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Effects of Psychodysleptics on Aggressive Behavior of Animals

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In 1943 when HOFMANN discovered *d*-lysergic acid diethylamide (LSD), psychiatrists and clinical psychologists became interested in the effects of the psychodysleptic on the brain and behavior. Since the administration of LSD produced mental and physical states that resembled the conditions of schizophrenic patients, the drug was dispensed as an adjunct in the study and treatment of mental disorders. However, as the psychiatrists and other clinicians recognized the need for basic information regarding the side effects of LSD, preclinical investigation to determine the physiological, biochemical, toxicological, and behavioral effects of the compound on laboratory animals was intensified. Moreover, the research was expanded to study the physiological and behavioral effects of other hallucinogens, such as mescaline, psilocybin, bufotenine, 2,5-dimethoxy-4-methylamphetamine (DOM), and ibogaine. One of the most interesting behavioral effects of the psychotomimetic substances studied by scores of investigators was the aggressive behavior of several species of animals. Literature published before 1966 on psychodysleptics and aggression has been reviewed as a part of a comprehensive survey on the effects of several kinds of central nervous system drugs on aggressiveness [29]. The purpose of the present review is to update the survey of the literature concerning the effects of psychodysleptics on the aggressive behavior of animals. Since most of the reports on the influence of hallucinogens on human aggression were anecdotal and the experiments were not conducted under rigorously controlled conditions, they were not included in this review.

To determine the effects of psychodysleptics on animal aggressiveness, most researchers have applied one or more of the main tests of aggression, namely isolation-induced [28, 31], shock-induced [2, 23], and predatory tests [15, 22]. Each test measures a different kind of aggressive behavior. Isolation-

Table I. Effects of LSD on aggression

Dose, mg/kg	Route	Post-injection time, min	Species	N[1]	Aggression test	Results (aggression)	Reference
0.050	i. p.	45	mouse	18	isolation-induced (14)[2]	depression, $p < 0.05$	[15]
0.250	i. p.	45	mouse	18	isolation-induced (14)	not significant	[15]
0.500	i. p.	45	mouse	18	isolation-induced (14)	depression, $p < 0.05$	[15]
0.1–0.8	i. p.	5	mouse	120	isolation-induced (35)	decrease, $ED_{50} = 0.265$ mg/kg	[28]
0.1–1.6	i. p.	15	mouse	100	isolation-induced (35)	decrease, $ED_{50} = 0.365$ mg/kg	[28]
0.2	i. p.	30–480	mouse	6	isolation-induced (28)	inhibition	[30]
0.01	oral	–	mouse (aggressive)	6	isolation-induced	increase, $p < 0.005$	[14]
0.01	oral	–	mouse (defensive)	7	isolation-induced	decrease, $p < 0.05$	[14]
0.1	i. p.	60–150	mouse	–	shock-induced	increase, $p < 0.05$	[10]
0.222	intercerebral	–	mouse	10	attack on object	increase, followed by a stuporous condition	[9]
0.002–0.030	oral	–	mouse	40–50	spontaneous	reduction	[20]
0.001–0.004	i. p.	1–10	rat	6	isolation-induced	increase	[21]
0.025–0.100	–	30	rat	–	shock-induced	increase	[1]
0.05	i. p.	30 and 120	rat	7	predatory	not significant	[15]
0.5	i. p.	30 and 120	rat	6	predatory	not significant	[15]
5.0	s. c.	20	rat	5	spontaneous	increase in 'fighting'	[19]
0.001–0.016	i. p.	15	rat	150 pairs	food competition	decrease, $p < 0.01$	[25]
0.001–0.2 mg/cat	intraventricular	3–45	cat	–	spontaneous	not significant	[32]
0.05 mg/kg	intraventricular	–	cat	–	spontaneous	hostile response	[16]
0.8 mg (per cat)	intraventricular	3–45	cat	–	spontaneous	'sham rage'	[32]

Table I (continued)

Dose, mg/kg	Route	Post-injection time, min	Species	N[1]	Aggression test	Results (aggression)	Reference
3 mg	s. c.	0–120	cat	1	spontaneous	'sham rage'	[32]
1	i. v.	1–110	rhesus monkey	8	reaction to handling	marked tameness	[7]
0.1	i. m.	–	rhesus monkey	–	biting response	not significant	[4]
1 and 5	i. m.; i. p.	–	rhesus monkey	–	biting response	inhibition	[4]
0.1, 0.2, and 0.3 μg/fish	i. m.	30	fish	10	isolation induced (7–10)	inhibition	[17]
Immersed (25 μg/ml LSD sol.)			fish	15	spontaneous	increase	[6]
Immersed in treated water (5mg/l)		120–180	newt	–	spontaneous	increase	[5]
0.03 μg/mg	i. p.	30	ant	10	predatory	not significant	[13]
0.03 μg/mg	i. p.	60	ant	10	predatory	decrease, $p < 0.01$	[13]
0.03 μg/mg	i. p.	180	ant	10	predatory	decrease, $p < 0.01$	[13]
0.025–0.1 μg/mg	oral	60–180	ant	10	predatory	decrease, $p < 0.05$	[10]

[1] N refers to the total number of animals tested.
[2] The numbers in parentheses denote the total number of isolation days.

induced aggression is observed when a mouse, housed individually for 3 or 4 weeks, spontaneously attacks an intruding mouse placed in the home cage of the former. The shock-induced aggression, described sometimes as 'fighting' is considered to be *defensive* behavior. It is aroused in a pair of rats via an electric foot-shock that both animals are subjected to while they are in a shock-box. In a predatory situation, a predator, i. e. a rat, attacks and kills an interspecific victim (e. g. a mouse) when the latter is introduced into the resident cage of the predator. A few investigators have studied the effects of hallucinogens on aggression by confronting an animal with an object [4, 9] or by grouping together strange conspecific subjects and observing spontaneous aggression [16, 20].

LSD Studies

The survey of the literature revealed that LSD was bioassayed more often than any of the other psychodysleptics. Numerous investigators evaluated the psychotogenic drug in several species and in various aggression tests. In order to facilitate comparison the relevant experimental conditions, procedures and results of the published LSD studies were summarized, tabulated, and listed in the order of species (table I). The data show that many doses of lysergide were evaluated by different routes, and the behavioral tests were conducted at numerous postinjection times. Some LSD experiments were conducted with a few subjects, while others were performed with a substantial number, e. g. 150 pairs [25]. The psychotogenic drug decreased aggressive behavior of mice in the majority of the mouse experiments and it increased aggression in only three studies. Most investigators who tested rats or cats reported that LSD increased aggression. However, EVARTS [7] and also CHEN and WESTON [4] found that the dose of 1 mg produced tameness in rhesus monkeys. The difference between the responses shown by the rat, by the cats, and by the monkeys might have been due to species difference. Although in most of the mouse studies results of a statistical test of significance or dose-response analysis have been reported, in most of the rat, cat, and monkey studies the results of a statistical analysis have not been published.

Mescaline Studies

The reports on the influence of mescaline on aggressiveness are summarized in table II. All the mouse studies except one have shown that mescaline

Table II. Effects of mescaline on aggression

1–30	i. p.	23	mouse	120	isolation-induced (35)[2]	decrease, $ED_{50} = 5.413$ mg/kg	[26]
5	i. p.	30–480	mouse	6	isolation-induced (28)	inhibition	[30]
10 and 50	i. p.	–	mouse	–	isolation-induced	inhibition	[11]
0.4	intercerebral	–	mouse	10	attack on object	increase; followed by 10 min depression	[9]
2.2	intercerebral	–	mouse	10	attack on object	inhibition; depression	[9]
50	i. p.	20	rat	8 pairs	shock-induced	prolonged the attacks, $p < 0.05$	[18]
50	i. p.	15	rat	8	shock-induced	increase in duration of aggressiveness; $p < 0.05$	[3]
10 and 50	i. p.	–	rat	–	predatory	not significant	[11]
1–3 mg in 0.5 ml of 0.5% saline	intraventricular	30	cat	5	predatory	inhibition	[22]
1 mg/kg	intraventricular	–	cat	–	spontaneous	not significant	[16]
0.1, 0.2, and 0.3 μg/fish	i. m.	30	fish	10	isolation-induced (7–10)	inhibition	[17]

[1] N refers to the total number of animals tested.
[2] The numbers in parentheses denote the total number of isolation days.

Table III. Effects of psychodysleptics on aggressive behavior

Dose, mg/kg	Route	Post-injection time, min	Species	N[1]	Aggression test	Results (aggression)	Reference
Adrenochrome							
0.6	intraventricular	4	cat	–	spontaneous	not significant	[16]
Bufotenine							
10	i. p.	30	mouse	18	isolation-induced (14)[2]	not significant	[12]
10	i. p.	90	mouse	18	isolation-induced (14)	not significant	[12]
10	i. p.	30	mouse	18	isolation-induced (28)	not significant	[12]
10	i. p.	90	mouse	18	isolation-induced (28)	decrease, $p < 0.01$	[12]
5–30	oral	–	mouse	40–50	spontaneous	decrease	[20]
10	i. p.	45	rat	16	predatory	decrease, $p < 0.001$	[12]
5	i. v.	1–105	rhesus monkey	8	reaction to handling	marked tameness	[7]
10	i. m.; i. v.	–	rhesus monkey	–	biting response	inhibition	[4]
2,5-Dimethoxy-4-methylamphetamine (DOM)							
0.4–1.2	i. p.	40	rat	60 pairs	food competition	dose-dependent decrease	[27]
Ibogaine							
10	i. p.	30	mouse	18	isolation-induced (14)	not significant	[12]
10	i. p.	90	mouse	18	isolation-induced (14)	decrease, $p < 0.01$	[12]
10	i. p.	30	mouse	18	isolation-induced (28)	not significant	[12]
10	i. p.	90	mouse	18	isolation-induced (28)	not significant	[12]
20	i. p.	30–480	mouse	6	isolation-induced (28)	inhibition	[30]
10	i. p.	45	rat	12	predatory	not significant	[12]

Table III (continued)

Dose, mg/kg	Route	Post-injection time, min	Species	N[1]	Aggression test	Results (aggression)	Reference
N-*methyl-3-piperidyl-benzilate (JB-336)*							
5	i. p.	30	mouse	18	isolation-induced (14)	decrease, $p < 0.02$	[12]
5	i. p.	90	mouse	18	isolation-induced (14)	not significant	[12]
5	i. p.	30	mouse	18	isolation-induced (28)	not significant	[12]
5	i. p.	90	mouse	18	isolation-induced (28)	decrease, $p < 0.01$	[12]
5	i. p.	45	rat	12	predatory	not significant	[12]
10	i. p.	45	rat	12	predatory	decrease, $p < 0.01$	[12]
Phencyclidine							
1	i. p.	45	mouse	18	isolation-induced (14)	decrease, $p < 0.05$	[15]
1	i. p.	45	mouse	18	isolation-induced (28)	not significant	[15]
5	i. p.	45	mouse	15	isolation-induced (14)	increase, $p < 0.05$	[15]
5	i. p.	45	mouse	15	isolation-induced (28)	not significant	[15]
5	i. p.	30 and 120	rat	7	predatory	not significant	[15]
0.3–15	i. m.	3–240	rhesus monkey	–	biting response	inhibition	[4]
1.5	i. m.	15–120	rhesus monkey	25	spontaneous	decrease	[8]
Psilocybin							
1–8	i. p.	30	mouse	80	isolation-induced (35)	decrease $ED_{50} = 2.096$ mg/kg	[26]
10	i. p.	30	mouse	15	isolation-induced (14)	not significant	[12]
10	i. p.	90	mouse	15	isolation-induced (14)	decrease, $p < 0.05$	[12]
10	i. p.	30	mouse	15	isolation-induced (28)	not significant	[12]
10	i. p.	90	mouse	15	isolation-induced (28)	decrease, $p < 0.01$	[12]
10	i. p.	45	rat	12	predatory	decrease, $p < 0.001$	[12]

[1] N refers to the total number of animals tested.

[2] The numbers in parentheses denote the total number of isolation days.

decreased aggressive behavior. According to the observation of HALEY [9], a low dose of 0.4 mg/kg temporarily increased aggression in mice; however, a higher dose of 2.2 mg/kg inhibited biting response. Although KOSTOWSKI and REWERSKI [11] found that the intraperitoneal injection of 50 mg/kg of mescaline had no significant effect in a 'killer rat test', SBORDONE and CARDER [18] reported that a similar administration of the hallucinogen significantly prolonged the 'attacks' of 8 pairs of rats subjected to foot-shock pain. Other research indicated that mescaline inhibited predatory response in cats [22] and isolation-induced aggression in fish [17].

Various Psychodysleptics

The data on the effects of other psychodysleptics, namely adrenochrome [24], bufotenine, DOM, ibogaine, *N*-methyl-3-piperidyl-benzilate (JB 336), phencyclidine, and psilocybin are summarized in table III. The drugs are arranged in alphabetical order and the results of the experiments are grouped on the basis of species. Most compounds at various doses decreased aggression in mice, rats, and rhesus monkeys. Some experiments have shown that the differential effects of some identical compounds on the same species were due to not only difference in dose but also difference in postinjection testing time and predrug housing conditions. For example, KOSTOWSKI *et al.* [12] observed that when a group of mice were isolated for 28 days and tested 30 min after intraperitoneal injection of 10 mg/kg of bufotenine, their aggressiveness, scored in terms of frequency of attack was not significantly different from that of the control group. But, when a similar group of mice, isolated for the same period, were injected in an identical manner and tested *90* min after treatment, they showed a significant decrease in aggression (table III). KOSTOWSKI *et al.* [12] also reported that a group of mice isolated for 14 days, injected with 10 mg/kg (i. p.) of ibogaine and tested 90 min later, revealed a significant decrease in attack behavior. However, another identical group of mice, isolated for *28* days and given the same treatment of ibogaine and tested under similar conditions, showed no significant alteration in aggression.

The results of most studies indicated that psilocybin significantly decreased aggression (table III). UYENO [26] found that isolated albino Swiss-Webster male mice injected with 8 mg/kg of psilocybin and tested 30 min after the treatment significantly decreased attack behavior. However, KOSTOWSKI *et al.* [12] noted that 10 mg/kg of the psychotomimetic had no

significant effect on isolated albino Swiss male mice tested after a similar postinjection time. The discrepancy is probably due to the difference in the type of sample (method of selection of subjects) and in the test procedure. UYENO equated the experimental and control groups in terms of initial or predrug aggressive behavior, whereas KOSTOWSKI *et al.* used groups that were not equated. In UYENO's study, each isolated animal injected with psilocybin or saline was confronted by a nonisolated, noninjected mouse, whereas in the experiment of KOSTOWSKI *et al.*, 3 isolated animals were pitted simultaneously.

Conclusion

The findings of the studies examined in this review indicate that a high percentage of the psychodysleptics produced a decrease in aggressive behavior. Although a majority of the investigators found that LSD decreased aggression in mice and in rhesus monkeys, some researchers observed that it increased aggressiveness in rats and cats. Most of the LSD studies reporting an increase in aggression was conducted with only a few subjects. Moreover, the results of a statistical test of significance or of a dose-response analysis of 3 or more doses were not published. Therefore, it is difficult to interpret the results and deduce definite conclusions regarding the increase.

Since mental illness is often manifested in an unreasonably aggressive or hostile manner in which an individual interacts with others, it is pertinent to determine at the preclinical stage whether or not a new candidate compound to be tested in a clinic has any effect on aggression. Therefore, a reliable and valid animal aggression test, such as the mouse isolation-induced test and the rat predatory test, is considered to be an integral part of a battery of preclinical screening tests.

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