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Cannabis and Aggression in Animals

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The effects of cannabis on aggressive behavior in animals depend on the nature of the aggressive behavior being observed. "Irritable" aggression tends to be increased by cannabis whereas "predatory" and "inter-male" aggression tend to be reduced. If aggressive behavior is examined in these terms, then cannabis is seen to have a differential rather than a dual effect on aggression in animals.

In the late 11th century A.D., a secret society of assassins was founded in which the members allegedly fortified themselves by eating or smoking hashish before they went out on their assignments of death. Although this anecdote has long since been relegated to the category of myth, it is still often cited as an example of the violence-inducing properties of cannabis.[1,2] The issue regarding the relationship between marihuana and aggression itself, however, is still rather equivocal despite several case studies in which the frequency of marihuana use among convicted criminals has been examined (e.g., Bromberg, 1934, 1939; Charen and Perelman, 1946; Ausubel, 1958; Bloomquist, 1971; Grinspoon, 1971; Tinklenberg and Woodrow, 1972). Other

[1]The term cannabis, marihuana and hashish will be used interchangeably without distinction.

[2]The active principles in cannabis are the cannabinoids of which *trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC = Δ^1-THC) and *trans*-Δ^8-tetrahydrocannabinol (Δ^8THC = Δ^6THC) are presently considered to be the most potent (Mechoulam, 1970). Although some of the other cannabinoids such as cannabidiol, cannabinol, and cannabigerol are pharmacologically inactive themselves (Edery, Grunfeld, Ben-Zivi and Mechoulam, 1971), evidence has recently been accumulating that these otherwise inactive cannabinoids can affect the activity of Δ^9THC (Jones and Pertwee, 1972; Fernandes, Warning, Christ, and Hill, 1973; Karniol and Carlini, 1973) so that on a Δ^9THC mg/kg basis, the potency of crude cannabis extracts can be expected to be different from that of Δ^9THC per se. In addition to these naturally occurring substances, two homologues derived from D, L-synthetic tetrahydrocannabinol have been widely used in psychopharmacological investigations. These homologues are the *n*-hexyl derivative, pyrahexyl (also known as synhexyl) and the demethylheptyl derivative, DMHP.

studies include governmentally sponsored inquiries (e.g., Indian Hemp Drug Commission, 1893-1894; White House Conference on Narcotics and Drug Abuse, 1962; Interim Report of Canadian Government Commission of Inquiry, 1970; National Commission on Marihuana and Drug Abuse, 1972) and a number of private surveys examining the relationship between self-admitted aggressive behavior and marihuana usage among non-criminals (e.g., Blum, 1969; Goode, 1972).

Without going into the details of these studies, many of which have been recently and ably reviewed by Kaplan (1970), Grinspoon (1971) and Tinklenberg and Murphy (1972), it must be kept in mind that much of the data upon which these reports are based were derived from retrospective subjective and uncritical case analyses, the scientific limitations of which are generally recognized.

In acute experimental studies, involving introspective impressions of their feeling and attitudes, human subjects given Δ^9THC or cannabis have reported feeling less aggressive following drug usage (Hollister, Richards and Gillespie, 1968; Abel, 1972; Salzman, Kochansky and Porrino, 1973; cf. Interim Report of Canadian Government, 1970). However, it must be kept in mind that the dosage of drugs used in these studies were relatively low, the studies themselves were acute, and the subjects were in good physical and "mental" health. By contrast, many of the reports linking marihuana and aggression come from underdeveloped Eastern countries in which the cannabis that is used is much more potent, its usage is chronic, and the subject population is often underfed.

The importance of these and several additional variables in the relationship between cannabis and aggression has recently been subjected to experimental investigation in animals and the following discussion will review this body of literature for purposes of summarizing and elucidating the nature of some of the important considerations which bear on this particular relationship.

CONCEPTUAL FRAMEWORK

Aggression is herein defined as behavior that involves attack or the threat of attack to another animal. Numerous investigators have pointed out, however, that aggression is not a unitary construct, and instead one must speak of kinds of aggression. In this regard, Moyer (1960) has identified and operationally defined seven basic classes of aggressive behavior. These are irritable, predatory, inter-male, fear-induced, territorial defense, maternal and instrumental. Each of these kinds of aggression, he contends, may have a distinct neurological and endocrinological basis and consequently, a given manipulation may increase one kind of aggression, decrease another, and have

no effect on a third. Although the marihuana literature, for the most part, tends to ignore these various distinctions, this review will attempt to discuss the various findings in this context. Since the data are not sufficient to deal with all seven of these types of aggression, only irritable, predatory and inter-male aggression will be examined.

IRRITABILITY

Irritable aggression can arise as a result of pain, frustration, or increased "drive." In general, any situation that causes discomfort may result in "irritable" aggression. The behavior itself is characterized by the absence of any prior attempt at escape and in its extreme form it has been labelled as "uncontrollable rage" (Moyer, 1968).

During the course of a study dealing with the effects of cannabis extract on maze learning in rats, Carlini and Kramer (1965) called attention to the fact that drug-treated animals began to attack each other in their cages following injection. When further studies were designed specifically to investigate this phenomenon, the authors were unable to reproduce the original observations. However, the attacking behavior was again observed incidently in a number of different situations and Carlini and Masur (1969) hypothesized that the salient difference in the conditions under which aggression appeared following treatment with marihuana, was whether the animals were chronically food deprived prior to and during the experiment.

To test the hypothesis, male and female rats were housed in cages and were food deprived for 22 hr each day. During this time, each animal was injected intraperitoneally with cannabis extract (10 mg/kg) and observations were made of the amount of time the animals engaged in spontaneous fighting behavior.

Initially, there was no sign of aggressiveness, but after 15-18 daily drug treatments, the animals began to attack their cagemates vigorously within 30-40 min after injection. This behavior then persisted for 2-4 hr. Thereafter, the aggressiveness diminished and gradually the animals became docile once more. The phenomenon appeared equally in males and females, although it did not manifest itself in all pairs throughout the experiment. A subsequent dose-reponse study indicated that doses of 2.5-5 mg/kg of cannabis extract were insufficient to produce clear-cut effects but that at doses of 10 and 20 mg/kg the phenomenon was reliably elicited. Starvation itself, however, did not induce this behavior. Furthermore, rats that were previously food deprived and then fed at the time of injection did not engage in spontaneous fighting. Apparently, chronic starvation up to and including the time of injection was the critical determinant for the production of cannabis-induced aggressiveness. Subsequent studies (Carlini and Masur, 1970) have replicated this finding and

have shown that it appears to be specific to cannabis since it does not occur with amphetamine (2.0 and 4.0 mg/kg), amylbarbital (20 mg/kg), caffeine (50, 100 and 200 mg/kg), mescaline (40 mg/kg) or LSD (0.2 mg/kg).

In light of the association between hunger and cannabis-induced aggression, Carlini, Hamaoui and Martz (1972) tested the possibility that there may be some specific aspect of food deprivation such as hypoglycemia, acidosis or vitamin deficiency which may have been the main factor contributing to this phenomenon.

To examine the role of glucose, they food deprived rats and injected them (ip) with cannabis extract (10 mg/kg) until "fierce" aggressiveness was observed (Day 11). On Day 13 of the treatment, 30 min after the cannabis injection, the animals were injected with 100-800 mg/kg of glucose (ip) and aggressiveness was observed for a further 30 min. Appropriate placebos were also administered to control for factors associated with the injection procedure. On Day 16, glucose solutions were injected 5 min before cannabis administration. A third group of animals were allowed to drink a 10% glucose solution on Days 14 and 15 of drug treatment.

Although the intraperitoneal injection of glucose had no effect on cannabis-induced aggressiveness, when the rats were allowed to drink the 10% glucose solution, aggressiveness ceased to occur. The investigators suggested that this suppression of aggression following access to a glucose solution was probably not due to an elevation of blood glucose alone since if this were the case, the intraperitoneal injection ought to have had the same effect. However, no explanation for the effect of ad lib. glucose was forthcoming.

Additional experiments of this nature were also conducted using ammonium chloride and lactic acid in an attempt to study the contribution of changes of pH due to acidosis associated with food deprivation. Neither treatment had any effect on cannabis-induced aggression indicating that acidosis was probably not a potentiating factor in the phenomenon.

Studies were also conducted to assess the effects of different diets. Groups of rats received either regular laboratory chow, or corn as their only food, or a protein-free diet for their 2 hr feeding period. None of these treatments reduced aggression indicating that a lack of certain nutritional elements per se was probably not involved. Moreover, if the animals were allowed to eat ad lib., aggression did not appear, even if the diets lacked specific nutritional factors.

In a final study, the role of environmental temperature was studied. Different groups of rats were housed at different environmental temperatures throughout the experiment and it was found that the lower the temperature, the more violent the fighting, and the sooner it began to appear. Thus, in rats housed at 14°C, fighting began after the first injection of cannabis, whereas at 27°C, fighting did not appear until the fifteenth injection (cf. Carlini and Masur, 1969).

In summarizing the results of this study, Carlini and his coworkers suggest that stress itself rather than undernourishment appears to be the main factor contributing to cannabis-induced aggression. This conclusion is based on the fact that when food or glucose is available ad lib., no aggression occurs following cannabis treatment, and ad lib. diets that lack complete nutritional balance do not affect cannabis-induced aggressiveness. However, rats that are subjected to cold stress do exhibit aggression following cannabis.

In a subsequent experiment, Alves, Goyos, and Carlini (1973) examined the effects of cannabis on aggression in rats undergoing deprivation of rapid eye movement (REM) sleep. It is known that REM deprivation increases irritability in animals and man (Clemes and Dement, 1967; Morden, Conner, Mitchell, Dement and Levine, 1962) and therefore REM sleep deprivation constituted another situation in which the relationship between stress and marihuana-induced aggression could be observed.

Rats were deprived of REM sleep by placing them on a small platform surrounded by water. Control animals were left on larger platforms. Food was available ad lib. for both groups. Under such conditions, the rats on the small platform tend to fall off since REM sleep is associated with muscle relaxation and this results in their falling into the water and thus awaking. The rats on the larger platform do not fall into the water when they go into REM sleep because of the size of the platform.

Twenty-four to 96 hr after remaining in these conditions, the animals were taken from the platforms and were housed in pairs in wire cages after which they were injected (ip) with either cannabis extract (5-20 mg/kg), Δ^9THC (2.5-20 mg/kg), mescaline (40 mg/kg), D-amphetamine (0.5-2.0 mg/kg), LSD (0.01-0.04 mg/kg) or ethyl alcohol (400 or 800 mg/kg).

Animals deprived of REM sleep and injected with placebos did not fight whereas a dose-related increase in fighting was produced by Δ^9THC and the cannabis extract. Although there was a slight increase in aggressiveness associated with all of the other test drugs, the intensity and duration of such behavior fell far short of that observed with marihuana. Control animals that were placed on the larger platforms did not exhibit aggressiveness regardless of the drug condition.

To examine the effects of a different kind of stress on cannabis-induced aggression, Carder and Olson (1972) administered Δ^9THC (0.12-2.0 mg/kg, ip) to pairs of rats undergoing electric foot shock treatment. Such pain-producing stimulation is known to be a reliable method of initiating aggression in animals (Ulrich and Azrin, 1962). In general, the experimental procedure involves placing two animals in an enclosed apparatus which contains an electrifiable grid floor. The current is then turned on and the duration, number, and intensity of attacks are recorded. Pretreatment of either one or both of the subjects with 0.12-0.50 mg/kg Δ^9THC was observed to increase markedly the number of shock-induced attacks (cf. also Carlini and Masur,

1969, 1970; Dubinsky *et al.*, 1973) whereas doses of 1.0 and 2.0 mg/kg decreased aggressiveness. However, when rats were previously familiarized with the shock conditions, the drug no longer increased fighting behavior. To account for this observation, the investigators suggest that this second experiment involved acute administration of drug and that familiarity with the test environment may have decreased the novelty (fear?) of the situation and this could have contributed to the decrease in shock-induced aggression in cannabis-treated animals. This possibility could also explain the lack of effect of Δ^9THC on shock-induced fighting reported by Manning and Elsmore (1972).

To test the hypothesis concerning the role of stress further, Carlini and Gonzalez (1972) submitted rats to another situation which did not involve food deprivation but did contain yet another element of stress, namely, withdrawal from morphine which has previously been observed to induce aggression in rats (Boshka, Weisman and Thor, 1966). Accordingly, Δ^9THC (5 mg/kg, ip) was administered to rats undergoing withdrawal from morphine and their behavior was compared with placebo or amphetamine (2.0 mg/kg, ip) treated animals. Neither of these two latter groups exhibited the same amount of aggression during morphine withdrawal as was observed in the group treated with Δ^9THC.

Since depletion of serotonin has been reported to increase excitability and aggressive behavior in laboratory animals (e.g., Koe and Weissman, 1968; Lintz and Harvey, 1969), Palermo-Neto and Carlini (1972) investigated whether changes in the levels of serotonin would affect cannabis-induced aggression in starved and satiated animals. Accordingly, rats were food deprived and subsequently injected with cannabis extract (20 mg/kg, ip). After aggressiveness occurred, animals were injected (ip) with parachlorophenylalanine (pCPA) (300 mg/kg) 17 hr before the next cannabis administration. Treatment with pCPA in this manner potentiated cannabis-induced fighting in starved rats but did not affect aggression in satiated animals, suggesting a possible role for serotonin in cannabis-induced aggression (Palermo-Neto and Carvalho, 1973).

In a subsequent study, Palermo-Neto and Carvalho (1973) examined the effects of chronic cannabis pretreatment on the aggressive behavior of rats of different "emotionalities" (as measured by open field behavior). Rats were initially screened in the open field and were then divided into two groups depending on the number of boluses eliminated (an index of emotionality, cf. Denenberg, 1969). They were then food deprived for 22 hr daily and were injected with cannabis extract (20 mg/kg ip) or placebo each day for 30 days.

Analysis of the data indicated that the rats could be clearly differentiated according to their defecating scores. When such separation was made, there were no differences between the groups in motor activity. Following chronic treatment with cannabis, food-deprived rats with a high index of

defecation (which is generally accepted as an indication of increased emotionality in rats) began to engage in fighting behavior after fewer drug treatments than did animals with low indices of defecation. Aggression increased for both groups, however, as drug treatment continued but did not appear in control animals that were not food deprived regardless of their defecation indices. The experiment thus indicated that "emotionality" was a contributing factor to the induction of aggression by cannabis in animals undergoing stress.

Irritable aggression is also often observed in animals following destruction of certain specific brain areas depending on whether these sites have excitatory or inhibitory function. In the rat, for example, "rage" typically occurs folllowing destruction of the septal area of the limbic system (Brady and Nauta, 1953). In this regard, Δ^9THC (10-80 mg/kg, ip) has been observed to increase the excitability and aggressivity of rats with septal lesions at 1 hr after injection. At 3 hr post-injection, however, the drug has been observed to exert a taming reaction (Dubinsky *et al.*, 1973).

In addition to increasing aggressiveness, Masur and her associates (Masur, Martz, Bieniek and Korte, 1971; Masur, Karniol, and Palermo-Neto, 1972) have studied the effects of Δ^9THC on the behavior of rats in a food competition situation. To examine this relationship, rats were food deprived and were trained to run through a runway from a start box to an identical goal box at the other end (for food reward). A guillotine door bissected the runway which was wide enough to allow only one animal to pass through at a time. Rats were trained to run in both directions and after this preliminary training, pairs of rats were introduced into either end of the apparatus and as soon as they reached the middle of the runway, the guillotine door was raised and the rat that pushed the other back into the opposite end box was classified as the "winner." One animal in each of these pairs was injected with Δ^9THC (2.5 mg/kg, ip) prior to testing whereas the other received a placebo injection. Two days later drug conditions were reversed so that ultimately all animals were tested with both drug and placebo. The experiment was then repeated with a higher dose (5.0 mg/kg) of drug.

Analyses of the data indicated that although animals receiving the drug had a greater latency to enter the runway, those that did so were mostly "winners" in the competition as indicated by the withdrawal of their opponents into their start boxes. When the drug conditions were switched, the former "losers" now became "winners." The same results also occurred following administration of 5.0 mg/kg of mescaline (ip) however (cf. also Masur *et al.*, 1972).

In a second experiment, rats were tested in a T maze containing two large arms with starting boxes on either end and a stem with a runway that led to a goal box containing food. To enter the goal box, the rat had to pass through a small opening located at the intersection of the apparatus.

After preliminary training, pairs of rats were submitted to the food

competition situation such that one animal was tested after receiving Δ^9THC (2.5 mg/kg, ip) while the other received only placebo. Using this method, rats given the drug were mainly losers. However, in this second experiment, the investigators report that the animals receiving the drug did not wait at the guillotine door as did the control animals, but rather they continued to run along both arms "exploring" the maze.

As pointed out by Masur, these two experiments demonstrate that the effect of the drug in a food competition situation depends greatly on the test conditions. In the first experiment, both rats faced each other and had nowhere else to go except forward or backward. If the drug tended to increase aggressiveness as noted by the previous studies cited above, this would have contributed to the advantage of the animals receiving Δ^9THC. Likewise, if it increased torpidity, this could also have added to the advantage of the drug-treated animals since they would not move forward or backward (see below).

In the T maze situation, the movement of the rat was not restricted and hence an increase in "locomotor" activity would not necessarily result in an entry into the goal runway. Unfortunately, only one dose of Δ^9THC was examined in the T maze situation. Hence, it is not possible to conclude from this study that Δ^9THC directly affected dominance behavior.

In commenting on the results of the first experiment, van Riezen and Rijk (1972) described a study similar to that reported by Masur in which the anti-anxiety drug, diazepam, likewise made "loser" rats "winners." Close observation, however, suggested that the lack of defensive posture and perseverant "stubborn" behavior on the part of drug-treated animals was the primary reason for their success since their opponents typically gave up and simply withdrew back into their start box. In light of this observation they conducted a second study in which a small plug of cotton was inserted into the tunnel instead of a live opponent. Although this plug could be pushed away with a minimum effort, previous "winner" rats did not do so but instead waited for a time and then withdrew themselves from their cotton opponent. In light of Masur *et al.*'s (1971) observation that the drug-treated animals had a greater latency to enter the runway, the point raised by van Riezen and Rijk is worth noting in relation to these experiments.

PREDATORY AGGRESSION

This type of aggression generally involves the attacking of some natural object of prey and in this respect it is regarded as being different from other forms of aggression since it is relatively stimulus specific and has a neurological basis that is distinct from that subserving other types of aggression (Moyer, 1968). The occurrence of mouse killing (muricide) by rats was first

described by Karli (1956) in a series of experiments in which he reported that although 70% of the wild rats he studied killed mice, only 12% of domesticated rats exhibited this response. Frog killing by rats has also been subsequently observed (Bandler, 1969). Following Karli's original publication, a number of experiments have been conducted in laboratory animals, showing that predatory behavior can be increased if rats are exposed to cyclic or chronic food deprivation, food competition (Heimstra and Newton, 1961; Heimstra, 1965). Muricidal behavior can also be induced in nonkiller rats by electrical (King and Hoebel, 1968; Panksepp, 1971) or cholinergic stimulation of the hypothalamus (Smith, King and Hoebel, 1970). However, foot shock does not induce such behavior (Karli, 1956). A number of drugs such as amphetamine and certain antidepressants have been reported to inhibit predatory aggression in rats at doses that do not produce gross motor debilitation (Barnes, Cunningham, Pernethy and Gogerty, 1967; Horovitz, Piala, High, Burke and Leaf, 1966; Kulkarni, 1963) whereas many sedatives, tranquilizers and antipsychotics have little effect on such behavior, even at doses that produce gross motor upset (Janssen, Jageneau and Niemegeers, 1962; Horovitz, *et al.*, 1966; Horovitz, Ragozzina and Leaf, 1965).

To test the effects of Δ^9THC on predatory behavior, Kilbey, Harris and Moore (1971) administered different doses of this drug (0.1-2.5 mg/kg, iv) to rats and observed their behavior after frogs were placed in their cages. Following this treatment, the animals were tested for motor impairment on a rotating rod test. The drug was observed to increase kill latency and also to impair motor coordination.

In a second experiment, food-deprived rats were tested in the same manner and again latencies were increased, probably a result of impaired motor ability, motor depression, or both.

A similar experiment of this nature was reported by McDonough, Manning and Elsmore (1972). Rats that were allowed free access to food and water, were injected (ip) every other day with either placebo or Δ^9THC (6.4 mg/kg) for 7 days. The test for predatory aggression involved introducing a small turtle into each subject's home cage for a 10-min period and noting the occurrence or non-occurrence of attacks (physical injury to the turtle). Analysis of the data indicated that there was a significant reduction by about 50% in predation. However, since there was no concomitant measure of motor activity, it is not certain whether this suppression of predatory behavior was direct or whether it was the result of an impairment or depression of locomotor activity.

Using mice as prey, Ueki, Fujiwana and Ogawa (1972) studied the effects of chronic administration (30 days) of Δ^9THC (6 mg/kg, ip) on rats fed ad lib. or subjected to hunger stress and housed singly or in groups of six, compared to placebo treated subjects.

None of the rats housed individually or in groups exhibited muricide

following administration of placebo. However, individually housed animals began to show muricide even on the first day of Δ^9THC injection and the incidence of such behavior was reported to be greater in isolated animals undergoing starvation. However, no statistical analysis of any of these observations was reported and inspection of the graphical presentation of the results was not convincing since it indicated that the incidence of muricide occurring was in some cases as low as two animals per subgroup and usually the maximum was three to four compared with no control subjects. Nor is it clear from the study how muricide was scored on an individual basis for subjects in the grouped condition. This latter study can thus be regarded as only descriptive and subjective.

On the other hand, a similar experiment by Alves and Carlini (1973) suggested a dual effect of cannabis on predatory behavior depending on whether the drug was given acutely or chronically. In this study, nonkiller and killer rats were injected (ip) with cannabis extract (20 mg/kg) and mice were placed in their cages. The drug was observed to increase the latency to kill for all of the killer rats although eventually all animals did kill the mice placed in their cages. The increased latency for attack probably reflects the depressant action of the drug on motor activity. In the case of nonkiller rats, these animals were divided into four sub-groups. One group was subjected daily for 40 days to 22 hr food deprivation and an injection (ip) of 20 mg/kg of cannabis. A mouse was placed into the home cage immediately after injection. From days 41-45, food was made available ad lib. for these animals. A second group was treated similarly except that food was available ad lib. for the 40 day period of drug treatment. A third group was subjected to food deprivation but was injected daily with placebo; the fourth group was fed ad lib. and received only placebo injections.

The previously nonkiller rats exposed to starvation and chronic cannabis treatment begin to exhibit muricide about 10 days after drug administration began and the incidence of such behavior decreased when cannabis was no longer given. Animals fed ad lib. and given cannabis also exhibited a small increase in muricidal behavior. However, muricide did not appear in either of the two placebo treated groups. The results were interpreted as suggesting that cannabis has a dual effect on predatory behavior since it suppressed muricide when given acutely, but induced such activity when given chronically. Moreover, cannabis-induced muricide was markedly potentiated if the rats were subjected to hunger stress. However, this latter observation suggests that the increase in muricidal behavior following chronic cannabis treatment was due to irritability rather than to some direct effect on the neural mechanisms underlying predation.

In an experiment on muricidal behavior reported by Dubinsky, Robichaud and Goldberg (1973), a mouse was placed into the cage of each rat before and after administration (ip) of Δ^9THC. The drug was observed to

block muricide at doses of 2.5, 5.0 and 10.0 mg/kg, whereas rotorod performance was not impaired at these doses.

In cats, "predatory" aggression can be produced by electrical stimulation of the ventromedial area of the hypothalamus. By monitoring the intensity of the current required to produce this behavior, changes in responsiveness can be examined in relation to drug action. In this context, Dubinsky and coworkers (1973) observed that although doses of 10 and 20 mg/kg of Δ^9THC (ip) produced ataxia and increased the latency to attack prey objects, the drug did not block the response itself.

These data thus suggest that cannabis does not have the same effect on predatory aggression as it does on irritable aggression since the drug tends to suppress the former and increase the latter.

The neural mechanisms underlying these types of aggression, however, are both different (Moyer, 1968). In this regard, Roberts and Kiess (1968) observed that cats would learn to perform correctly in a Y-maze for the opportunity to attack a rat. Likewise, rats will learn mazes for the opportunity of killing mice (Myer and White, 1965). This suggests that attack and killing behavior in animals may have reward properties and that brain stimulation resulting in such behavior may have similar positive motivational properties. In the rat, predatory behavior can be elicited by lower intensities of electrical stimulation of the same areas of the brain that result in self-stimulation, suggesting that attack behavior may indeed be "pleasurable" (DeSisto and Huston, 1971). If attack behavior is reinforcing and thus has motivational properties, then the depressant action of cannabis on such behavior may be due to its effects on the motivational mechanisms underlying aggression. Such a possibility is also suggested in the case of inter-male aggression as well (see below).

INTER-MALE AGGRESSION

When male mice have been kept in isolation for periods of 4 weeks or more, they become hyperreactive to environmental stimulation. Under such circumstances, if two previously isolated mice are brought together, they typically begin to fight. Since such behavior is elicited by a rather specific situation (male mice do not attack female mice), it is considered to be a distinct class of aggressive behavior (Moyer, 1968) akin to territoriality. The intensity of such behavior, however, varies according to strain (Valzelli, 1967). In addition to mice, rats, cats, dogs, monkeys, etc., also exhibit aggression following extended periods of isolation (Hatch, Balazo, Wiberg and Grice, 1963; Kuo, 1967; Mason, 1960).

One of the earliest studies of the effects of cannabis on inter-male aggression consisted of an examination of changes in such behavior following

treatment with hashish (Garattini, 1965). Mice that had been kept in isolation for 4 wk were placed together three per cage and the latency to begin as well as the amount of fighting that occurred following placebo or hashish injections (100, 200 and 400 mg/kg ip) was determined. Animals receiving the drug were observed to be less aggressive than control animals. However, at these doses, it is possible that this result was due to nonspecific effects of the drug on motor activity. In a similar study (Santos, Sampaio, Fernandes and Carlini, 1966), mice that had been isolated and had previously exhibited or had not exhibited aggression towards intruders were injected (ip) with cannabis extract (2.5-80.0 mg/kg) or placebo and a new intruder was introduced into its cage. Immediately after being tested for aggressiveness, each subject was placed into an activity cage.

The results indicated that the drug did not increase aggression in mice that had previously not been fighters. In fighting mice, however, the drug markedly reduced aggression at doses that did not affect spontaneous locomotor activity. The data were interpreted as indicating that cannabis has a "taming" effect on aggressiveness in mice. A similar reduction in isolation-induced fighting has also been reported by Dubinsky and coworkers (1973; cf. also Siegel and Poole, 1969).

Subsequent to the study by Santos and coworkers (1966), Carlini (1968) examined the effects of chronic treatment with cannabis extract (20 mg/kg, ip) on fighting behavior in mice. Again, the first injection of the drug was observed to suppress aggressiveness. However, by the fourth injection there were no significant differences in aggressiveness between drug-treated and control animals, suggesting that tolerance to the suppressant effects of cannabis on aggression had occurred. However, this observation was not clear cut since part of the effect was due to a reduction of aggressiveness in the control animal following repeated testing.

In a somewhat different experiment Kilbey (1971) trained mice to traverse a T maze for the opportunity to fight another mouse. Administration of Δ^9THC (1.0 and 2.5 mg/kg, iv) was observed to increase the latency to begin fighting and decrease the number of responses to the fight-rewarded side of the maze although actual running times were not significantly affected. These data thus corroborate the previous finding that cannabis attenuates inter-male aggression and indicates that this effect cannot be attributed to motor impairment.

Cherek, Thompson and Heistad (1972) have also studied the effects of Δ^9THC on the opportunity to attack another animal. In their experiment, pigeons were trained to peck one of two keys for food reinforcement on a fixed-interval 2 min schedule. This schedule has previously been shown to induce aggression in pigeons (Cherek and Heistad, 1971). To measure aggression, a target pigeon was restrained in a Plexiglas box on one side next to the experimental animal. Responses made to a second key on a fixed ratio 2

schedule, resulted in the activation of a motor that pulled a shield away, thus exposing the target bird located behind the Plexiglas screen. Following stabilization of key pecking behavior, such that the baseline rates of responding on each schedule were roughly equal, the experimental subjects were injected with Δ^9THC (0.125-1.0 mg/kg, im).

Although a dose-dependent decrease in responding on the food reinforcement schedule was observed, marked decreases in the number of target responses occurred at doses that had little or no effect on food-reinforced responding.

This latter study thus corroborates previous findings that Δ^9THC has a rather selective effect on conspecific aggression since such behavior was suppressed at doses that did not affect food reinforced responding.

A lack of tolerance to this effect of cannabis on inter-male aggression has been reported by Ham and van Noordwijk (1973) for both mice and hamsters following daily intraperitoneal doses of 50 mg/kg of Δ^8THC or 5 mg/kg of Δ^9THC. The results, however, could have been due to motor impairment and accumulation of the drug (cf. Agurell, Nilsson, Ohlson and Sandberg, 1969) rather than some direct effect of the drug on aggression. But taken in conjunction with the previous studies, this does not seem as cogent an explanation as that involving some direct action of cannabis on inter-male fighting.

An interesting study by Gonzalez, Matsudo and Carlini (1971) examined the acute and chronic effects of cannabis on the fighting behavior of siamese fighting fish (*Betta splendens*). The aggressive behavior of these fish constitutes an unconditioned, relatively stereotypic form of behavior which can be elicited reliably by the physical presence of another fish or by its own mirror image. As such, this behavioral pattern has been used to study the effects of various drugs on aggression. For example, fish treated with tranquilizers such as meprobamate, chlorpromazine, or reserpine refuse to fight (Walsazek and Abood, 1956).

In the experiment by Gonzalez and coworkers (1971), fish were placed into a test aquarium containing either 0.5 μl/ml of Δ^9THC or 1 μg/ml of cannabis extract or a control solution and 2 hr later the metal barriers separating two aquaria were removed, thus allowing the fish to see each other. "Fighting" was measured as the amount of time during a 5 min period, that the fish exhibited their characteristic aggressive display behavior. The fish were then returned to their "home" aquaria without drugs and were not tested again until the next day. Testing was then continued for the next 30 days.

Both the cannabis extract and the Δ^9THC were observed to depress fighting behavior upon acute administration. However, with chronic exposure to the drug, fighting behavior began to reach levels not different from control fish. Although the investigators report that motor coordination did not appear to be affected and the fish did react normally to stimuli, they did observe

signs of mild depression of swimming behavior on the part of drug treated animals.

As with predatory aggression, it should also be pointed out that inter-male aggression may have reinforcement value for mice and fish. Thus, if mice are interrupted at different stages of fighting, those that were winning or holding their own, are more inclined to resume fighting than are those which have been defeated (Lagerspetz, 1964). Likewise, if an opponent is placed in a goal box, the access to which involves passing over an electrified grid, animals that had previously been fighting are more likely to cross the grid than are animals that had not been previously fighting (Lagerspetz, 1964). In the case of fighting fish, it has been shown that the opportunity to engage in aggressive display activities has reinforcement properties since the frequency of behaviors that lead to visual presentation of a mirror image tend to increase with such reinforcement and extinguish when the reinforcement is withdrawn (Hogan, 1967; Goldstein, 1967; Thompson, 1963). Consequently, it is possible that the suppression of inter-male aggression produced by cannabis is due to the drug's effects on neural mechanisms underlying motivation in general (cf. Carlini, Masur, Karniol, and Leite, 1972; McGlothlin and West, 1968; Tylden, 1967; Thurlow, 1971) rather than on neural mechanisms underlying aggression per se.

SUMMARY AND CONCLUSIONS

The nature of the evidence dealing with the effects of cannabis on aggressiveness in animals is such that we must distinguish between the acute and the chronic effects of the drug and the condition of the subject at the time of drug treatment.

Given acutely, cannabis appears to have a depressant effect on aggressive behavior which is likely due to either or both its suppression of locomotor activity and depression of motivation in general. The suppressant effects of this drug on spontaneous motor activity are well known. References to an "amotivational syndrome" associated with cannabis have also begun to appear in the literature (Carlini *et al.*, 1972; McGlothlin and West, 1968; Tylden, 1967; Thurlow, 1971) and may account in part for the loss of interest in food, water, and sex as a consequence of treatment with this drug in animals (e.g., Abel and Schiff, 1969; Manning, McDonough, Elsmore, Saller and Sodetz, 1971; Scheckel, Boff, Dahhen and Smart, 1968; Merari, Barak and Plaves, 1973). Interestingly, tolerance to the effects on consummatory behavior does not seem to occur in animals although tolerance to depression of motor activity does develop following chronic treatment with cannabis (e.g., Abel, McMillan and Harris, 1974; McMillan, Harris, Frankenheim and Kennedy, 1970).

There is an exception to the observation that acute administration of cannabis suppresses aggression. If the subject is undergoing stress at the time of drug treatment, then an increase in aggressiveness may occur following acute administration of the drug. Thus rats maintained in cold environments or subjected to REM sleep deprivation or foot shock, immediately prior to or during drug treatment, exhibit increases in aggressiveness following a single injection of cannabis (Carlini *et al.*, 1972; Alves *et al.*, 1973; Carder and Olson, 1972).

In the case of prolonged food deprivation and chronic treatment with cannabis, aggressive behavior has also been observed to increase. In this regard, Carlini and his coworkers (e.g., Alves *et al.*, 1973; Alves and Carlini, 1973) have argued that cannabis possesses a dual action on behavior. Initially, they contend that acute doses produce depression of activity which "masks" the drug's other behavioral effects. With chronic treatment, however, tolerance to the drug's depressant effects develops and the previously "masked" effects begin to emerge resulting in excitatory behavior.

This hypothesis is contradicted, however, by their own data which shows that aggressive behavior will manifest itself after a single acute injection of cannabis if the animals were previously stressed (e.g., Carlini *et al.*, 1972; Alves *et al.*, 1973) and by the fact that increases in locomotor activity have been observed following acute treatment of animals with low doses of cannabis (e.g., Abel, 1970; Carlini, Santos, Claussen, Bienek, and Korte, 1970; Davis, Moreton, King and Pace, 1972). The fact that chronic treatment with cannabis does not induce aggressive behavior unless the animals are also chronically starved may simply mean that the stress associated with food deprivation takes longer to develop than does the stress arising from shock or cold. It is possible, therefore, that rather than there being a dual effect of cannabis on aggression, that there is a differential effect of cannabis on the various kinds of aggressive behavior that have been identified. Thus, cannabis appears to potentiate "irritable" aggression whereas it tends to suppress predatory and inter-male aggression. Interestingly, these latter two forms of aggression tend to be limited to particular stimulus situations and tend to have an underlying motivational basis (see above). Consequently, the effects of cannabis on these kinds of aggression may arise as a result of some indirect effect on the neural pathways underlying the motivation to be aggressive rather than directly on the neural pathways involved in these two types of aggression. Irritable aggression, on the other hand, can be evoked by a wide range of stimuli and occurs almost like a reflex in response to noxious situations. In this kind of situation, cannabis appears to be a potentiating influence.

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