Amphetamines: Aggressive and Social Behavior

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INTRODUCTION

The potential of sudden, intense acts of violence is one of the most attention-getting facets of amphetamine action. Hippies of the 1960s warned: "Speed kills." At that time, reports from law enforcement personnel, psychiatrists, and drug abusers themselves could be viewed to indicate that "amphetamines, more than any other group of drugs, may be related specifically to aggressive behavior" (Ellinwood 1972). Neurotoxic effects of amphetamines and, more recently, their designer derivatives on neurons containing dopamine and serotonin--two neurotmnsmitters of paramount significance in neurobiological mechanisms of aggressive, defensive, social, and sexual behavior--have added a new dimension to the current wave of stimulant abuse (Seiden and Vosmer 1984; Ricaurte et al. 1985).

In fact, amphetamines may be associated with extreme changes in aggressive and social interactions: intense and sudden acts of aggression as well as total withdrawal from any social intercourse. These striking, seemingly opposite shifts in social and aggressive behavior under the influence of amphetamines and related substances are the product of numerous pharmacological, behavioral, and environmental, as well as genetic determinants. Another paradox about amphetamines and related psychomotor stimulants is their calming effect on excessively aggressive children and adolescents diagnosed with attention deficit disorder. The neurobiological mechanisms for the multiple effects of amphetamines on aggressive behavior have been most often related to those relevant to the motor-activating and motor-arousing effects of these drugs. Yet, mechanisms of amphetamine action specific to their effects on aggressive and social behavior have eluded a satisfactory delineation.

AMPHETAMINES AND HUMAN AGGRESSIVE AND SOCIAL BEHAVIOR

Case Reports and Surveys

Case reports and survey data provide a complex account of the link between amphetamines and aggressive behavior, leading to sharply differing

opinions on the severity and nature of the problem. As recently reviewed (Miczek 1987), a series of clinical observations and surveys of institutionalized drug abusers and delinquents point to greatly varying representation of amphetamines in these individuals during the commission of violent and criminal behavior. For example, several descriptions of murders and other intense violent behavior attribute these seemingly unpredictable and drastic changes in behavior to amphetamine abuse (Ellinwood 1971; Siomopoulos 1981). Frequently, clinical analyses suggest that chronic amphetamine intoxication, particularly by the intravenous route, produces a psychotic paranoid state, including frightening delusions that may result in aggressive acts (Kramer 1969; Angrist and Gershon 1969; Ellinwood 1971; Siomopoulos 1981).

Some surveys found sizable proportions of prison populations and juvenile delinquents to have committed their crimes of violence while intoxicated by amphetamines (Hemmi 1969; Simonds and Kashani 1979); conversely, others reported rare cases and very small percentages of juvenile delinquents and excessively hostile individuals as having abused amphetamine (Tinklenberg and Woodrow 1974; Tinklenberg et al. 1977; Gossop and Roy 1976). The reliability of several of these surveys is compromised by the lack of adequately matched samples in highly selected populations of institutionalized individuals. Reliability is also compromised by reliance on notoriously variable verbal reports for the details of the dose and frequency of amphetamine intake, as well as on the exact nature of the drug. It may very well be that the unusual and intense violent acts are more prominent among chronic high-dose abusers than they are among occasional amphetamine abusers. This possible distinction needs to be investigated systematically. So far, no reports have been published showing that substituted amphetamines are linked to a high incidence of excessively violent behavior or other offensive social behavior.

Attention Deficit Disorders

Reductions in aggressive behavior after treatment with amphetamine and other psychomotor stimulants are seen in children and adolescents who have been diagnosed with hyperkinesis or attention deficit disorder. There is considerable disagreement about these diagnostic categories and about whether the violent outbursts and uncontrolled episodes of aggressive behavior are limited to the early developmental period or continue into adulthood (Mendelson et al. 1971; Minde et al. 1972).

The early report by Bradley (1937) on beneficial treatment effects with amphetamine in aggressive, destructive, irritable, and hyperactive boys was repeatedly confirmed by double-blind, placebo-controlled studies, Significant reductions in aggressive behavior and improvements in social interactions were found after treatment with 10 to 40 mg/day of *d*- or *l*-amphetamine for boys and girls, 5 to 14 years of age, who had been diagnosed as

hyperkinetic, autistic, explosive, unsocialized, or emotionally disturbed (Conners 1969; Conners 1972; Winsberg et al. 1972; Winsberg et al. 1974; Arnold et al. 1973; Maletzky 1974).

Experimental Studies on Human Aggression

Earlier experimental studies on amphetamine and human behavior focused on performance measures as well as on eating and sleep disorders. None of these studies identified an increase in aggressive behavior as a problematic side effect (Leventhal and Brodie 1981; Laties and Weiss 1981). As a matter of fact, controlled studies on amphetamine and human social behavior, acute doses of *d*-amphetamine (5 to 30 mg) were found to increase socializing and speaking with no indications of aggressive acts (Griffiths et al. 1977). However, antifatigue and endurance-enhancing effects of amphetamines may contribute to the effects of these substances on aggressive behavior.

In an experiment that exposes a human subject to a competitive task leading to prize money, acute amphetamine doses (5 and 10 mg) increased aggressive responses such as delivering blasts of noise or subtracting money from the presumed competitor (Cherek et al. 1986). At the higher dose (20 mg), the rate of aggressive behavior declined, but the rate of money-winning responses increased, further indicating a dissociation between amphetamine effects on aggressive and nonaggressive responses. In contrast to amphetamine, acute administrations of caffeine only decreased aggressive responses, regardless of whether the subject was strongly or moderately provoked by loss of prize money (Cherek et al. 1983). This experimental approach to the study of human aggressive behavior under controlled laboratory conditions fulfills the demands for accurate, objective, and reliable behavioral measures. It is unclear, however, whether or not this experimental preparation is a valid model of clinically significant problem behavior. Future studies with hyperaggressive individuals or those prone to stimulant-induced aggressive behavior will be needed to validate the laboratory situation.

AMPHETAMINES AND AGGRESSION IN NONHUMAN SUBJECTS

Amphetamine Aggressiveness

More than four decades ago, Chance (1946a; Chance 1946b) observed episodes of rapid running, audible vocalizations, upright postures, biting, and, eventually, increased lethality after administration of near-toxic doses of amphetamine (greater than 10 mg/kg) to mice that were housed in groups. This so-called "amphetamine aggressiveness or rage," most often studied in laboratory rats and mice, but also in chicks, consists of fragmented agonistic acts and postures embedded in stereotyped motor routines (Randrup and Munkvad 1969; Hasselager et al. 1972). The phenomenon of amphetamine aggressiveness in otherwise placid laboratory rats or mice has limited

behavioral validity and appears to be primarily of pharmacological or toxicological interest; like motor stereotypies, the so-called amphetamine aggressiveness is reduced by experimental compromises of the nigrostriatal dopamine system such as synthesis inhibitors, receptor antagonists, and neurotoxic or electrolytic lesions in this region.

Traditional Research Methodologies

Amphetamine, cocaine, and other psychomotor stimulants have been examined with traditional research methodologies involving isolation-induced aggression in mice; pain-induced aggression in mice, rats, or squirrel monkeys; brain stimulation-induced aggression in cats; or mouse killing by rats. The results show an inconsistent mixture of increases, decreases, or no effects. Among the most important determinants of amphetamine effects on aggressive and defensive responses are the stimulus situation, species, prior experience with these types of behaviors (table 1) and, most critically, dosage and chronicity of drug exposure.

TABLE 1. *Doses of amphetamines for modulating behavior*

Aggression		Nonaggressive	
Increases	Decreases	Motor Activity	References
Isolation-Induced Aggression in Mice			
None	10.0 IP	10.0 IP	Melander 1960
None	ED_{50} > 3 IP	ED_{50} 3 IP	DaVanzo et al. 1966
None	5.0 IP	N/S	Valzelli 1967
2.0 IP	> 2.0 IP	> 2.0 IP	Charpentier 1969
None	4.0 IP	4.0 IP	Le Douarec and Broussy 1969
2.0 IP	6.0 IP	N/S	Welch and Welch 1969
None	10.0 IP	N/S	Scott et al. 1971
4.0 IP	8.0 IP	4.0, 8.0 IP	Hodge and Butcher 1975
None	8.0 IP	8.0 IP	Miczek and O'Donnell 1978
None	0.25-1 PO	> 1.0 PO	Krsiak 1979
None	5 IP	N/S	Essman and Valzelli 1984

TABLE 1. (Continued)

Aggression Increases	Aggression Decreases	Nonaggressive Motor Activity	References
Pain-Induced Aggression in Mice			
8.4 PO	None	9.3 PO	Stille et al. 1963
0.1 IP	None	N/S	Kostowski 1966
0.5 PO	None	> 0.5 PO	Hoffmeister and Wuttke 1969
None	5.0 PO	2.5 PO	Tedeschi et al. 1969
Pain-Induced Aggression in Rats			
None	3.0 IP	N/S	Lal et al. 1968
0.25-1 IP	4.0 IP	N/S	Crowley 1972
1.0 IP	3.0 IP	N/S	Powell et al. 1973
3.48 IP	N/S	N/S	Mukherjee and Pradhan 1976
None	> 2.5 IP	N/S	Sheard 1979
Pain-Induced Aggression in Squirrel Monkeys			
None	0.3, 1 IM	0.03-1 IM	DeWeese 1977
0.125-1 SC	2.0 SC	> 2 SC	Hutchinson et al. 1977
0.125-1 SC	2.0 SC	> 2 SC	Emley and Hutchinson 1972; Emley and Hutchinson 1983
Extinction-Induced Aggression in Rats			
0.1 IM	0.5, 1.0 IM	0.1-1.0 IM	Miczek 1974
Brain Stimulation-Induced Aggression in Rats			
None	2.0 IP	2.0 IP	Panksepp 1971
Brain Stimulation-Induced Aggression in Cats			
5-7.5/cat IP	10/cat IP	N/S	Sheard 1967
None	>4 IP	N/S	Baxter 1968
None	0.3, 0.8 IP	N/S	MacDonnell and Fessock 1972
0.125-0.5 IP	1-1.5 IP	N/S	Marini et al. 1979
0.5-3 IP	N/S	N/S	Maeda et al. 1985

TABLE 1. (Continued)

Aggression Increases	Aggression Decreases	Nonaggressive Motor Activity	References
Drug-Induced Aggression in Mice			
l-dopa			
2.0 IP	N/S	N/S	Lal et al. 1970
Drug-Induced Aggression in Rats (Withdrawal from Opiates)			
2.0 IP	N/S	N/S	Florea and Thor 1968
ca. 3-11/day PO	N/S	N/S	Thor 1971
1-4 IP	N/S	N/S	Lal et al. 1971
2.0 IP	N/S	N/S	Carlini and Gonzalez 1972
2.0 IP	N/S	N/S	Puri and Lal 1973
2.0 IP	N/S	N/S	Gianutsos et al. 1975
Mouse Killing in Rats			
None	2-15 IP	4-5 IP	KarLi 1958
None	ED_{50} 1.5 IP	ED_{50} 6.6 IP	Horovitz et al. 1965; Horovitz et al. 1966
None	0.5-2 IP	> 2 IP	Kulkarni 1968
None	ED_{50} 0.8 IP	ED_{50} 4.2 IP	Sofia 1969
None	ED_{50} 1.8 IP	1-3 IP	Salama and Goldberg 1970; Salama and Goldberg 1973
None	5.0 IP	N/S	Valzelli and Bemasconi 1971
None	2, 4 IP	1, 1.5 IP	Vergnes and Chaurand 1972
None	ED_{50} 0.18 IP	> 0.18 IP	Malick 1975
None	1.5 IP	N/S	Gay et al. 1975
None	ED_{50} 0.6 IP	N/S	Malick 1976
None	0.75-3 IP	N/S	Gay and Cole 1976
None	2.0 SC	N/S	Posner et al. 1976
None	2 IP	N/S	Barr et al. 1976
None	ED_{50} 1.15 IP	N/S	Barr et al. 1977
None	0.5-2 IP	N/S	Barr et al. 1979
None	1-3 IP	2-3 IP	Russell et al. 1983

NOTE: All doses are expressed in mg/kg; N/S=Data not specified, PO=oral injection.

SOURCE: Miczek 1987.

Low acute amphetamine doses enhance pain-induced aggressive/defensive reactions in mice, rats, and squirrel monkeys (Kostowski 1966; Hoffmeister and Wuttke 1969; Crowley 1972; Powell et al. 1973; Emley and Hutchinson 1972; Emley and Hutchinson 1983). For example, squirrel monkeys subjected to electric shocks to their tails, bite a rubber hose more frequently after being administered amphetamine (0.06 to 1.0 mg/kg, SC) (Emley and Hutchinson 1972; Emley and Hutchinson 1983; Hutchinson et al. 1977). In rats, these pain-induced aggressive/defensive responses increase with doses of 0.1 to 1.0 mg/kg (Crowley 1972).

Intermediate to higher amphetamine doses routinely decreased or disrupted isolation- and extinction-induced aggressive behavior and pain-induced aggressive/defensive reactions in mice, rats, and squirrel monkeys while increasing nonaggressive motor activity (Melander 1960, DaVanzo et al. 1966, Miczek 1974; Hodge and Butcher 1975; Krsiak 1979). It may also be mentioned that amphetamines, as well as other psychomotor stimulants, reliably block mouse-killing behavior in selected laboratory rats (Horovitz et al. 1965; Kulkami 1968; Malick 1976; Russell et al. 1983). In this screening test for antidepressant drugs, the antimuricidal effect of amphetamines may be considered a false positive (Howard and Pollard 1983).

This complicated pattern of amphetamine effects in the traditional models of aggression, each relying usually on a single index, may be conveniently interpreted to reflect how amphetamine's effects on aggression depend on the particular measurement technique. Yet, such conclusions are not heuristic. More recently, an ethological approach to the study of drug action on aggression has focused on biologically valid test situations and detailed behavioral measurements, in an effort to gain insight into causative and functional determinants of aggressive, defensive, submissive, and flight behaviors (Miczek et al. 1984). In the following, an examination of the most important pharmacological and behavioral determinants of amphetamine effects on aggressive and defensive behavior in several animal species will emphasize the lawful, systematic nature of these drug behavior interactions and, at the same time, highlight their social and environmental constraints.

BEHAVIORAL DETERMINANTS OF AMPHETAMINE EFFECTS ON AGGRESSION

Differentiation Between Attack, Defense, Submission, and Flight

In animal species commonly used in laboratory research, social aggregation and dispersion are achieved by agonistic behavior patterns with various acts, postures, movements, and signals. Confrontations between a territorial resident and an intruder, between a dominant and lower-ranking group member, between rival males or females, between a lactating female and a

potential threat to her offspring can be reproduced and studied under controlled laboratory conditions. Amphetamine differentially alters attack and threat behaviors vs. defensive and flight reactions.

In situations of social conflict, amphetamine increases the frequency of escape and defensive responses to threats and attacks by a stimulus animal in mice, rats, cats, rhesus monkeys, and squirrel monkeys in a dosc-dependent manner (Hoffmeister and Wuttke 1969; Crowley et al. 1974; Miczek and O'Donnell 1978; Miczek 1979; Schlemmer and Davis 1981; Haber et al. 1981). Even in the absence of a distinctive behavioral stimulus from an opponent, amphetamine induces escape and defensive responses in mice. Krsiak considered these unprovoked defensive and escape responses as signs of "timidity" (Krsiak 1975; Krsiak 1979; Poschlova et al. 1977).

Amphetamines decrease attack and threat behavior by dominant animals toward lower-ranking group members, by territorial residents toward an intruder, by lactating females defending their litter, and play fighting by juveniles, mainly due to distortions in the perception of socially significant signals and the disruption of integrated sequences of threat and attack behavior (Miczek and Gold 1983; Miczek et al. 1989). Large and intense increments in aggressive behavior after amphetamine administration may occur suddenly in mice, rats, cats, and several primate species, under limited conditions. Several determinants for these infrequent but important amphetamine effects have begun to be identified, such as the base rate of aggressive behavior before any amphetamine administration, previous experiences with aggressive and defensive behavior, and the level of habituation to an aggression-provoking situation.

Baseline

Studies of amphetamine effects on behavior, mainly shaped and controlled by schedules of reinforcement, have led to the general principle of rate dependency; low rates of behavior tend to be increased by amphetamine-like drugs, intermediate rates are less altered, and high rates are decreased (Dews and Wenger 1977). This principle applies only rarely to the effects of amphetamines on aggressive behavior (Miczek and Krsiak 1979). In isolated mice, amphetamine increased the incidence of aggressive behavior only in those subjects that were selected for their near-zero levels during vehicle control tests. Amphetamine decreased aggressive behavior in animals with high rates during vehicle control tests (Krsiak 1975; Krsiak 1979). These results lend themselves to a rate-dependency interpretation. Comparisons between separate groups of subjects, one displaying a low rate of aggressive behavior, the other a high rate, however, are less persuasive evidence for rate dependency of amphetamine effects than is the demonstration of differential drug effects on low and high rates of behavior within the same subject.

A minute-by-minute analysis of rates of attack behavior during either a 5- or 28-minute confrontation between a resident and an intruder shows a high rate of aggression in the initial phase of the encounter and a gradual decline in the later phase (figure 1). This decrement from high to low rates

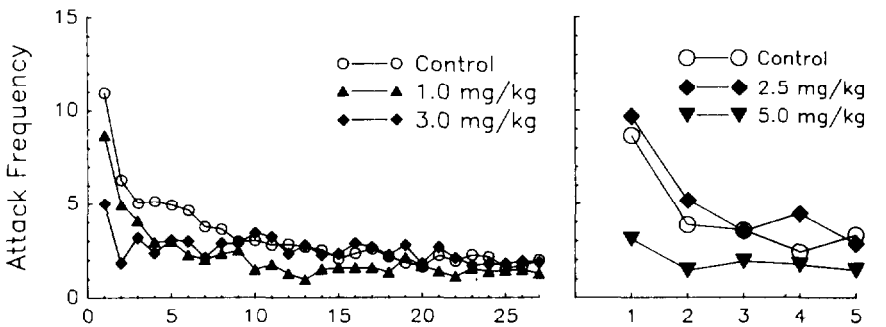

FIGURE 1. *Effect of* d*-amphetamine on the frequency of attack bites by a male resident mouse toward a male intruder during 28-minutes (left) or 5-minutes (right) confrontations*

NOTE: The resident mouse was adminstered an acute dose of amphetamine 30 minutes before confrontation. Frequency of attacks is minute-by-minute average.

of aggression could be due to fatigue, habituation, or changes in the stimulus qualities of the intruder animal. Contrary to the effects of drugs such as alcohol, there was no evidence that amphetamine increased either the high attack rates in the early phase of the encounter or the lower rates

of attack in the later phase (Miczek, unpublished observations). Also, higher amphetamine doses that decreased attack behavior at the start of an encounter did not lead to any rebound in the later phases, even during 28-minute encounters. Apparently, once an aggressive interaction has been initiated, and the opponent reacts with defensive and flight responses, amphetamine does not increase further the rate of aggressive behavior within the same encounter.

Habituation

A substantial increase in aggressive behavior is seen when amphetamine is administered to animals that are repeatedly confronting an intruder (Winslow and Miczek 1983). Specifically, during 2-hour sessions, resident male mice pursued, threatened, and attacked intruders 10 times, each 5-minute encounter being separated from the next by 5 minutes. 'The threat and attack behavior exponentially declined over the course of the 10 consecutive encounters; half of all aggressive behavior was displayed during the first 3 encounters, and the remaining 7 encounters were characterized by very low levels of aggressive behavior (Winslow and Miczek 1984). It is in this later phase of the habituation process that amphetamine more than doubled the rate of attack behavior (figure 2). These amphetamine effects on attack and threat behavior were dissociated from those on elements of motor activity such as walking, rearing, or grooming, in terms of timecourse and dose-effect curve. This pattern of effects suggests a direct action of amphetamine on the habituation process, an elementary form of learning, in addition to the well-known antifatigue effects of amphetamine.

Burst-Like Pattern of Aggressive Behavior

Amphetamine substantially alters the characteristic temporal pattern of agonistic behavior (Miczek 1983; Miczek et al. 1989). Normally, epochs or bursts of intense and frequent threat and attack behavior alternate with periods of relative behavioral quiescence, as, for example, in confrontations between a resident mouse and an intruder. The intervals that separate consecutive attacks are exponentially distributed, with 70 to 80 percent of all intervals being very short and constituting the steep portion of this distribution; the remaining long intervals represent the gaps that separate bursts of attacks. Amphetamine, at doses that did not alter the frequency or duration measures of aggressive behavior, increased the size of the aggressive bursts, and at higher doses abolished the characteristic burst pattern (figure 3).

Sequences of aggressive behavior that are composed of characteristic acts and postures following each other rapidly are disrupted. These disorganizing effects parallel the analysis of amphetamine effects on other intricately patterned behaviors such as feeding, maternal care, play behavior, or reproductive interactions. For example, amphetamine suppresses play

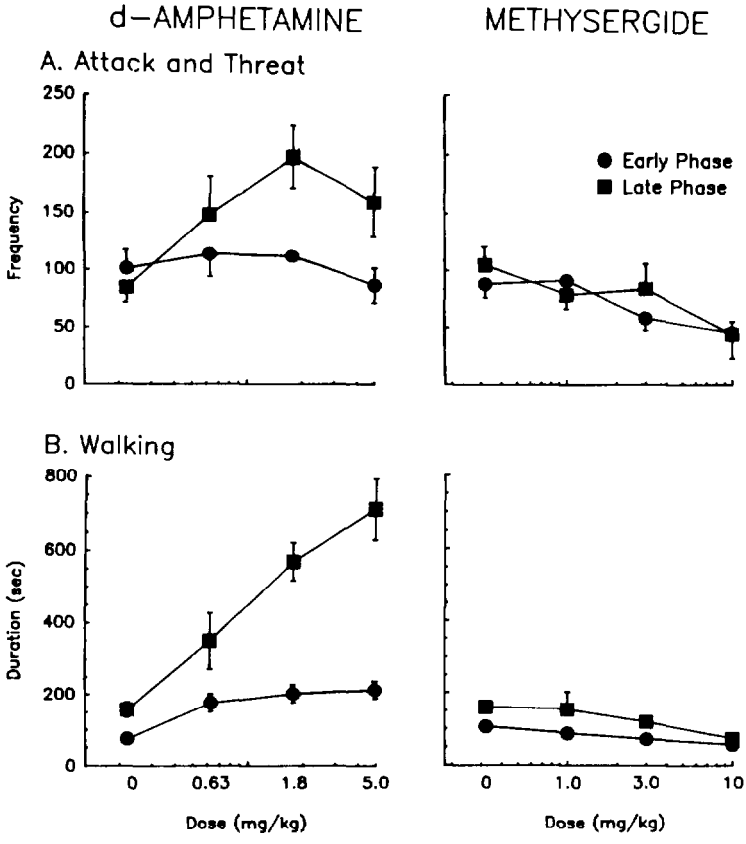

FIGURE 2. *Effects of* d*-amphetamine and methysergide on the cumulative frequency of attack bites and sideways threats (top) and walking duration (bottom) during the initial and later resident-intruder confrontations*

NOTE: Confrontations were in a sequence of 10 consecutive 5-minute trials. each trial seperated from the next by a 5-minute interval.

SOURCE: Winslow and Miczek 1983.

behavior in juvenile rats, an effect that is not antagonized by dopamine or norepinephrine receptor antagonists (Beatty et al. 1984). Similarly, maternal care is severely disturbed in female vervet monkeys under the influence of amphetamine (Schirring and Hecht 1979). These findings and those of others emphasize the disintegrative effects of amphetamine on patterns of

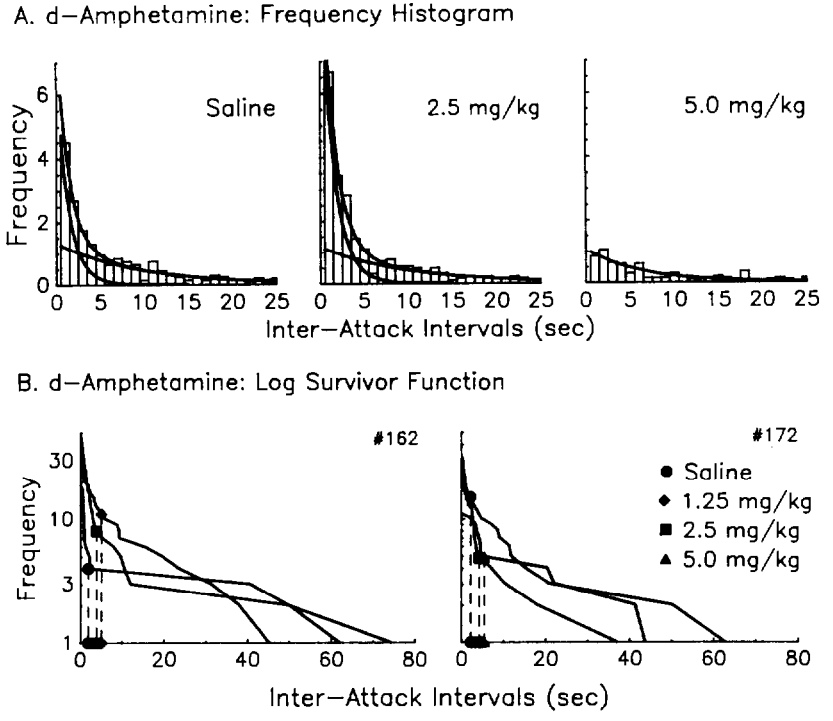

FIGURE 3. *Frequency historgrms of interval length between consecutive attack bites by a resident mouse toward an intruder after saline control, 2.5, or 5.0 mg/kg* d-*amphetamine (n=20). B. Number of interattack intervals surviving to increasing durations from single encounters under saline control conditions, 1.25, 2.5, and 5.0 mg/kg* d-*amphetamine.*

NOTE: Superimposed on the histograms are curves of a mixed exponential distribution and the component distributions. The length of attack bouts is estimated from the intersection of the component distributions. The intervals between attacks that represent the gaps between bouts are shaded.

SOURCE: Miczek et al. 1989.

social interaction (Kjellberg and Randrup 1971; Kjellberg and Randrup 1973; Garver et al. 1975; Miczek 1981b).

PHARMACOLOGICAL DETERMINANTS

Dose

Dose-dependent biphasic effects on aggressive behavior may be seen in several, but not all animal species and situations (Miczek and Krsiak 1979;

Miczek 1987). The paramount importance of dosage for amphetamine effects on aggressive and social behavior is illustrated by experiments in male rats confronting an opponent, either in a competitive situation or as an intruder into their homecage, showing aggression-enhancing effects at low acute doses (Miczek 1974; Miczek 1979). On occasion, increases in aggressive behavior after administration of low acute amphetamine doses have also been seen in fish, mice, and selected rhesus and stumptail macaque monkeys (Weischer 1966; Haber et al. 1981; Winslow and Miczek 1983; Smith and Byrd 1984; Kantak and Miczek 1988). A much more consistent observation, however, is the amphetamine-related increase in defensive, submissive, and flight reactions, which systematically increase with dose, up to a level at which motor stereotypies begin to interfere with the display of these behaviors (Hoffmeister and Wuttke 1969; Miczek 1974; Miczek and O'Donnell 1978).

Ongoing experiments with methylenedioxymethamphetamine (MDMA) show a systematic dose-dependent decrease in attack and threat behavior in mice confronting an intruder into their homecage (Miczek et al., unpublished observations). The decrement in aggressive behavior appears to be behaviorally specific; it is obtained at MDMA doses (0.3, 1, 3 mg/kg) that are lower than those necessary to decrease measures of conditioned performance under the control of schedules of positive reinforcement. Because of species-dependent neurotoxicity, MDMA's effects on aggressive behavior need to be explored in other species, including primates.

Chronicity

Tolerance or sensitization may result from repeated exposure to amphetamines, depending on the interval between consecutive amphetamine administrations (Segal et al. 1980; Robinson and Becker 1986). with continuous drug exposure resulting most often in tolerance, and intermittent administration in behavioral sensitization. Most of the evidence on the determinants of tolerance and sensitization to amphetamine derives from studies on the motor-activating effects of these drugs as measured in situations promoting locomotion, circling, or stereotyped movements.

Unfortunately, only a few experimental studies have focused on the effects of repeated amphetamine administration on aggressive and social behavior, although it is precisely this condition that is associated with the most troubling clinical experiences. Methamphetamine, given in daily increasing doses. decreased aggressive behavior in seven different mouse strains and genera, except for grasshopper mice (Richardson et al. 1972). Daily administration of *d*-amphetamine or cocaine for 2 to 4 weeks to resident mice confronting an intruder failed to shift the dose-effect function for these drugs' effects on any element of threat and attack behavior, while augmenting the stereotypy-inducing effects (O'Donnell and Miczek 1980). Slow-release amphetamine capsules, implanted subcutaneously in rats that

lived in large all-male colonies, produced hyperactivity and social withdrawal in the initial phase of drug exposure; after about a week a high incidence of startle, threat, and defensive responses was seen (Ellison 1978; Eison et al. 1978). Similar, chronically implanted amphetamine capsules in vervet monkeys again resulted in hallucinatory-like grooming, grasping, and head movements, and disrupted social interactions without evidence for tolerance development (Nielsen and Lyon 1982). These progressively more pronounced social withdrawal and motor stereotypies are also seen in groups of macaques or marmosets that are administered amphetamine daily (Garver et al. 1975; Ridley et al. 1979). So far, neither tolerance nor sensitization to amphetamine's effects on withdrawal from all social and aggressive interactions has been seen in the very few studies that either examined changes in the ongoing rate of these behaviors during the course of repeated amphetamine administration or that tested for shifts in dose-effect functions before, during, and after chronic amphetamine exposure.

The only evidence on chronic amphetamine administration and heightened aggressiveness derives from the studies, discussed earlier, on group-housed placid laboratory rats or mice. The behavioral validity of these phenomena under near-toxic dosage conditions, however, needs to be resolved.

Opiate Withdrawal

Amphetamine effects on aggression are markedly modulated by opiates and opioid peptides. Withdrawal from prolonged exposure to opiates may lead to increased defensive and aggressive responses in mice and rats and increased hostility in humans (Lal et al. 1971; Gossop and Roy 1976; Kantak and Miczek 1986). Amphetamine and cocaine, as well as dopaminergic agonists, increase further the already high levels of defensive responses in aggregated rats undergoing withdrawal from opiates, leading in extreme cases to the death of the subjects (Lal et al. 1971; Puri and Lal 1973).

Locomotor-activating effects of amphetamine have previously been linked to dopamine release (Iversen 1977), and it has been suggested that the aggression-enhancing effects may be mediated by a similar mechanism (Gianutsos and Lal 1976). Enhancement of aggression by treatment with a combination of *l*-dopa and *d*-amphetamine can be blocked with the dopamine receptor antagonist haloperidol (Lal et al. 1975); aggression induced by challenge with amphetamine during morphine withdrawal is blocked by either haloperidol or alpha-methyl-para-tyrosine (Lal 1975; Puri and Lal 1973).

The dramatic heightening of aggressive behavior in morphine-withdrawn animals may be due to dopamine receptor upregulation (Gianutsos et al. 1975; Lal et al. 1975). Morphine and methadone inhibit dopamine receptors in the central nervous system (CNS) suggesting possible disuse

supersensitivity and hyperactivity of the receptor during withdrawal (Puri and Lal 1973; Martin and Takemori 1986). Further enhancement of morphine-withdrawal aggression by amphetamine has been interpreted to reflect stimulation of supersensitive dopamine receptors (Puri and Lal 1973; Kantak and Miczek 1988).

Recently, it was found that single-housed mice that had been undergoing withdrawal for 48 hours (after removal of a subcutaneously implanted 75-mg morphine pellet) showed an elevation of attack and threat behavior that was doubled when these mice were challenged with amphetamine, cocaine, *l*-dopa, or apomorphine (figure 4) (Kantak and Miczek 1986;

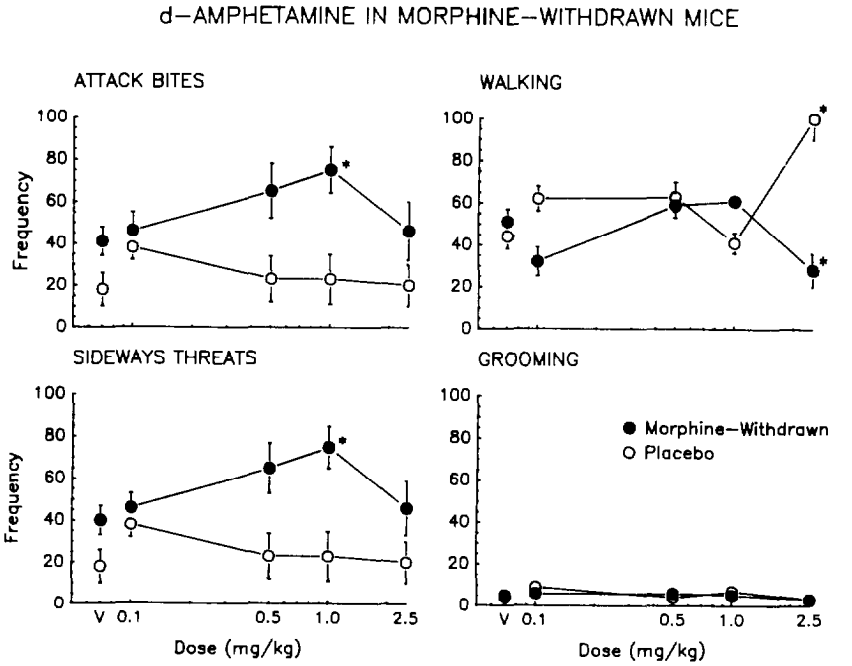

FIGURE 4. *The frequency of attack, threat, walking, and grooming (mean ±SEM per 5 minutes) following saline or 0.1, 0.5, 1.0, or 25 mg/kg* d-*amphetamine*

$p<0.05$ compared to vehicle control.

NOTE: These doses were administered to male resident mice implanted with either placebo pellets (open circles) or morphine pellets (solid circles) subsequently withdrawn 48 hours prior to testing.

SOURCE: Kantak and Miczek 1988.

Kantak and Miczek 1988). Similarly, Lal et al. (1971) and Thor et al. (1970) found that in aggregated rats, amphetamine enhances defensive

upright postures and audible squeals most strongly about 72 hours after termination of a chronic morphine injection schedule. Mice that have been in withdrawal for 5 hours, however, do not show this enhancement when challenged with amphetamine (Miczek and Tidey, unpublished observations). This difference in the reaction to amphetamine may reflect changes in sensitivity of dopamine receptors over time: shortly after withdrawal from opiates, a lessened sensitivity to amphetamine's heightening effects on aggression is seen; later a supersensitivity emerges.

To assess this possibility, selective dopamine receptor agonists were administered to mice 5 hours after subcutaneous morphine pellet removal (Miczek and Mohazab 1987). Challenge with either quinpirole, a selective D2 agonist, or SKF 38393, a selective D1 agonist, or a combination of both did not result in heightened aggression. In fact, the studies with combined administration of D1 and D2 agonists indicate that, in the presence of D1 receptor activation by a small dose of SKF 38393 (3.0 mg/kg), very large doses of D2 receptor agonists are necessary to modify aggressive behavior in these mice, suggesting a subsensitivity of D2 receptors. This particular timecourse relates solely to the aggression-enhancing effects; the authors and others (Bläsig et al. 1973; Lal 1975; Kantak and Miczek 1988) have noted that different autonomic and somatic opiate withdrawal signs emerge at earlier times after morphine pellet removal or termination of a chronic injection schedule.

The sub- and supersensitivity to amphetamine's aggression-modulating effects during withdrawal from morphine depend on the time since the last exposure to opiates; it will be intriguing to determine how the relevant opioid and dopamine receptor populations are altered at these behaviorally critical phases of opiate withdrawal. The display of aggressive, defensive, and submissive behavior is accompanied by marked changes in the functioning of brain opioid peptides in the absence of any drug exposure (Miczek et al. 1986); it will also be interesting to determine how amphetamine's effects in individuals with differential experiences with aggressive or submissive behavior may involve alterations in brain opioid peptides and their receptors.

ANTAGONISM OF AMPHETAMINE EFFECTS ON SOCIAL AND AGGRESSIVE BEHAVIOR

The most consistent and potent antagonism of amphetamine effects on increased motor activity and stereotyped movements is obtained with antagonists at dopamine receptors of the D2 subtype (Creese et al. 1982). This is not the case with amphetamine's disruptive effects on social and aggressive behavior, So far, no antagonists have been identified that reverse amphetamine's disruption of sexual, play, maternal, or aggressive behavior. In many ways, this situation parallels the clinical experiences, in being

unable to reverse the negative symptoms of both amphetamine-induced and endogenous psychoses with classic neuroleptics (Crow 1985).

Dopamine Receptor Antagonists

Haloperidol and chlorpromazine potently decrease aggressive and social behavior as well as many other behavioral functions in various animal species and humans. The marked potency and long-lasting nature of the antiaggressive effects of the neuroleptics with dopaminergic receptor-blocking properties may be the reason why these types of drugs are most frequently used in treating pathologically violent individuals (Itil 1981; Leventhal and Brodie 1981; Sheard 1984; Tupin 1985). The poor behavioral specificity of their antiaggressive effects, however, renders the phenothiazines, butyrophenones, or thioxanthines as less than ideal choices; this pattern of effects is already apparent in preclinical studies (Malick 1979; Miczek and Winslow 1987).

Recently, the effects of more selective dopamine receptor antagonists on aggressive behavior were explored. In resident mice confronting an intruder into their homecage; quinpirole (0.1 to 1.0 mg/kg) potently reduced pursuit, threat, and attack behavior; however, it also reduced concurrent motor activity. This pattern of effects paralleled haloperidol effects in the same species and situation. However, the D1 receptor agonist SKF 38393 more selectively, although less potently, decreased aggressive behavior by resident mice, in the absence of concurrent changes in motor functions. These studies highlight the problem of identifying a dopamine antagonist that could be useful in the blockade of amphetamine effects, but would not suppress behavior on its own.

Dopaminergic receptor antagonists do not antagonize the disruptive effects of amphetamine on aggression. In squirrel monkeys, *d*-amphetamine (1.0 mg/kg) disrupted agonistic and social behavior; haloperidol pretreatment did not prevent this disruption (figure 5, right) (Miczek and Yoshimura 1982). Similarly, *d*-amphetamine decreased attack and threat behavior in resident mice confronting an intruder haloperidol pretreatment failed to reverse this disruption, but further decreased aggressive behavior in amphetamine-treated mice (figure 5, left) (Miczek 1981a). By contrast, the large activation of motor activity, as evidenced by increased time spent in locomotion, was effectively antagonized by haloperidol in mice as well as in squirrel monkeys (figures 5). Similarly, play fighting in juvenile rats is profoundly disrupted by amphetamine, and this disruption is not reversed by haloperidol or chlorpromazine (Beatty et al. 1984). By contrast, in those situations where low, acute doses of amphetamine enhance aggressive behavior, dopaminergic receptor antagonists attenuate this enhancement. These observations suggest differential mechanisms for the aggression-heightening effects of amphetamine as distinct from the disruptive actions on social and aggressive behavior. The neurobiological mechanisms for

amphetamines' disruption of social and aggressive behavior remain to be elucidated.

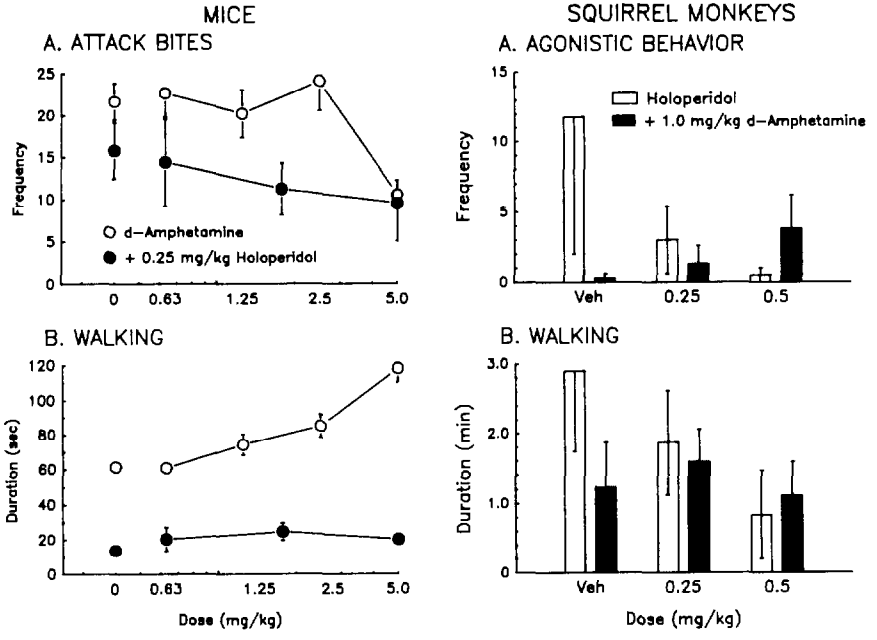

FIGURE 5. *Mice: Frequency of attack bites (A.) and the duration of walking across cage (B.) by resident male mice after administration of* d-*amphetamine alone (open circles), and after pretreatment with haloperidol (0.25 mglkg, solid circles). Squirrel monkeys: Frequency of aggressive behavior (A.) and walking (B.) by dominant squirrel monkeys in established social groups following administration of amphetamine alone (open bars), and combined with haloperidol (0.25, 0.5 mg/kg, IM, solid bars).*

KEY: Vertical lines at each data point represent ± 1 SEM

Noradrenergic Receptor Antagonists

Antagonism of several characteristic effects of amphetamine and cocaine by the alpha adrenergic receptor antagonist prazosin is a most recent example of noradrenergic mechanisms in the actions of psychomotor stimulants (Tessel and Barrett 1986). We investigated whether or not prazosin may attenuate the disruptive effects of amphetamine on social and aggressive behavior in mice and squirrel monkeys (Miczek, unpublished observations). Pretreatment with prazosin (0.4 mg/kg) attenuated the disruption of attack

bites and sideways threats in resident mice treated with higher doses of amphetamine, but no such attenuation was found of amphetamine-disrupted aggressive behavior by dominant squirrel monkeys after prazosin pretreatment (figure 6). By contrast, amphetamine's hyperactivity, measured

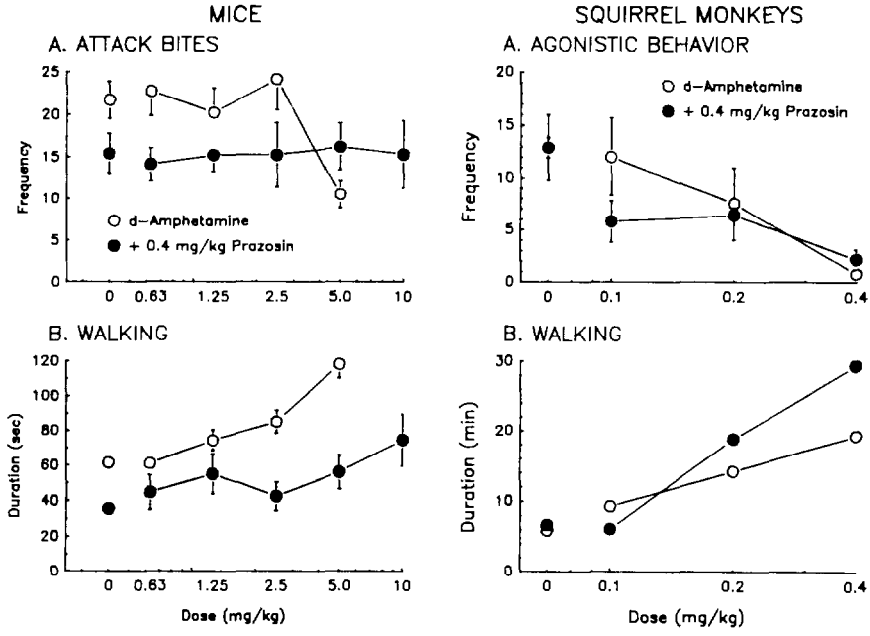

FIGURE 6. *Left: Frequency of attack bites (A.) and duration of walking across cage (B.) by resident male mice after administration of* d-*amphetamine alone (open circles), and after pretreatment with 0.4 mglkg prazosin (solid circles). Right: Frequency of aggressive behavior (A.) and walking (B.) by dominant squirrel monkeys in established social groups following administration of amphetamine alone (open circles), and after pretreatment with 0.4 mg/kg prazosin, IM (solid circles).*

KEY: Vertical lines at each data point represent ± 1 SEM.

as time spent in locomotion, was attenuated by prazosin pretreatment both in mice and squirrel monkeys. Previously, we have observed that pretreatment with phenoxybenzamine or propanolol did not attenuate the suppression of aggressive behavior in amphetamine-treated resident mice (Miczek 198la). In juvenile rats, the suppression of play fighting by amphetamine was also not reversed by phenoxybenzamine or propranolol (Beatty et al. 1984). Again, although the evidence is limited to a few

receptor antagonists and to laboratory rodents, so far there is no evidence pointing to the possible attenuation or reversal of amphetamine's disruptive effects on social and aggressive behavior by noradrenergic receptor antagonists. The negative evidence from efforts to antagonize amphetamine's effects on aggressive behavior with noradrenergic receptor antagonists suggests that these amphetamine effects do not involve noradrenergic mechanisms.

Opioid Antagonists

Opioid receptor antagonists have been found to modulate brain dopamine-mediated behavioral and cellular functions such as motor activity, drug self-administration, and brain stimulation reward (Koob and Bloom 1988).

Naloxone has been found to attenuate the increased motor activity in rats and guinea pigs after amphetamine administration (Holtzman 1974; Haber et al. 1978; Hitzemann et al. 1982; Andrews and Holtzman 1987). Similarly, opiate antagonists reduced the enhancement of rewarding electrical brain stimulation by amphetamine and cocaine (Bain and Kometsky 1987), and intracerebral injections of opiate antagonists into the nucleus accumbens selectively blocked heroin self-administration and motor activation in rats (Amalric and Koob 1984; Vaccarino et al. 1985). Although independent studies have found marked changes in social, aggressive, defensive, and submissive behavior after either opiate antagonists or psychomotor stimulants, the potential antagonism of amphetamine effects on these behaviors by opiate receptor antagonist has not been investigated until recently.

In experiments with mice and squirrel monkeys, we confirmed and extended the antagonism of amphetamine-induced motor hyperactivity by naltrexone; at the same time, however, amphetamine's disruption of aggressive and social behavior was not reversed by naltrexone (Winslow and Miczek, in press). Specifically, in mice, the resident's attack and threat behavior toward an intruder was even further reduced by amphetamine after naltrexone pretreatment (figure 7). Squirrel monkeys that are dominant within their social group exhibit significantly lower levels of aggressive display toward other group members and initiate fewer social interactions after amphetamine treatment; naltrexone did not block these effects. The interactive effects of amphetamine and naltrexone on locomotor behavior are consistent with the proposed modulation of dopamine-mediated functions by opioids; however, the interaction between amphetamine and naltrexone on social behavior appears to involve a different mechanism.

SUMMARY

Clinical case reports and survey data point to incidences of intense violence in certain individuals self-administering high doses of amphetamine via the

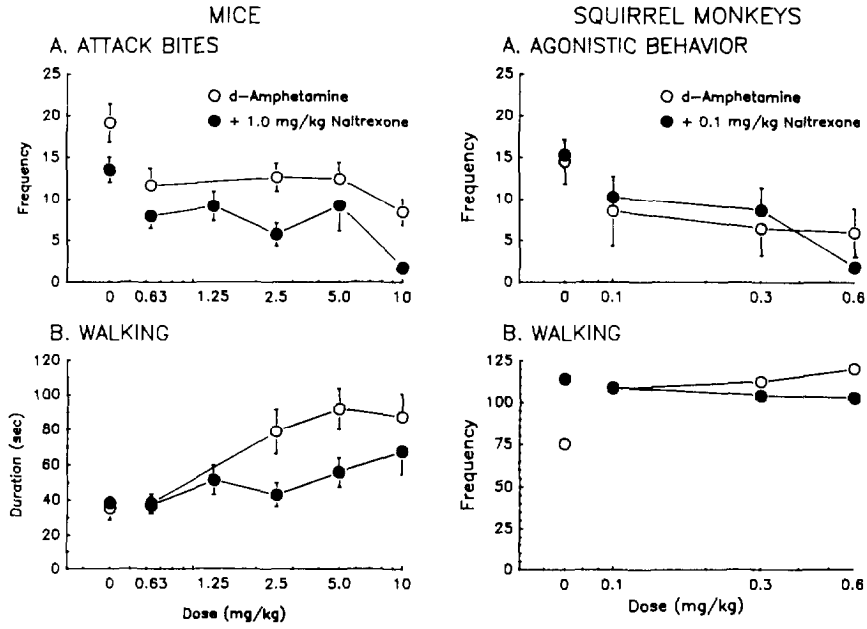

FIGURE 7. *Left: Frequency of attack bites (A.) and duration of walking across cage (B.) by resident male mice after administration of* d*-amphetamine alone (open circles), and after pretreatment with 1.0 mg/kg naltrexone (solid circles). Right: Frequency of aggressive behavior (A.) and walking (B.) by dominant squirrel monkeys in established social groups following administration of amphetamine alone (open circles), and after pretreatment with 1.0 mg/kg, IM, naltrexone (solid circles).*

KEY: Vertical lines at each data point represent ± 1 SEM.

SOURCE: Winslow and Miczek 1988.

intravenous route. It is unclear how common this amphetamine effect is, what circumstances promote its occurrence, and which characteristics predispose an individual to exhibit this effect,

Amphetamine may engender a dose-dependent biphasic effect on aggressive behavior in experimental situations, both with human and animal subjects, as, for example, in subjects that have habituated to an aggression-provoking stimulus. Most often, however, amphetamines disrupt social, sexual, matemal, and aggressive behavior patterns in a dose-dependent manner;

neither tolerance nor sensitization appears to develop to these disruptive effects.

Amphetamine consistently enhances defensive and flight reactions in various experimental situations and animal species. This effect appears to be mediated by brain dopaminergic systems. So far, no dopaminergic, noradrenergic, or opioid antagonists have been found that attenuate, reverse, or prevent the disruptive effects of amphetamines on social and aggressive behavior. The evidence from opioid-withdrawn subjects strongly suggests a profound modulatory influence by opioid peptides on the aggression-altering effects of amphetamines.

DISCUSSION

QUESTION: You know the serine compound is very potent. Have you tried lower doses on a rate-decreasing effect of the stimulant drug?

ANSWER: I tried 0.3 and 1.0. In mice, 0.3 does not have an effect in itself. In rats, 0.3 could be quite disruptive. So there is quite a bit of a species difference. The range of dose is very different in mice and rats.

QUESTION: What do you think causes the aggressive decreasing effects? Are the mice stereotyping or perseverating on some other object?

ANSWER: In the studies we did in mice, rats, and monkeys, we looked carefully at motor changes that might intrude into the behavior and prevent the animals from showing the behavior, not in this dose range. They are nonoverlapping dose ranges. You have to go to higher doses to see stereotypic and motor-activating effects.

In fact, Cherek made that point in one of the very first studies. You cannot see further increases in monetary reinforced behavior. But you see a decline in aggressive behavior. And that is true in other species and humans, too. So the most significant point is that the disruptive effects are due to the intrusion into the repertoires of other repetitive routines.

COMMENT: One of the first studies that was done with SCH compound 23390 showed that it had pronounced antiaggressive effects. This was a Canadian study of people who were in backward, isolated conditions. It had a fairly pronounced effect there.

I think one of the things that is confusing in the aggressive homicide literature is the fact that at low doses, i.e., 10, 20, 30 milligrams for a 70-kilogram person, there is a calming effect. This was one of the things that we used to see with hyperactive children. Many of those hyperactive children were indeed aggressive-hyperactive children, and the amphetamines

had a very pronounced effect on that. This probably represents a low-level activity.

In really aggressive people who have taken amphetamines a long time, you see what is called the reactive phase of aggressiveness.

Let me give you an example of this, which is particularly true in homicides. The individual is engaged in an activity and suddenly misinterprets something. He wakes up in the back of a car and smells poison gas and hits someone over the head with a pipewrench. Or he is robbing a store and someone smiles. There is a sudden impulse and he kills an individual.

If you look at the court records, you see that story repeatedly, i.e., this reactive component. And you can see the same thing in chronic animals. You do have to take them out to a 3- or 6-month period to see those effects. During long-term chronic use, the dopamine at that point is markedly depleted. We are talking about animals that have 20 or 30 percent of the original dopamine levels a month or so after they have been given the last dose of amphetamine.

So I think we are talking about two or three different phenomena, and I think it is very important that we make those distinctions.

RESPONSE: I left aside the hyperactivity issue because that is a literature study in itself. It is also limited to adolescents, children, and juveniles, although there are some reports in adults as well. But there the therapeutic range for amphetamine is 20, 30, or 40 milligrams, and for methylphenidate it is slightly higher, which is actually the preferred agent.

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ACKNOWLEDGMENTS

This review and research were supported in part by U.S. Public Health Service research grant DA 02632 and AA 05122. Mr. J.T. Sopko provided expert assistance in preparing the illustrations, the computerized bibliographic data base, as well as in conducting the experimental work.

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