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α-Benzyl-*N*-methylphenethylamine (BNMPA), an impurity of illicit methamphetamine synthesis: pharmacological evaluation and interaction with methamphetamine

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Abstract

Methamphetamine is a popular drug of abuse, readily synthesized in clandestine laboratories. Illicitly obtained methamphetamine is frequently impure, containing various purposefully added diluents and adulterants, as well as impurities of manufacture and origin. Few impurities have been studied in vivo and limited information exists concerning their pharmacology/toxicology. One such impurity of manufacture is α-benzyl-*N*-methylphenethylamine (BNMPA). Acute toxicity and spontaneous activity (locomotor) studies were conducted with this compound alone and in combination with S(+)-methamphetamine (METH) in male, ICR mice. In the acute toxicity studies, BNMPA was evaluated for convulsant activity. While BNMPA also produced some behavioral disturbances similar to those seen with methamphetamine (e.g., stereotopy) at doses greater than 30 mg/kg, no tonic-clonic convulsions were noted until pre-terminal convulsions at 50 mg/kg. METH alone produced tonic-clonic convulsions at terminal doses of 70 mg/kg. When BNMPA was given in combination with METH, there was no readily apparent change in the convulsion profile from that of METH given alone. In spontaneous activity studies, doses of BNMPA ranging from 1 mg/kg to 50 mg/kg failed to alter locomotor activity significantly from controls though 5 mg/kg METH alone significantly increased spontaneous activity. In addition, increases in spontaneous activity elicited by 5 mg/kg METH were not affected when METH was given with 5 mg/kg BNMPA. While BNMPA appears to have toxic effects in the central nervous system (CNS), the failure to affect locomotor activity or alter either METH-induced increases in spontaneous activity or METH-induced convulsions suggests that the two agents are producing their effects through distinct mechanisms.

Keywords: Methamphetamine; Methamphetamine impurities; Pharmacological activity; Pharmacological interactions

1. Introduction

The use of stimulants, including amphetamine, methamphetamine, phenmetrazine, methylphenidate, diethylpropion and propylhexedrine, reached epidemic proportions during the late 1940s and early 1950s when these compounds were used by soldiers, factory workers and prisoners of war in Japan during World War II. After World War II, a surplus on the Japanese market permitted sales without a prescription, with peak use occurring about 1954 (Brill and Hirose, 1969). In the 1960s, methamphetamine abuse became a social problem in the United States. In fact, by 1970, 50% of legally manufactured amphetamine and related compounds were being sold illegally on the black market. The Controlled Substances Act of 1970 stringently regulated the manufacture of these stimulants and forced manufacturers to decrease sales to retail pharmacies (Morgan and Kagan, 1978). Because methamphetamine is easily synthesized in crude laboratories, it quickly became the 'stimulant of choice', and a dramatic increase has occurred in the illicit production and use of methamphetamine hydrochloride over the past several years. Endemic areas for this increase include the Pacific coast

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states, Hawaii and other Pacific rim countries, such as Japan and Korea (Heischober and Derlet, 1989).

During the middle decades of the 20th century in which amphetamines were heavily used and available through legitimate manufacturing channels, these drugs were considered remarkably safe and only rarely responsible for death (Kalant and Kalant, 1975). Prior to the institution of the Controlled Substances Act in 1970, the world medical literature contained only 43 reports of deaths associated with amphetamines in a 35-year period. As with any legally manufactured drug, these compounds were subject to strict manufacturing and purification requirements and would not be expected to contain any impurities. However, since 1980, as clandestinely manufactured compounds have become the primary source of amphetamine/methamphetamine, these compounds have consistently ranked among the twenty most frequently mentioned drugs in emergency room patients as well as medical examiner cases (Drug Abuse Warning Network, 1991). It is well known that side reactions and incomplete conversions ('impurities of manufacture') can easily occur in most of the illicit synthetic methods of production and 'street chemists' rarely, if ever, take the time or expense to purify their product. In fact the addition of even more diluents and adulterants is the norm (Morgan and Kagan, 1978). Impurities of manufacture are numerous and are characteristic of a particular synthetic method. They have been extensively reviewed elsewhere (van der Ark et al., 1978; Sinnema and Verweij, 1981; Soine, 1989; Verweij, 1989). These contaminants, of which α-benzyl-*N*-methylphenethylamine (BNMPA) is only one, may be contributing to the apparent increased toxicity of methamphetamine.

Depending on the synthetic route used and the skill of the chemist, impurities of manufacture may range from 3 to 30% of the sample (Soine, 1986). Long-time abusers in whom tolerance to the drug has developed may use as much as 5000–15 000 mg of methamphetamine per day (Derlet and Heischober, 1990) and consequently may be consuming these impurities in relatively high quantities.

When one considers the apparent increase in emergency room visits and medical examiner cases since illicit manufacture became the primary source of methamphetamine and the possibility of ingestion of large quantities of impurities, it is surprising that the information concerning the pharmacology of the impurities of manufacture is very limited. The work that has been done is summarized in Table 1. There is no literature describing the activity of the remaining impurities of manufacture. However, even these limited studies indicate that the α-benzyl compounds elicit convulsions at much lower doses than AMPH and METH indicating greater central nervous system (CNS) stimulation at the brainstem and cord levels. This certainly points out the potential danger of street drugs containing substantial amounts of these impurities.

The purpose of this study was to further evaluate the pharmacology and toxicology of BNMPA, alone and with S(+)-methamphetamine (METH). It is important

Table 1
Pharmacology/toxicology of impurities found in illicitly synthesized METH

Compound	Species	End point	Dose (mg/kg)	Route of administration	Reference
2-(phenylmethyl)Phenethylamine	Rabbits	Lethality (LD_{50}) (hypotension)	198.5	Continuous i.v. infusion	Moisset de Espanes and Weksler, 1953
2-(phenylmethyl)Phenethylamine	Rabbits	Lethality (LD_{50}) (hypotension)	31.7	Single i.v. dose	Moisset de Espanes and Weksler, 1953
2-(phenylmethyl)Phenethylamine	Rabbits	Lethality (LD_{50}) (hypotension)	160	Subcutaneous	Hano and Wojewodzki, 1961
2-(phenylmethyl)Phenethylamine	Man	Death	Unknown	Unknown	Anonymous, 1981
Phenyl-2-propanone	Mice	Loss of righting ability (LRA_{50})	215	Intraperitoneal	Barfknecht et al., 1971
Phenyl-2-propanone	Mice	LD_{50}	520	Intraperitoneal	Barfknecht et al., 1971
Phenyl-2-propanol	Mice	LRA_{50}	330	Intraperitoneal	Barfknecht et al., 1971
Phenyl-2-propanol	Mice	LD_{50}	540	Intraperitoneal	Barfknecht et al., 1971
BNMPA	Mice	Convulsions (CD_{50})	54.09	Intraperitoneal	Noggle et al., 1985
BNMPA	Mice	LD_{50}	78.2	Intraperitoneal	Noggle et al., 1985
α-Benzylphenethylamine	Mice	CD_{50}	45.49	Intraperitoneal	Noggle et al., 1985
α-Benzylphenethylamine	Mice	LD_{50}	63.25	Intraperitoneal	Noggle et al., 1985
d,l-Amphetamine sulfate	Mice	LD_{50}	7	Subcutaneous	Nielsen et al., 1967
d,l-Amphetamine sulfate	Mice	CD_{50}	90	Intraperitoneal	Noggle et al., 1985
d,l-Amphetamine sulfate	Mice	LD_{50}	91.14	Intraperitoneal	Noggle et al., 1985
d,l-Methamphetamine HCl	Mice	CD_{50}	56.96	Intraperitoneal	Noggle et al., 1985
d,l-Methamphetamine HCl	Mice	LD_{50}	57.19	Intraperitoneal	Noggle et al., 1985

to consider the interaction of BNMPA with METH since, as an impurity of METH manufacture, BNMPA is ingested with METH and would rarely, if ever, be consumed by itself. While the classic mechanisms of drug interactions were considered (variously described as 'synergy', 'additivity', 'superadditivity', etc.), the toxicity of BNMPA must also be broadly defined to include antagonism of any of the effects of METH. For example, if BNMPA significantly depressed the euphoric effects produced by METH, the METH user would ingest more of the METH to reach the feeling he/she was used to until the toxic level of METH was approached.

2. Materials and methods

S(+)-methamphetamine (METH) and *d*-amphetamine sulfate (AMPH) were purchased from Sigma Chemical Company (St. Louis, MO). BNMPA was synthesized as described in a previous publication (Moore et al., 1995).

Male ICR mice, weighing 18–20 grams on delivery, were purchased from Harlan (Dublin, VA). Water and food (Rodent Laboratory Chow, Ralston-Purina Co., St. Louis, MO) were available ad libitum in both the test and home cages. Groups of 5 mice were housed in standard mouse cages (18 × 29 × 13 cm) with wood chip bedding in a controlled temperature room (22–24°C) with a 12-h light-dark cycle.

2.1. Spontaneous activity studies

Spontaneous activity was measured as the number of interruptions of 16 photocells/cage in an Omnitech Spontaneous Activity System (Omnitech Electronics, Columbus, OH). The locomotor arena is a 2.5 × 20 × 33.5 cm clear plastic cage with a wire mesh top. Results were compiled using Digiscan, v. 2.2 software (Omnitech Electronics, Columbus, OH).

In an initial experiment, mice were moved to the test room on the day before testing for acclimation. On the test day, subjects were placed individually in the activity chambers for an adaptation period of 30 min. After the adaptation period, they were removed from the chambers and given an i.p. injection of either saline, 1, 3, 5 or 10 mg/kg BNMPA, 5 mg/kg METH or 5mg/kg METH combined with 5 mg/kg BNMPA. Spontaneous activity counts were taken in 10-min bins for a total of 30 min. There were 12 animals in each dosage group.

A second experiment was conducted to examine the effects of BNMPA under different conditions and to compare its activity to another stimulant (AMPH). Four groups of 6 mice each were established and brought to the testing room the day before testing. Following a 10-min adaptation period in the test chamber, the mice were given i.p. injections of either saline, 10 or 50 mg/kg BNMPA, or 5 mg/kg AMPH. Spontaneous activity counts were taken in 10-min bins for a total of 40 min.

2.2. Acute toxicity studies

Our primary interest in this study was the interaction of BNMPA and METH. However, prior to looking at the interaction of these compounds, it was necessary to establish a baseline effect for each compound individually under the same operating conditions in which the interaction studies would be conducted. The purpose of the initial study was to establish a dose-response relationship for BNMPA and METH alone. The observer was blind to all drug conditions.

On the day before testing, all mice were moved to the test room for adaptation. On the test day, each of the 10 mice in a group were marked and weighed. Subjects were administered intraperitoneally (i.p.) either saline, BNMPA (0, 10, 30, 50, 70 or 80 mg/kg) or METH (0, 10, 30, 50 or 70 mg/kg). There were 10 mice in each dosage group. Immediately following the injections, the observer lifted each mouse gently by the tail, observed quickly for the appearance of tonic or clonic convulsions, then gave a slow 180° turn and observed again for convulsions. Scores were given as follows (Evans and Balster, 1993):

0 = no effect in either observation;

1 = tonic convulsion when mouse is lifted and turned;

2 = tonic convulsion when mouse is lifted and not turned OR tonic-clonic convulsion when mouse is lifted and turned;

3 = tonic-clonic convulsion when mouse is merely lifted; and

4 = tonic-clonic convulsion observable either before mouse is lifted or after release.

The purpose of the second study was to evaluate whether BNMPA would alter the effects of METH. All conditions were identical to the above protocol except the injections. Subjects received either saline, 1, 3, 5 or 10 mg/kg METH alone or one of those doses combined with 10 mg/kg BNMPA.

2.3. Statistical analysis

Total activity counts were analyzed using ANOVA, and the Newman-Keuls test was used for post-hoc analysis when appropriate. Differences were considered significant at the $P < 0.05$ level.

The Kruskal-Wallis one-way analysis of variance was used to analyze the categorical data in the acute toxicity studies. The dose which caused 50% of the mice to exhibit seizure activity (CD_{50}) was calculated using the method of Litchfield and Wilcoxon (1949).

3. Results

3.1. Spontaneous activity

The interaction bar plots for the means of the total

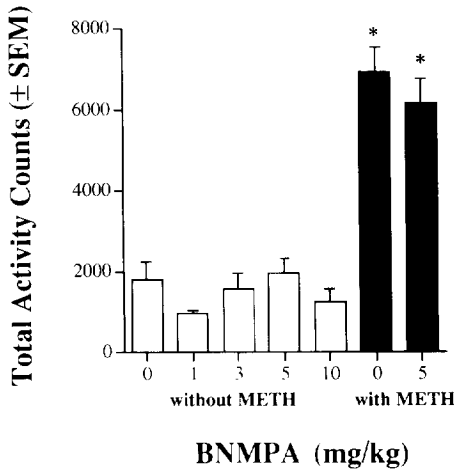

Fig. 1. The locomotor effects (mean activity counts ± S.E.M.) of saline, BNMPA (1, 3, 5 or 10 mg/kg) and METH (5 mg/kg) alone and combined with 5 mg/kg BNMPA ($n = 12$). *Significantly different from saline and each of the doses of BNMPA (significance level = 5%).

counts for experiments 1 and 2 are shown in Figs. 1 and 2, respectively.

Fig. 1 depicts the mean total activity counts for the 30-min observation period plotted versus dosages of BNMPA alone and in combination with METH. A significant effect of treatment with METH was found when compared to controls and all doses of BNMPA alone ($F(6,77) = 34.3$, $P < 0.05$). METH combined with BNMPA exhibited significantly more activity than each of the other treatments ($P < 0.05$) except METH alone. There were no significant differences in the first 10-min time bin.

The mean total activity counts for the 40-min observation period plotted versus 10 and 50 mg/kg doses of BNMPA and 5mg/kg AMPH alone is shown in Fig. 2.

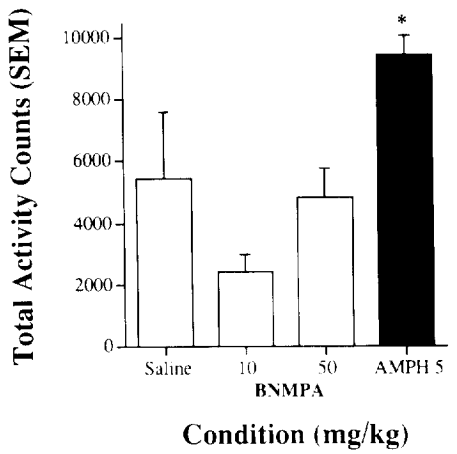

Fig. 2. The locomotor effects (mean activity counts ± S.E.M.) of saline, BNMPA (10 or 50 mg/kg) and AMPH (5 mg/kg) ($n = 6$). *Groups which are significantly different from saline and each of the doses of BNMPA alone (significance level = 5%).

Table 2
Convulsant behavior in mice following intraperitoneal injections of BNMPA

Score	Saline controls	BNMPA (mg/kg i.p.)				
		10	30	50	70	80
0	8	8	8	3	1	0
1	2	2	0	0	0	0
2	0	0	1	0	0	0
3	0	0	0	0	0	0
4	0	0	1	7	9[a]	10[a]

[a]Five mice treated with 70 mg/kg BNMPA and 9 mice treated with 80 mg/kg BNMPA died after exhibiting seizures.

Numbers are number of animals out of a group of 10 that exhibited each scored behavior ($CD_{50} = 41$ mg/kg; confidence limits = 33–50).

ANOVA reveals a significant effect ($F(3,20) = 5.3$, $P < 0.05$). The group that received AMPH alone differed significantly from all other groups ($P < 0.05$). No other significant differences were found. There were no significant differences in the first 10-min time bin.

3.2. Acute toxicity study

Results are compiled for BNMPA, METH and BNMPA combined with METH in Tables 2–4, respectively. BNMPA as well as METH elicited stereotopy, catatonic-like states and 'popcorn-like' hyperactivity beginning at 30 mg/kg and 10 mg/kg, respectively. However, because this behavior did not meet the convulsion criteria, these animals were scored as 0 in this study. All of the animals that exhibited spontaneous clonic-tonic convulsions at any point during or throughout the 1-h observation period of this study were scored as 4 whether or not they recovered after 1 h. The number of animals that died following tonic-clonic convulsions during the observation period are indicated in each table.

Spontaneous tonic-clonic convulsions were observable with BNMPA at doses lower than those causing

Table 3
Convulsant behavior in mice following intraperitoneal injections of METH

Score	Saline controls	METH (mg/kg i.p.)			
		10	30	50	70
0	8	5	6	4	2
1	2	2	1	1	0
2	0	3	3	4	2
3	0	0	0	0	0
4	0	0	0	0	6[a]

[a]These mice died subsequent to exhibiting convulsions.

Numbers are number of animals out of a group of 10 that exhibited each scored behavior.

Table 4
Convulsant behavior observed following intraperitoneal injections of combinations of S(+)-methamphetamine (METH) and BNMPA in mice

Score	Saline controls		METH (1 mg/kg)		METH (3 mg/kg)		METH (5 mg/kg)		METH (10 mg/kg)	
	Alone	BNMPA	Alone	BNMPA	Alone	BNMPA	Alone	BNMPA	Alone	BNMPA
0	8	9	1	6	3	6	4	5	4	5
1	2	1	3	3	0	0	0	0	0	0
2	0	0	5	1	7	4	6	5	6	5
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0

The first column under each dose is the dose of METH alone; the second column under each dose is that dose of METH combined with 10 mg/kg BNMPA. Numbers are number of animals out of a group of 10 that exhibited each scored behavior.

lethality (CD_{50} = 41 mg/kg; confidence limits = 33–50; $\chi^2(5) = 40.8$, $P < 0.05$). A significant effect of convulsions was found with METH ($\chi^2(4) = 14.1$, $P < 0.05$) but not until reaching a lethal dose. One animal in the 50 mg/kg METH alone group died acutely following injection without exhibiting convulsions.

In the interaction study, there was also a significant effect of convulsions ($\chi^2(9) = 23.3$, $P < 0.05$). However, as can be seen in Table 4, BNMPA had little influence on METH-induced convulsions. One animal in the 1 mg/kg METH alone group died after exhibiting convulsions.

4. Discussion and conclusions

Human society has a strong and pervasive commitment to the use of drugs, and to the frequent concurrent use of a diversity of biologically active substances. This seems to be especially true of those drugs which exert potent effects upon the activities of the central nervous system (CNS). Persons who are abusing CNS stimulants such as METH are often polydrug abusers (Lynch and House, 1992). This picture is further complicated when these drugs are obtained from illicit manufacturers since these compounds often contain various unknown diluents, adulterants and impurities of either manufacture or origin. Because of this commitment to multiple drug use and the use of illicitly manufactured drugs, we have to face the problems generated by drug interactions.

One of the defining behavioral characteristics of psychomotor stimulants (METH, AMPH, cocaine, etc.) is their ability to elicit increases in motor activity. At low doses, these drugs produce an alerting response characterized by increases in exploration, locomotion, grooming and rearing (Robbins and Sahakian, 1983). The majority of evidence indicates that the neurochemical effects of these stimulants underlying their ability to increase motor activity involve dopaminergic systems (Johanson and Fischman, 1989). This was observed in our study with METH and AMPH but not BNMPA. Although it is possible BNMPA may have had locomotor effects which were short-lived, no significant differences were observed in the first 10-min time bin of either spontaneous activity experiment. Seizures, while also often associated with stimulant abuse, tend to occur only at very high doses (Weiner, 1985; Cameron et al., 1992; Ritz and George, 1993). Seizure induction is generally associated with non-dopaminergic systems (Bloom, 1985; Ritz and George, 1993).

It should be noted that BNMPA is structurally more similar to benzphetamine than either methamphetamine or amphetamine. Benzphetamine is a sympathomimetic amine that represented an attempt to produce a drug with anorectic properties while decreasing the central stimulant properties of this class of drug (Brooks et al., 1982). In fact, among the major behavioral effects of stimulants such as amphetamine, the only one found to be mediated by a non-dopaminergic projection was anorexia (Robbins and Sahakian, 1983). Because of this structure-activity relationship and review of the mechanisms of action of drugs in the stimulant class noted above, it is not surprising that BNMPA produced convulsant behavior and lethality but failed to elicit locomotor stimulation. Thus we can conclude that not only does the structure of BNMPA predispose it to have a low affinity for the dopaminergic receptors responsible for locomotor activity, but it may also have a greater affinity for GABA, glutamate (NMDA) or serotonergic ('seizurgenic') receptors. In one reported case of benzphetamine poisoning (Brooks et al., 1982) autopsy findings suggested a significant convulsant episode prior to death with the cause of death being circulatory collapse.

Based on the acute toxicity studies, we would have expected to have induced spontaneous convulsions in at least 50% of the animals when dosed at 50 mg/kg in the spontaneous activity experiments. These may not have been noted in this study since the animals cannot be observed while they are in the activity chambers.

This study may not be representative of what can be expected in true METH abusers. The primary routes of administration for METH in humans are intravenous and smoking. Both of these routes allow a substantial amount of drug to bypass 'first-pass' metabolism

whereas intraperitoneal injections do not. Intraperitoneal injections were chosen for this study since this route of administration has the largest data base with which to compare this relatively unstudied compound. Even with intraperitoneal injection and 'first-pass' metabolism, methamphetamine would still produce its effects on spontaneous activity since the primary metabolite of methamphetamine is amphetamine. The apparent primary route of BNMPA metabolism is hydroxylation/glucuronide conjugation (Moore and Poklis, 1995). These mechanisms tend to inactivate compounds.

Second, this study was done following a single dose of METH and BNMPA. The pattern of methamphetamine use in abusers is high doses (sometimes several thousand mg per day) over very long periods of time. Under these conditions, BNMPA and related lipophilic compounds (which have a much larger partition coefficient than amphetamine/methamphetamine) (Brooks et al., 1982) will be stored in tissues (including the CNS) for prolonged periods. It may be that only with extended exposure will BNMPA accumulate to pharmacologically/toxicologically significant doses.

Observations in this study suggest several directions for further investigations into the pharmacology/toxicology of BNMPA. These should include dopamine and serotonergic receptor binding studies to elucidate the mechanism of seizure production in the absence of locomotor stimulation. Additionally, chronic toxicity studies as well as looking at other routes of administration would further characterize the role of long-term abuse of illicitly manufactured methamphetamine in its toxicity.

While BNMPA appears to have toxic effects in the CNS, the failure to affect locomotor activity or alter METH-induced increases in spontaneous activity or convulsions suggests that the two agents are producing their effects through distinct mechanisms.

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