N,N*-dimethylamphetamine had normal striatal DA and DOPAC levels (Table 2). Similarly, methamphetamine-treated rats had substantial depletions of striatal 5-HT and 5-HIAA (Table 2), whereas rats treated with the higher doses of *N,N*-dimethylamphetamine had normal striatal 5-HT levels. Similar findings with 5-HT axonal markers were obtained in the hippocampus and neocortex.

4. Discussion

The results of the present study indicate that *N,N*-dimethylamphetamine, when given at a behaviorally equivalent dose as methamphetamine, does not to produce toxic effects on DA or 5-HT neurons in the rat brain, as evidenced by its failure to produce long-lasting DA or 5-HT deficits. It would therefore appear that the addition of an alkyl (methyl) substituent to methamphetamine's nitrogen not only attenuates its neurotoxic activity, but also separates its behavioral and neurotoxic effects, because behaviorally equivalent doses of methamphetamine and *N,N*-dimethylamphetamine were tested. The fact that *N,N*-dimethylamphetamine is without neurotoxic activity even when given at a dose that would be expected to produce behaviorally equivalent effects as metham-

Table 1
Potency of methamphetamine and *N,N*-dimethylamphetamine in drug discrimination studies

Discriminative effects	Methamphetamine	*N,N*-Dimethylamphetamine	Relative potency
% Drug appropriate responding	0.63 (0.45– 0.90)	3.41 (2.69– 4.32)	5.39 (3.64– 8.18)
Response rate	2.87 (0.49–16.71)	9.43 (4.01–22.15)	4.83 (1.56–16.46)

ED_{50} values for each drug are given, as well as the relative potency between the two. 95% Confidence intervals are given in parentheses. Relative potency is the dose of *N,N*-dimethylamphetamine that produces effects comparable to those produced by 1.0 mg/kg of methamphetamine. Drug units are expressed as mg/kg.

Table 2
Effect of behaviorally equivalent doses of *N,N*-dimethylamphetamine and methamphetamine on rat striatal DA and 5-HT axonal markers 2 weeks later

Treatment	DA	5-HT
Saline control ($n = 6$)	11.00 ± 0.4	0.24 ± 0.02
Methamphetamine [a] (10 mg/kg; $n = 6$)	5.60 ± 1.7 [b]	0.11 ± 0.02 [b]
N,N-Dimethylamphetamine (100 mg/kg; $n = 6$)	10.10 ± 1.3	0.21 ± 0.02
	DOPAC	5-HIAA
Saline control ($n = 6$)	0.98 ± 0.01	0.37 ± 0.02
Methamphetamine (10 mg/kg; $n = 6$)	0.46 ± 0.02 [b]	0.21 ± 0.02 [b]
N,N-Dimethylamphetamine (100 mg/kg; $n = 6$)	1.20 ± 0.01	0.35 ± 0.02

Values shown are expressed as μg/g.
[a] Each drug was given subcutaneously every 6 h for a period of 30 h (5 total injections). Since only 6 of 10 rats treated with the high dose regimen of *N,N*-dimethylamphetamine survived, only 6 of 10 rats in the other groups were analyzed.
[b] Significantly different from saline control; $P < 0.05$; ANOVA, Duncan's multiple range test.

phetamine is notable in one other respect. It strongly suggests that the failure of *N,N*-dimethylamphetamine to produce neurotoxic effects is unlikely to be related to failure to achieve sufficiently high levels of the drug in brain, since behavioral equivalence would otherwise not be observed.

How *N*-methylation exerts such strong influence on the toxic activity of methamphetamine toward brain dopamine and serotonin neurons is unclear. It could be that the *N*-methyl substituent alters the ability of methamphetamine to influence endogenous DA [13,30,33,39], 5-HT [4,7,8], or glutamate, [35,36] systems, since each of these has been implicated in the neurotoxicity of methamphetamine. For instance, it is conceivable that *N*-methylation decreases methamphetamine-induced DA release, a process that has been implicated methamphetamine neurotoxicity [1,12,22]. Alternatively, it may be that the *N*-methyl substituent interferes with some other action of methamphetamine that is crucial for the expression of methamphetamine neurotoxicity. In this regard, it would be of interest to compare the ability of the two drugs to influence core temperature, since temperature has been found to be an important factor in methamphetamine neurotoxicity [5,6,10]. It would also be of interest to compare and contrast the relative affinities of methamphetamine and *N,N*-dimethylamphetamine for DA and 5-HT transporters, both on nerve endings and in storage vesicles, as effects on monoamine storage could underlie the toxicity of methamphetamine [9]. Finally, possible effects of *N*-methylation on methamphetamine metabolism and/or clearance also need to be considered, since such effects could also conceivably influence methamphetamine's neurotoxic action [3].

At first glance, the present results on the effects of *N,N*-dimethylamphetamine on brain DA neurons would appear to be at odds with those previously reported [25]. In particular, in the present study, *N,N*-dimethylamphetamine was without toxic effect on dopamine neurons, while in a previous study [25], *N,N*-dimethylamphetamine produced significant, dose-related DA deficits. It is likely, however, that the basis for the different findings is due to the fact that DA deficits in the previous study were documented in mice, whereas the present study used rats. For reasons that remain to be elucidated, mice appear to be unusually sensitive to DA neurotoxic effects of amphetamine derivatives, including methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), and *p*-chloroamphetamine [21]. In rats, none of these amphetamine derivatives produce evidence of DA neurotoxicity, yet they all produce signs of 5-HT neurotoxicity not only in the rat but also in the guinea pig, squirrel monkey and rhesus monkey [23,29,31,32,37]. Whether the effects in mice or in the other aforementioned experimental animals are predictive of effects in humans remains to be determined.

The finding that *N*-methylation dissociates the neurotoxic and behavioral pharmacologic effects of methamphetamine could have implications for other neurotoxic amphetamine derivatives with potentially useful pharmacologic activity (e.g. MDMA and fenfluramine). Specifically, *N*-methylation of MDMA and fenfluramine may permit separation of their neurotoxic and pharmacologic effects. Indeed, there is now direct evidence that the serotonin neurotoxic activity of at least one toxic amphetamine derivative, fenfluramine, can be dissociated from its pharmacologic activity (anorexia) through the use of fluoxetine [19,24]. There is also some indication that the same may hold for the psychoactive drug MDMA [18] and some of its congeners [15,16,20]. Together with the present results, these findings strongly suggest that separation of the neurotoxic and pharmacologic effects of toxic amphetamine derivatives can be achieved. Once this is accomplished, it should be possible to explore possible therapeutic effects of amphetamine analogs without running the risk of brain neurotoxic injury.

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