Empirical Evidence of the Effects of Amphetamine on Aggression

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The effect of methamphetamine (MA) on aggressive behavior has not been studied. However, anecdotal evidence provided by numerous judicial and clinical workers suggests a high correlation between aggressive acts and the use of drugs, most prominently stimulants such as MA. The effects of the D- and L-isomers of amphetamine on aggressive behavior have been studied in rats, mice, humans, and nonhuman primates. In this chapter we assume that the effects of MA on aggressive behavior are similar to the effects of amphetamine. This is most likely, but not necessarily the case. Speculation has been made that the potential combination of the induced psychoactive effects of amphetamines can lead to dangerous and aggressive behavior (Wright and Klee, 2001). However, there is a body of research suggesting that high doses of amphetamine essentially reduce aggressive behavior (antiaggressive effects), while lower doses may potentiate aggressive responses. Rodents and primates are frequently used as analogous models for humans in experimentation because ethical considerations preclude the use of human subjects. Further, the brain structures of these animals are similar enough to those of humans to allow us to gather a great deal of insight into the human condition by understanding the effects of drugs in nonhuman animals. It has been shown that continued and consistent amphetamine use can sometimes result in paranoia and delusions, accompanied by other latent conditions such as mood swings and depression. It is the goal of this chapter, therefore, to illustrate the relationships between amphetamine use and intraspecies aggressive behavior.

Administration of Amphetamines to Rodent Subjects

As mentioned above, ethical concerns preclude the use of humans in many experimental situations; however, we can understand many features of the

human central nervous system by understanding the brains of other animals. The animal most widely used in the area of amphetamine experimentation is the rodent, which has an analogous, rather than homologous, brain structure to humans. In the following sections, we examine the modification of aggressive behavior in rodents by amphetamines. The various aspects of aggressive behavior include the tendency for provoked attack, the influence of environment on behavior, social factors, and the neurological basis of aggression.

Behavioral Observations

When using nonhuman subjects to study aggressive behavior, the typical research methodologies most usually employed by experimenters include pain-, isolation-, and brain stimulation-induced aggression. However, when making a comparison between animals of different species the outcomes of these tests yield varying and somewhat contradictory results, which in turn hampers one's ability to generalize to the human population. Additionally, it has been found that the most important aspects of amphetamine-stimulated aggressive and defensive responses vary with the nature of the species involved, the stimulus situation, prior experience with these certain behaviors, and the dosage and chronicity of drug exposure; the last is of primary concern (Miczek and Tidey, 1989).

When observing the effects of amphetamines on the aggressive responses of rodent subjects, the behavioral categories most commonly analyzed are nonsocial exploration, social exploration, immobility, threat/attack, escape/avoidance, and defensive/submissive reactions. The nonsocial exploration category includes behavioral elements such as exploring the surroundings. It has been shown in various studies that acute doses — single or intermittent doses rather than chronic daily doses — of amphetamine increase significantly the occurrence of such exploratory behavior (Moro et al., 1997).

In the mouse, social exploration involves crawling over and under other mice, grooming, sniffing, and other social interactions. Increased social activity in response to amphetamine is dose dependent. In other words, as the dose of the drug increases, the amount of behavior observed also increases. In the case of amphetamine, as the dose of the drug is increased in mice, social exploration increases as well (Moro et al., 1996); however, no noticeable effect has been observed in subjects treated intermittently — two injections a week or injections on alternating days (Moro et al., 1997). Thus, the chronicity of administration clearly has an effect on the behavioral consequence. This suggests that a single dose of amphetamine can have effects very different from chronic doses.

Squatting, crouching, and a general lack of movement comprise immobility and are typically used as an index of fear (Blanchard et al., 1969). Previous literature shows that both the frequency and the mean duration of this behavior are significantly reduced after amphetamine administration (Moro et al., 1996). This means that treated mice spend considerably less time motionless with shorter intervals between the periods of movement, which clearly indicates a direct relationship between the administration of *d*-amphetamine (dextroamphetamine) and the rate of motor activity. It also suggests that amphetamine may have the effect of reducing fear. However, the effects of amphetamine seem to be complex. Flight from a potentially dangerous conspecific can also be a sign of fear. Whereas acute and intermittent administration of amphetamine causes an increase in flight from a conspecific, chronic administration causes a reduction in flight (Moro et al., 1997).

Threat/attack behaviors consist of upright, offensive stances, lunging, attacking, and chasing. Moro et al. (1996) found that the total duration of time spent in threat postures was increased by a low acute dose of amphetamine (0.25 mg/kg); however, the total duration of attacks was reduced significantly in comparison with a saline-treated control group at intermediate (1.5 mg/kg) or high (3 mg/kg) dose ranges (Moro et al., 1996; 1997). Furthermore, intervals between the attacks were considerably shorter for amphetamine-treated animals, resulting in a higher rate of attack (Moro et al., 1996). Taken together with the biphasic effect of amphetamine on the duration of attack, this result suggests that amphetamine changes the quality of attack in a dose-dependent manner.

Dose-Dependent Effects

Acute Administration

The administration of amphetamine causes dose-dependent changes in either the type of behavior observed or the intensity of the behavior observed. As described in the previous section, higher doses of amphetamine can result in a disruption in the patterns of aggressive behavior displayed by male mice (Miczek and Tidey, 1989; Moro et al., 1996). This effect was evidenced by (1) repeated attacks separated by shorter time periods and (2) treated mice showing less sensitivity to their opponents' displays of submission, which, consequently, caused continued attack (Moro et al., 1996). Other studies have shown that distorted perceptions of social signals caused a decrease in the attack and threat behavior of dominant animals to subordinates, in territoriality toward intruders, and in lactating mothers defending their litters (Miczek and Tidey, 1989).

There is a common belief among health-care workers and workers in the criminal justice system that amphetamine has a dose-dependent effect on aggressive behavior. Research shows, however, that *d*-amphetamine has quite different effects that vary in accordance with species, dose of amphetamine, and the type of stimuli used. Miczek and Tidey (1989) suggest that pain-induced aggressive or defensive reactions in rats and mice were noticeably increased after the administration of low doses of amphetamine. However, at intermediate to high dose levels these effects were reduced or disrupted, along with a decrease in isolation- and extinction-induced aggressive behavior. Moro et al. (1996) obtained similar results in an isolation-induced aggression experiment using 52 male mice. It was found that lower doses (less than 4 mg/kg) increased the occurrence of threat and attack behaviors (especially at 0.25 mg/kg) and produced other ambiguous outcomes, whereas intermediate to high doses (above 4 mg/kg) yielded clear antiaggressive effects. These findings consequently strengthened the principle of rate dependency or dose dependency, which is the idea that varying quantities of amphetamine will have diverse effects on the treated subject, otherwise known as *biphasic* effects. It is interesting to note that the frequency of escape and defensive responses to threat during times of social conflict was increased in a dose-dependent manner in a much less ambiguous way (Miczek and Tidey, 1989). Aggressive and defensive responses are mediated by very different neurological systems. Thus, one possible explanation for the perception that amphetamine leads to aggressive behavior may be a misperception of the nature of aggressive behavior. Caseworkers may be calling "defensive" responses "aggressive" responses.

Chronic Administration

Chronic administration — repeated or regular administration over a certain time period — of a drug can have very different effects when compared with acute administration. This is because neurochemical changes occur in the brain after repeated drug administration. Thus, chronic administration of a drug can lead to behavioral changes even when the user is not actively under the influence of the drug. Acute effects of a drug that has been administered chronically (i.e., when a chronic user stops using for a period of time and then starts again) can also have effects different from acute effects of a drug that has not been administered chronically. This sequence occurs potentially because the drug can alleviate withdrawal.

Tolerance to the antiaggressive effects of amphetamine has been shown with a daily dose of 1.5 mg/kg for 7 days (Moro et al., 1997). Chronic and acute administration of amphetamine led to increases in defensive and escape

behaviors, and no statistically significant differences were discovered between one group of mice that had received seven daily injections of amphetamine and another that had received the same dosage of saline (Moro et al., 1997).

Note: By using selective antagonists it has been shown that dopamine receptors of the D2 subtype (see Chapter 5 on Physiology) are most effective in reducing the increased motor activity brought on by amphetamine intoxication (Miczek and Tidey, 1989). This inhibition does not, however, carry over to the disruptive effects on social and aggressive behavior. It would appear that agonism of the D2 receptor is most likely not associated with amphetamine control of aggressive behavior. Other dopamine receptor antagonists such as haloperidol and chlorpromazine have been found to reduce aggressive and social behavior, yet none has reversed the effects of amphetamine on these actions (Miczek and Tidey, 1989).

Methodological Problems: Distinguishing between Aggressive and Defensive Reactions

A persistent problem in the pursuit of information regarding aggressive behavior is the ways in which the data are gathered and analyzed. As mentioned before, the typical methods of experimentation are isolation-induced and pain-induced aggression, as well as intruder–resident models. The problem is that both fear and anger can elicit attack. Pain-induced aggressive behavior is fear induced and thus neurologically very specific. Intruder-induced aggressive behavior is anger induced and thus neurologically very different from pain-induced aggressive behavior. There is no reason to predict that amphetamine would affect pain-induced aggressive behavior the same way it affects intruder-induced aggressive behavior.

Another difficulty worth mentioning is the interaction between behavioral categories and the confounding that may consequentially occur. One example is the decrease in immobility that is associated with amphetamine administration and the corresponding increase of escape/avoidance behaviors that may possibly arise from such escalation in locomotor activity. It seems reasonable that the stimulant effects of amphetamine could perhaps cause a sensation of irritability that would lead to higher rates of occurrence for defensive/offensive categories and otherwise confound the results for additional behavioral comparisons. It has been shown, however, that these amphetamine-related increases in motor activity are significant in regard to behavioral transitions such as avoidance and nonsocial exploration, but are not significant when transitions of attack are involved (Moro et al., 1996).

Amphetamines and Their Effects on Dominance Hierarchy in Primates

Humans are primates, as are monkeys and apes. Evolution tends to be very conservative and so the brains of humans are very similar to our cousins. In fact, genetically we are about 98% the same as our primate cousins. Although research that involves monkeys demonstrates the same dose-dependent effects of amphetamine as shown with rodent subjects, the resultant effects on aggressive behavior favor a positive rather than negative relationship (Smith and Byrd, 1984; Martin et al., 1990). Primarily, the effects that amphetamine has on primates' dominance rank have been examined. Analysis has suggested that these effects are a function of social status and group dynamics (Smith and Byrd, 1984).

Differences of Effects between Ranks

The behavior of dominant animals differs drastically from that of subordinate animals (for review, see Yudko, 1998). We tend to categorize dominant styles of behavior as aggressive and subordinate styles of behavior as defensive. Dominant and subordinate animals also differ from each other neurochemically and hormonally. We can identify the rank of a primate within its hierarchy by observing behavior. When amphetamine is administered to monkeys of different social status within an established colony, the subjects express behavior dependent on their position in the hierarchy. For example, treatment of *d*-amphetamine causes an increase in aggressive behavior — open mouth threats, biting, chasing — in low- and high-ranking monkeys, with little or no effect on those in the mid-ranks (Smith and Byrd, 1984). Similar effects were observed when measuring rates of affiliative behaviors — grooming, holding, huddling — between the subjects: high-ranking monkeys showed decreases in affiliation with little variance, low-ranking monkeys also displayed reductions but with a larger range of variance, and mid-ranking monkeys conveyed no significant decline in affiliative behaviors (Smith and Byrd, 1984). These findings are extremely important. They suggest that the effect of amphetamine on aggressive behavior is linked to the initial level of aggressiveness of the individual.

Additional discoveries have been made that further illustrate the diverse effects amphetamine has on the dynamics and hierarchy of primate interaction. Along with the fact that low- and high-ranking monkeys are principally affected comes a certain directionality of their aggressive displays. High-ranking subjects treated with *d*-amphetamine were more aggressive to adults and other superior members of the group, whereas those in the lower ranks displayed greater aggression to juveniles and those with inferior positions in the dominance hierarchy (Martin et al., 1990).

This type of effect, a drug causing individuals to act differently depending on preexisting personality traits, is not unique to amphetamine. A comparison of the animal and human literature on the effects of alcohol on aggressive behavior yields a similar result (Yudko et al., 1997). In fact, the effect of alcohol on aggressive behavior may be bidirectional. In other words, alcohol can cause aggressive behavior in a subclass of the population (i.e., in highly aggressive individuals but not in low to moderately aggressive individuals) and alcohol use can be caused by the need of the highly aggressive individual to self-medicate (this theory assumes that being very aggressive causes increased levels of stress and that alcohol is used by these individuals to alleviate that stress). This type of behavior can lead to a cyclic pattern in which the highly aggressive individual becomes involved in situations that cause stress. This person then drinks alcohol to alleviate that stress. The alcohol causes that person to become more aggressive, which causes more problems in the individual's life (brought about by aggressive behavior leading to negative outcomes), which causes more stress, which leads to more drinking. These results taken together with the above analysis of the effect of amphetamine on primate behavior suggest that the reports of human aggressive behavior being increased by amphetamine use are simply an artifact of highly aggressive individuals tending to take and be made more noticeably aggressive by amphetamine.

Dose-Dependent Effects

In contrast to the results reported from rodent research, greater rates of aggressive behavior were observed in correspondence with increases in dosage. Low doses (0.01 mg/kg) produced very little change in aggression whereas a rapid escalation was observed with subsequent increases (up to 1 mg/kg; Martin et al., 1990). In Smith and Byrd's (1984) study, the highest-ranking monkey displayed the largest increase in aggressive behavior in direct relation to the increase in dose, with rates of more than 30 times that of the control group at the highest dose (0.56 mg/kg). According to previous literature and current speculation, an adequately broad range of doses will yield an inverted U-shaped dose-effect curve that is typical of the behavioral effects of psychomotor stimulants (Martin et al., 1990). This finding indicates that increasingly larger doses of amphetamine would eventually lead to the reduction of aggressive behavior.

In regard to affiliative behaviors, one notices a dose-dependent effect on the rate of occurrence that almost parallels that of aggressive behavior. Over a range of doses (0.003 to 0.56 mg/kg) a considerable majority of subjects demonstrate a dose-related pattern of affiliative behavior with little or no effect at lower doses and large decreases at higher levels (0.3 to 0.56 mg/kg; Smith and Byrd, 1984). These results are also contrary to those found in

rodent experimentation, where clear increases of social exploration were observed in male mice following acute doses of amphetamine.

Amphetamines and Their Effects on Human Aggressive Behavior

Because the possession, use, and distribution of amphetamine are illegal and because the compound causes brain damage, ethical concerns have prevented experimental research on the behavioral effects of amphetamine. Thus, the available literature on the effects of amphetamine in human participants is all correlational. Although there have been reports of high correlations between violent crime and amphetamine use, these studies may be confounded because other drugs such as alcohol are often involved and users that commit these acts sometimes have aggressive tendencies beforehand (Wright and Klee, 2001). The existing literature does give some indication regarding the effects of various doses and the possible predictions one can make concerning the long-term effects on mental health, but until more research can be performed we are limited in our understanding the relationship of amphetamine with human aggressive behavior.

Subjective Analysis

The advantage of experiments involving human subjects is that people have the ability to describe their immediate emotional states and report their feelings and thoughts. However, these subjective analyses can sometimes be inaccurate, and in a sense become "contaminated" because of participants' biases or reservations concerning the personal information they disclose, especially if it involves substance abuse. In a self-report study involving amphetamine users from a metropolitan city in Australia, Vincent et al. (1998) reported that more than one third of the sample comprising 100 participants had experienced symptoms of depression and anxiety prior to their amphetamine use, and nearly one third had experienced previous mood swings and aggressive outbursts. In addition, some of the participants believed that their usage had intensified these conditions, and almost a quarter of the subjects felt symptoms of depression and anxiety attacks for the first time after they started using the drug, although not all of them associated these symptoms with their amphetamine use. Other research shows decreases in fatigue, increases in vigor, no significant changes in anger or confusion, and a moderate decrease in depression (Cherek et al., 1986). Different subjects from separate studies also show signs of excessive confidence and delusional paranoia (Wright and Klee, 2001).

In subjective experiments, it is important that the participants understand completely what it is that they are analyzing in order to obtain accurate results. When studying the effects of amphetamine on human aggressive behavior, it is essential that we distinguish this aggression from negligent, violent crime. Although there is no clear-cut line that separates the two, we can think of violent crime as forceful and offensive acts that violate the norm and possibly lead to malevolent physical violence, whereas aggression is a "hostile or destructive tendency or behavior" (Wright and Klee, 2001). One could therefore generalize from this distinction that violence has a more social, and perhaps even economic, connotation, whereas aggression appears to be associated more closely with psychological factors. In Wright and Klee's (2001) study the respondents were asked about any ongoing problems they may have been experiencing with amphetamine-related aggression, and were "encouraged to include in their response incidents that did not result in physical harm to others, but which had produced a conscious awareness of their own hostility." By making such a distinction, one can acquire accurate data that are more representative of the population.

Observed Behavior

Experiments have been carried out that use positive and negative reinforcement to examine the effects of amphetamine on aggressive behavior. In one such study, subjects were given the opportunity to gain points that were redeemable for a monetary reward by pressing an assigned button. This was the non-aggressive response. Their point values were systematically reduced by a fictitious partner from whom they could subtract points by pressing a different button, which was the aggressive response. Biphasic results similar to those reported in nonhuman research were observed, with lower doses (5 and 10 mg/70 kg) of *d*-amphetamine increasing the rate of aggressive responses and higher doses (20 mg/70 kg) reducing these occurrences to levels found after placebo administration (Cherek et al., 1986). Another noteworthy outcome was that while the rate of aggressive responses was decreased at the highest dose, the amount of non-aggressive responses remained unaltered.

Referring back to the Vincent et al. (1998) study, one can extrapolate generalized correlations between amphetamine use and the behavior and health of the user. One of the outcomes of this analysis was that symptoms such as depression and anxiety were likely to be intensified, and additional problems including paranoia and aggression could possibly arise with continued use. Furthermore, it was determined that a direct relationship existed between increasing severity of dependence and mental and physical health deficits, which was consistent with the fact that the sample used in the study

had considerably poorer mental and physical health and emotional functioning when compared to the general South Australian population. These data support the popular opinion that amphetamines can have severe and detrimental effects on both physical and mental performance.

Concluding Remarks

Research shows that the effects of amphetamine on aggressive behavior are complex and are dependent on the types of variables involved. One such variable would be the kind of species used for experimentation. It can be difficult to make comparisons between species, as they tend to produce differing results and have unique brain structures. For example, in experiments involving rodent subjects, higher doses of amphetamine lead to a decrease in aggressive behavior, whereas higher doses in monkeys cause an escalation in aggression. In addition, the affiliative behavior of primate subjects clearly has biphasic effects, with rates of occurrence decreasing steadily as the dose increases (Smith and Byrd, 1984), whereas rodent subjects exhibit clear increases in social exploration along the same scale (Moro et al., 1996). Such diversity between species often makes it difficult to generalize to the human population, and so carefully organized experimentation may be necessary to understand this variance.

Another complexity is the biphasic effects that amphetamine has on behavior. This dose-dependent condition can sometimes lead to difficulties in predictability since there is no clearly defined linear relationship. Even intraspecies effects can have large degrees of variance and so extensive sample sizes are necessary to gain a better perspective. It is interesting, however, that these biphasic results seemingly contradict the common belief that larger doses of amphetamine cause increases in aggressive behavior, when, in fact, it is smaller doses that elicit this condition.

When studying the effects of amphetamine on human behavior, several factors must be taken into consideration before any assumptions can be made. For example, the history of drug use of a patient, the patient's lifestyle, and the patient's social status and interactions are all possible influences on his or her drug habits and aggressive patterns of behavior. Wright and Klee (2001) report some interesting points in the area of amphetamine-related human aggressive behavior. For instance, correlations between amphetamine use and aggression are strongly associated with drug dealing rather than intoxication. Moreover, in regard to the subjects' patterns of amphetamine use, there were no significant differences between those who reported aggression and the rest of the sample, and no straightforward relationship could be found between amphetamine use and one's potential for aggressive behavior.

As one can see, the connection between amphetamine use and aggressive behavior is ambiguous and complex, with no easily discernible results. Since it is an illicit substance, the opportunities for human experimentation and research using this compound are extremely limited. Unfortunately, the only way we can obtain additional information regarding the subject is to increase the volume of current research and use larger sample sizes to enhance external validity and gain a broader perspective.

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