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Distinct features of seizures induced by cocaine and amphetamine analogs

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Abstract

Seizure-related emergencies caused by stimulants of abuse have been increasing. To better understand the nature of these drug-induced convulsions, we characterized the seizure patterns associated with high doses of cocaine, and the amphetamine analogs, methamphetamine, methylenedioxymethamphetamine (MDMA) and 4-methylaminorex. The features of the stimulant-induced seizures were distinct and included the following: (1) the duration of convulsive activity was shortest for cocaine and longest for methamphetamine, (2) only MDMA produced a secondary clonic phase after the initial ictal event, and (3) 4-methylaminorex manifested a very steep dose–response curve. Differential preventive profiles of anticonvulsant agents on the stimulant-induced seizures also were observed. For example, cocaine-related seizures were most effectively prevented by, while methamphetamine-induced seizures were completely refractory to, phenytoin pretreatment. The only anticonvulsants which appeared to influence methamphetamine-related convulsions were diazepam and valproate. A unique feature of 4-methylaminorex was that related seizures were almost completely blocked by the calcium channel blocker, flunarizine.

Keywords: Seizure; Methamphetamine; Cocaine; MDMA (methylenedioxymethamphetamine)

1. Introduction

The illicit use of potent central nervous system (CNS) stimulants, such as cocaine and amphetamine-like drugs, continues to be a major health problem. Of particular concern since 1990 has been the dramatic rise of emergency incidents and deaths resulting from stimulant overdosing (Olson et al., 1993). Although many studies have examined the neurochemical and behavioral toxicity associated with the use of high doses of these drugs (Gibb et al., 1994; Ricaurte et al., 1994; Segal and Kuczenski, 1994), surprisingly little research has examined the mechanisms of stimulant-induced seizures. Convulsions are an emergency consequence of high-dose stimulant consumption (Buchanan and Brown, 1988; Alldredge et al., 1989; Sanchez-Ramos, 1993) which have been particularly associated with cocaine overdosing (Koppel et al., 1996). In fact, many of the deaths resulting from cocaine overdoses are due to neuroregulatory mechanisms altered by protracted seizure induction (Mittleman, 1984; Meehan and Schechter, 1995). Cocaine-induced seizures are usually generalized with tonic–clonic features, self-limiting, and of short duration (Lowenstein, 1987). While the features of cocaine-related seizures are relatively well described, their mechanism is poorly understood.

Even though the occurrence of seizure activity after high doses of amphetamine-related drugs appears to be less frequent than cocaine overdosing, fatality associated with amphetamine overdoses is usually related to acid–base imbalances associated with prolonged seizure activity (Alldredge et al., 1989; Olson et al., 1993). Compared to cocaine, even less is understood about the nature of seizures induced by amphetamine analogs. It is important to elucidate similarities and differences in the seizure-evoking properties of the stimulants in order to treat more effectively those convulsions resulting from high doses of these drugs of abuse.

The present study examines and compares the phenotypic characteristics of seizures induced by cocaine, methamphetamine and the ''designer amphetamine''

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analogs, methylenedioxymethamphetamine (MDMA) and 4-methylaminorex. This study also assessed the ability of a variety of anticonvulsants with both known and unknown mechanisms of action to block behavioral seizures induced by these drugs. The results suggest that distinct mechanisms account for seizures induced by each of these stimulants and demonstrate that effective treatment may be dependent on the unique features of each stimulant.

2. Materials and methods

2.1. Phenotypic characterization of seizure activity

Varying doses of methamphetamine (75–400 μg), 4-methylaminorex (50–200 μg), cocaine (25–400 μg), and MDMA (125–500 μg) were administered intracerebroventricularly (i.c.v.) by free-hand injection into the right lateral ventricle of awake CF#1 mice (White et al., 1992, 1995). The total dose of each drug was dissolved in 5 μl of 0.9% saline and was delivered via a 1-μl Hamilton syringe within 10 s. The dose of each drug of abuse was either increased or decreased until a clear dose–response relationship was established. The dose required to produce seizures in 50% (CD_{50}) or 97% (CD_{97}) of the animals tested was calculated by probit analysis (Finney, 1971). No adverse behavioral effects were noted in control mice receiving an equivalent volume of vehicle i.c.v.

Phenotypic features of each drug was assessed at the CD_{97} for the convulsants. For these studies, groups of 8–10 mice received the CD_{97} of each respective drug and placed into individual observation cages where they were observed for 30–60 min for abnormal behavior. During this time, the investigator examined each mouse for any signs of clonic and/or tonic seizure activity, time of seizure onset and duration, and any other salient behavioral features.

The ability of a variety of selected drugs to block seizures induced by each of the drugs of abuse was established at the CD_{97} level for each drug. Groups of mice were pretreated with varying doses of each of the test drugs. At the time of peak pharmacological effect for each of the anticonvulsants and for atropine, mice were challenged with the CD_{97} of the drug of abuse. Mice were then observed for 30 min for the presence of seizure activity. For each of the anticonvulsant drugs tested in this study, the dose administered and the pretreatment period employed were based on the results of previous studies that defined the time to the peak anticonvulsant effect and median effective dose for each drug. In the mouse study, individual mice were pretreated intraperitoneally with either 10 mg/kg diazepam, 25 mg/kg phenobarbital, 10 mg/kg flunarizine, 400 mg/kg valproate, 20 mg/kg phenytoin, or 5 mg/kg atropine for 30, 60, 30, 120, 30, or 120 min, respectively. All anticonvulsant drugs were either dissolved or suspended in 0.5% methylcellulose and injected i.p. in a volume of 0.01 ml/g body weight. The doses and pretreatment times employed for the various anticonvulsants were based on maximally effective doses and pretreatment times for blocking maximal electroshock seizures. The dose employed for flunarizine was based on previous reports (Desai et al., 1995; Gasior et al., 1996).

When possible, the median effective dose (ED_{50}) for seizure protection was calculated by probit analysis (Finney, 1971).

2.2. Electroencephalographic (EEG) recording

For technical reasons, EEG studies were conducted in Sprague–Dawley rats rather than CF#1 mice. Male adult rats (200–250 g) were anesthetized with ketamine (80 mg/kg, i.p.) and xylazine (12 mg/kg, i.p.). Five stainless steel recording electrodes were surgically implanted over the frontal and parietal cortex; a sixth reference (indifferent) electrode was placed in the frontal sinus. All electrodes were then placed into an eight-pin recording assemble and permanently attached to the cranium by dental acrylic cement. The effect of methamphetamine and cocaine on EEG activity was assessed 1 week after surgery. For these studies, rats were placed into individual clear plastic observation cages and their EEG recordings were made by a Grass Model 810 Electroencephalograph (Quincy, MA) on chart paper. After a few minutes of baseline recording, individual rats received either vehicle, methamphetamine (45 mg/kg, i.p.) or cocaine (80 mg/kg, i.p.). In a separate experiment, the ability of phenytoin to modify cocaine- and methamphetamine-induced EEG seizure activity was assessed. For this study, rats were pretreated with phenytoin (10 mg/kg, i.p.) 30 min prior to receiving a single dose of the stimulants. Individual rats were then observed and EEG monitored for 60 min for the presence of both behavioral and electrographic seizure activity.

3. Results

3.1. Dose–response of the stimulants

To compare the seizure-initiating properties of commonly abused CNS stimulants, varying doses of cocaine, methamphetamine, MDMA and 4-methylaminorex were administered i.c.v. to conscious mice. All four drugs of abuse produced a dose-dependent increase in seizure frequency. The seizure response to the drug treatment was determined as either presence or absence of forelimb clonus. From these data the CD_{50} and CD_{97} were calculated. The data in Fig. 1 demonstrate that cocaine had the lowest CD_{50} dose while MDMA had the highest. For cocaine, methamphetamine and MDMA, the difference

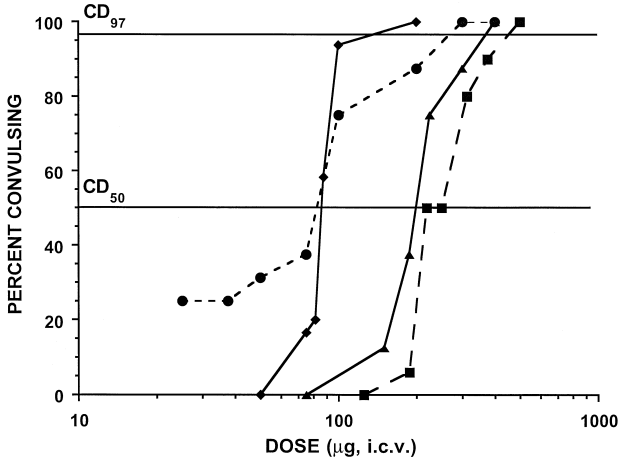

Fig. 1. Dose-dependent clonic seizure activity induced by i.c.v. administration of cocaine, methamphetamine, 4-methylaminorex and MDMA. Varying doses of each stimulant was injected i.c.v. into the lateral ventricle of 6 to 10 conscious CF#1 mice. The mice were observed for 30 min for the presence or absence of clonic seizure activity. At the CD_{97} level, 4-methylaminorex was the most potent followed by cocaine, methamphetamine and MDMA. At the CD_{50} level, 4-methylaminorex was equipotent to cocaine which was 3 to 5 time more potent than the other two stimulants tested. The curves are designated as follows: circles are cocaine, triangles are methamphetamine, diamonds are 4-methylaminorex, and squares are MDMA.

between the CD_{50} and CD_{97} doses was over 100 μg: in contrast, the difference between these two convulsive doses for 4-methylaminorex was only 20 μg, suggesting a very steep dose-seizure correlation for this stimulant.

3.2. Features of stimulant-induced seizures

Examination of the seizure behavior caused by the CD_{97} dose for the stimulants represented in Fig. 1 revealed very distinct patterns of response (Table 1). The duration of seizure activity was shortest for cocaine and MDMA (< 30 s) and longest for methamphetamine (> 3 min). The features of the seizures were similar for methamphetamine and 4-methlyaminorex including episodes of running, popcorn jumping, circling and some barrel rolling. In contrast, some cocaine-treated animals experienced running and popcorn jumping, but none experienced circling or barrel rolling. Only 4-methylaminorex caused myoclonic jerks and only MDMA consistently caused a secondary clonic phase which occurred more than 2 min after the initial ictal event.

3.3. Effect of various anticonvulsants on stimulant-induced seizures

The distinct behavioral patterns of the seizures produced by each stimulant suggested the possibility of differential mechanisms. Consequently, the effects of several anticonvulsant drugs on the seizure-initiating properties of these stimulants of abuse were tested. The percent of clonic seizures was determined after i.c.v. administration of the CD_{97} dose of each stimulant. As predicted by the different seizure behaviors produced by each stimulant, the ability of the anticonvulsant drugs to prevent the behavioral and seizure activity varied between the different stimulants. A summary of the findings is shown in Fig. 2 and reveals that differential effects were observed and depended on the anticonvulsant tested. For example, methamphetamine-induced seizures were the most resistant to the anticonvulsants with only diazepam and valproate able to reduce the methamphetamine-related convulsions incidence to approximately 70%. In contrast, cocaine-induced seizures were more likely to be prevented by pretreatment with phenobarbital and phenytoin. Both MDMA- and 4-methylaminorex-related seizures were dramatically reduced by pretreatment with valproate. Flunarizine, a

Table 1
Behavioral characterization of seizures induced by cocaine, methamphetamine (METH), MDMA and 4-methylaminorex (4-MAX) after i.c.v. administration
These are behavioral observation made on the mice used for Fig. 1. The CD_{97} dose of each drug was administered i.c.v. to conscious animals and the behavior scored by an observer blind to the treatment.

Drug (CD_{97})	Clonus onset[a]	Clonus duration[b]	Running[c]	Popcorn jumping	Barrel rolling	Circling	Myoclonic jerks[d] phase[e]	Secondary clonic
Cocaine (240 μg)	immediate	short	+/−	+/−	−	−	−	−
METH (340 μg)	immediate	prolonged	+	+	+/−	+	−	+/−
MDMA (410 μg)	immediate	short	+/−	−	+	+	−	+
4-MAX (110 μg)	intermediate	intermediate	+	+	+/−	+	+	−

[a] Immediate: < 20 s; Intermediate: 60–300 s.
[b] Short: < 30 s; Intermediate: 30–300 s; Prolonged: > 3 min.
[c] Cocaine and 4-MAX caused a single 2–3 s burst of running and/or popcorn jumping early; similar behavior was not observed at any time thereafter.
[d] Continuous, periodic 1-s jerks interrupted by quiescence.
[e] Initial clonic activity was followed by behavioral arrest for greater than 2 min followed by another clonic episode.
+: Behavior observed in all animals.
+/−: Behavior observed in some animals.
−: Behavior observed in none of the animals.

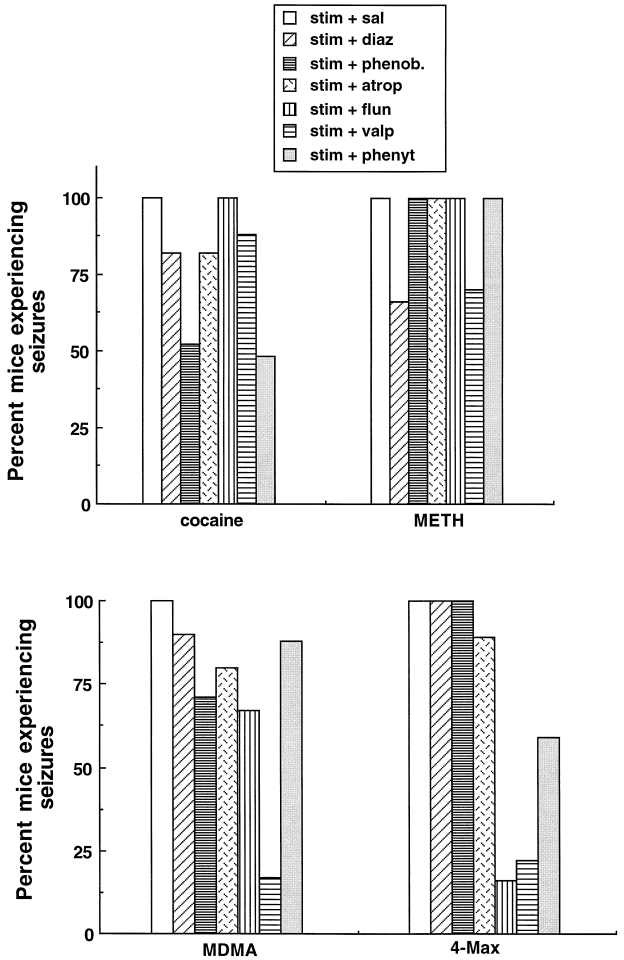

Fig. 2. Effect of anticonvulsant drugs (diazepam [diaz], phenobarbital [phenob], atropine [atrop], flunarizine [flun], valproate [valp], phenytoin [phenyt]) on the proconvulsant action of cocaine, methamphetamine (METH), MDMA and 4-methylaminorex (4-MAX). Separate groups of mice ($n = 8–10$) were pretreated with one of the drugs and at time of peak drug effect individual mice were challenged with the CD_{97} (administered i.c.v.) of the convulsant and observed for 30 min for the presence or absence of seizure activity. Results are plotted as a percent of animals displaying a clonic seizure in response to the convulsant.

Ca^{2+} channel blocker, exerted profound effects on 4-methylaminorex, but had no impact on the incidence of seizure produced by cocaine or methamphetamine treatments. It is important to note that no abnormal animal behavior was noted at the dose of each anticonvulsant administered when present alone.

3.4. EEG nature of seizures caused by cocaine and methamphetamine

Because cocaine and methamphetamine are the two stimulants most likely to be abused and to cause problems related to seizures, the nature of the convulsions elicited by these two drugs was examined further. These experiments evaluated the EEG characteristics of cocaine- and methamphetamine-induced seizures in rats. To mimic more closely the clinical situation, the stimulants were administered systemically rather than by the i.c.v. route. The doses for these experiments were determined by administering varying stimulant doses i.p. and by identifying the incidence of clonic seizures. In these experiments, the CD_{84} (dose which produced seizures in 84% of the animals tested) was selected for both cocaine and methamphetamine due to the high rate of fatalities which occurred with higher drug dose.

At the CD_{84} level, results obtained from the initial EEG studies demonstrated that the electrographic seizures induced by both methamphetamine and cocaine were generalized from their onset (results not shown). Furthermore, there did not appear to be any spatial separation in the onset of seizures from anterior to posterior surface of the skull. These EEG findings are consistent with the behavioral seizure which was characterized by bilateral clonus from its onset. Interestingly, the systemic CD_{84} dose in rats was higher for cocaine (60 mg/kg) than for methamphetamine (40 mg/kg) in contrast to the i.c.v. CD_{50} and CD_{97} doses in mice, which were higher for methamphetamine. This was probably due to the differences in administration techniques. Despite the apparent dosing differences between mice and rats, phenytoin pretreatment had a similar relative effect on seizures induced by cocaine and methamphetamine in both species (Fig. 3). Thus, phenytoin had no effect on methamphetamine-induced seizures, but profoundly reduced the incidence of cocaine-related clonic seizures. This was confirmed by the EEG tracings shown in Fig. 4. The frequency of spikes associated with methamphetamine-induced seizures was considerably greater than that observed after cocaine administration and was unaffected by pretreatment with phenytoin. In comparison, six out of eight of the phenytoin-pretreated rats demonstrated less electrographic seizure activity in the presence of cocaine than rats not pretreated. Alone, pheny-

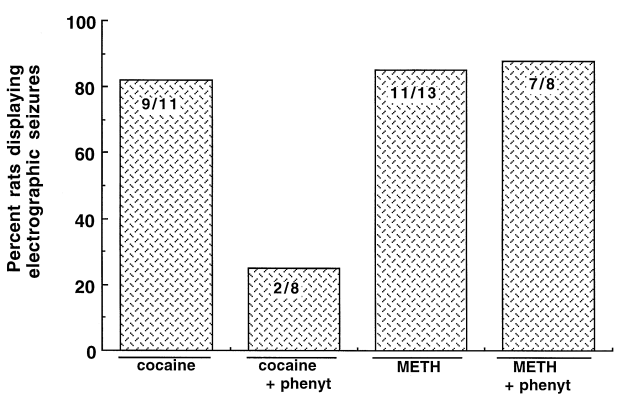

Fig. 3. Effect of phenytoin (Phenyt) on electrographic seizures induced by methamphetamine (METH; 40 mg/kg, i.p.) or cocaine (60 mg/kg, i.p.). Individual rats were pretreated with 10 mg/kg phenytoin 30 min prior to being challenged with either cocaine or methamphetamine. Results are plotted as a percent of animals displaying electrographic and behavioral seizures in each treatment group. The number of rats tested is shown in the columns (animals with clonic seizures/total rats tested).

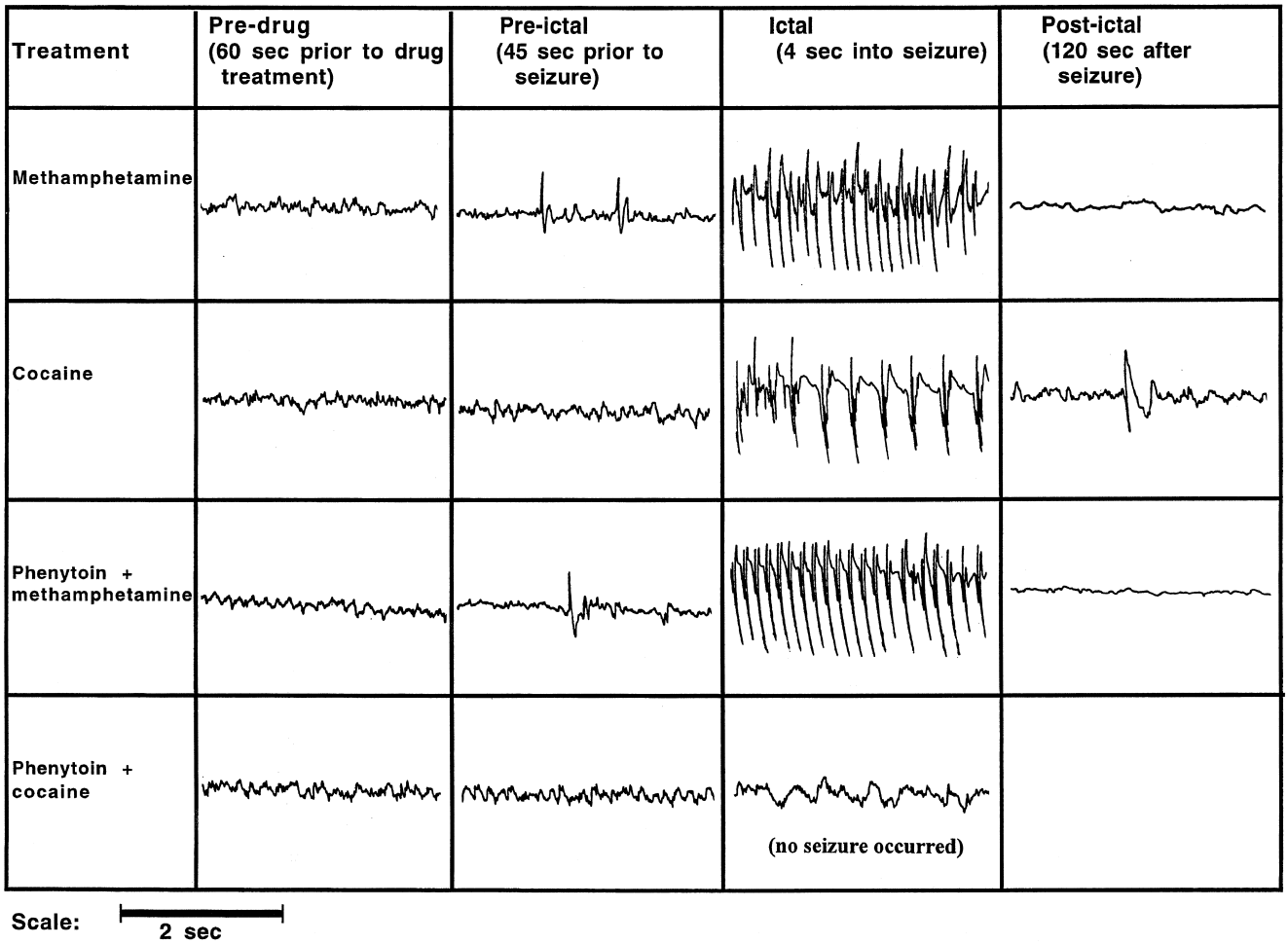

Fig. 4. Representative EEG tracings demonstrating the effect of phenytoin (10 mg/kg) pretreatment on electrographic seizures produced by systemic administration of methamphetamine (40 mg/kg, i.p.) or cocaine (60 mg/kg, i.p.) The effect of methamphetamine and/or cocaine on the EEG of conscious rats is shown in the top two sets of traces. As can be seen by the lower two sets of traces, phenytoin abolished the electrographic seizure discharge induced by cocaine but was without effect on methamphetamine-induced seizures.

toin did not produce any detectable changes in the EEG or animal behavior.

4. Discussion

Due to the frequent occurrence and potentially severe neurological consequence of seizures induced by high doses of illicit stimulants, this study identified and compared the features associated with forelimb clonus initiated by a single high dose of cocaine and the three amphetamine analogs, methamphetamine, MDMA, and 4-methylaminorex. In the initial studies, a mouse model was employed due to the ease with which drugs were injected i.c.v. into conscious animals. This strategy minimizes the confounding issues of pharmacokinetic factors created by the rapid metabolism of cocaine by plasma esterase activity and hepatic metabolism of methamphetamine and its analogs. Furthermore, direct i.c.v. administration also alleviates confounding factors associated with blood–brain barrier penetration. The CD_{50} and CD_{97} were calculated for each of the four drugs administered (Fig. 1). The results demonstrated that when injected directly into the ventricles, cocaine was the most, and MDMA was the least, potent at the CD_{50} level. In contrast, at the CD_{97} 4-methylaminorex was considerably more potent as a seizure-provoking drug than the other stimulants. These findings are due to an unusually steep dose–response curve for 4-methylaminorex (i.e., $CD_{50} = 90$ μg and $CD_{97} = 110$ μg) and suggest that abuse of this drug may be particularly dangerous due to this dramatic rise in seizure probability with small increases in dose. This seizure-inducing characteristic of 4-methylaminorex has been noted previously in other studies (Hanson et al., 1992).

Characterization of the stimulant-induced seizure behavior of these 4 drugs of abuse demonstrated very distinct patterns for each drug (Table 1). For example, the clonus onset for cocaine was very rapid and seizures persisted for less than 30 s. The short duration of action of cocaine in these studies may be due to the rapid inactivation of

cocaine by esterases (Ritchie and Greene, 1985). Seizure induction for methamphetamine was also rapid but, in contrast to cocaine, seizures persisted for over 3 min suggesting that methamphetamine was not inactivated nearly as quickly as cocaine. Interestingly, with an immediate onset and a duration less than 20 s, the MDMA-related seizures were somewhat more like that caused by cocaine than by its analog, methamphetamine. In the case of MDMA, it is not likely that the drug's short duration of the first seizure was the consequence of metabolic inactivation since there was always a secondary clonic phase which occurred 2 min after the initial clonic episode. This feature was somewhat unique to MDMA, although a similar response was seen in about 50% of the methamphetamine-treated animals. Most of the drugs produced some running with a tendency towards ''popcorn jumping''. However, other distinct locomotor behaviors such as circling, and barrel roll were present for the most part after all of the amphetamine analogs, but absent with the cocaine treatment.

Because the seizure phenotypes were distinct for each of the stimulants, we assessed the effect of selected anticonvulsants on seizures induced by the stimulants. For these studies, the CD_{97} of each stimulant was administrated i.c.v. to mice pretreated with antiseizure medication. As shown in Fig. 2, the ability of these drugs to alter the seizure-inducing properties of the stimulants varied substantially. Thus, methamphetamine-related seizures appeared to be the most refractory to preventive treatment. Only pretreatment with diazepam and valproate attenuated the seizure induced by methamphetamine administration. Noteworthy is the fact that seizures induced by all of the amphetamine analogs were diminished by valproate; in the case of MDMA and 4-methylaminorex, almost total protection was observed. MDMA- and 4-methylaminorex-induced seizures was distinguished by their sensitivity to the anticonvulsant action of flunarizine. Thus, 4-methylaminorex-related seizures were almost completely blocked (decreased by 87%) whereas MDMA-evoked seizures were only attenuated (decreased by 38%). For cocaine, the most effective antiseizure effect was caused by phenobarbital and phenytoin; in contrast, these two drugs were completely without effect on methamphetamine-induced seizures. In general, the anticonvulsant profiles for cocaine- and methamphetamine-induced seizures appeared to be the most dissimilar of this group of stimulants; thus, those antiseizure drugs with the greatest effect on cocaine, afforded no protection against methamphetamine-induced clonus. These very distinct profiles of response further support the likelihood that cocaine and methamphetamine initiate seizures by unique mechanisms. To examine this possibility further, surface EEG patterns where evaluated in rats that received a seizure-promoting dose of these two stimulants. For these studies, the dose–response of methamphetamine and cocaine was determined in rats by administering drugs i.p. and identifying the presence or absence of clonic seizures. From these data, the CD_{84} was calculated by probit analysis. Stimulant-induced lethality precluded employing higher doses. As shown in Fig. 4, the seizure patterns induced by cocaine and methamphetamine treatments were very different. Methamphetamine produced a higher frequency firing than cocaine. As would be expected from the mouse experiments shown in Fig. 2, phenytoin pretreatment abolished the bursting activity caused by cocaine, but had no significant effect on the electrographic seizures occurring after high-dose methamphetamine. The finding that phenytoin alone did not markedly affect the baseline EEG suggests that its ability to prevent both the behavioral and electrographic seizure is the result of its pharmacodynamic properties rather than a general CNS depression.

In summary, these findings reveal distinct characteristics of four stimulants of abuse which relate to their ability to initiate clonic seizures. Considering the features of the seizure behavior and the protective action of common antiseizure medication, the amphetamine analogs are the most similar, although some significant differences also exist even among these structurally related drugs. This study demonstrates that cocaine and methamphetamine, the two drugs most frequently abused and most likely responsible for stimulant-related seizures seen clinically, display disparate seizure patterns and are differentially influenced by therapeutic anticonvulsant drugs.

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