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Irritable Aggression Induced by Δ^9-Tetrahydrocannabinol in Rats Pretreated with 6-Hydroxydopamine

MICHIHIRO FUJIWARA,[1] YASUFUMI KATAOKA, YOZO HORI AND SHOWA UEKI

Department of Pharmacology, Faculty of Pharmaceutical Sciences Kyushu University 62, Fukuoka 812, Japan

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FUJIWARA, M., Y. KATAOKA, Y. HORI AND S. UEKI. *Irritable aggression induced by Δ^9-tetrahydrocannabinol in rats pretreated with 6-hydroxydopamine.* PHARMACOL BIOCHEM BEHAV **20**(3) 457–462, 1984.—Administration of Δ^9-tetrahydrocannabinol (THC) to grouped rats injected intraventricularly with 6-hydroxydopamine (6-OHDA) produced violent fighting accompanied by remarkable hyperirritability. This behavior was induced reproducibly from the 10th to 100th postoperative days. It was shown that this irritable aggression could be measured continuously and quantitatively in terms of degree of activity and/or vocalization using a newly designed analyzer. The effect of THC differed markedly from the action of apomorphine and methamphetamine in 6-OHDA pretreated rats. Apomorphine induced irritable aggression but not vigorous vocalization. On the other hand, methamphetamine induced much less irritable aggression than apomorphine-induced aggression. It is assumed that a THC-invoked imbalance in catecholamine agonistic and serotonin antagonistic action brought about by activation of supersensitized catecholaminergic receptor was operating to produce the aggression. Specifically, hypoactivity of serotonergic neurons might play a key role in the occurrence of THC-induced irritable aggression.

Tetrahydrocannabinol Irritable aggression 6-Hydroxydopamine Rat

Δ^9-TETRAHYDROCANNABINOL (THC), the main active ingredient of cannabis, produces an increase in spontaneous locomotion in the rat when given in low doses and, conversely, bizzare behavior such as catalepsy, walking backward and pivoting when given in high doses. After THC treatment, rats exhibit sedation and crouch down in a corner of the cage. Body contact often causes a squealing or hissing. Carlini *et al.* [2,3] reported that chronic administration of cannabis extract for 2 weeks to rats housed two per cage induced fighting between cagemates. It was also found that a single dose of cannabis extract produced similar fighting in rats deprived of REM sleep for 4 days.

We [12] have previously reported that administration of THC to rats housed individually caused hyperirritability as well as the manifestation of aggressive behavior toward inanimate (rod) and animate (mouse and rat pup) objects. These forms of aggression persisted for over 100 days after the treatment as long as isolation was maintained [12]. In contrast, rats housed in groups of 5 per cage never exhibited these types of aggressive behavior following THC treatment, indicating that isolated housing is an important factor in the manifestation of THC-induced aggression [10, 13, 22]. We then discovered that administration of THC to group-housed rats in which brain serotonin (5-HT) had been depleted by treatment with p-chlorophenylalanine or 5,6-dihydroxytryptamine induced only muricide but not appreciable signs of irritable aggression [9]. We also found that administration of THC to rats in which brain catecholamine neurons had been destroyed by 6-hydroxydopamine produced remarkable hyperirritability and squealing rather than muricide (Fig. 1). In the present study, irritable aggression such as vigorous activity and vocalization induced by THC was objectively recorded using a newly designed apparatus and was compared with those aggressive behaviors induced by apomorphine and methamphetamine.

METHOD

Subjects

Male Wistar rats weighing 200–250 g at the time of surgery were supplied by Kyushu Laboratory Animals. The animals were anesthetized with pentobarbital (30 mg/kg IP) and placed in a stereotaxic apparatus (Narishige). 6-Hydroxydopamine hydrobromide (6-OHDA) (Sigma) dissolved in 20 μl of 0.9% of saline containing 0.1% ascorbic acid, was injected via a 35-gauge cannula into each of the lateral ventricles of the brain according to the stereotaxic atlas of König and Klippel [18]. 6-OHDA (250 μg×2) was

[1]Requests for reprints should be addressed to M. Fujiwara at the present address: Department of Pharmacology, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka 814-01, Japan.

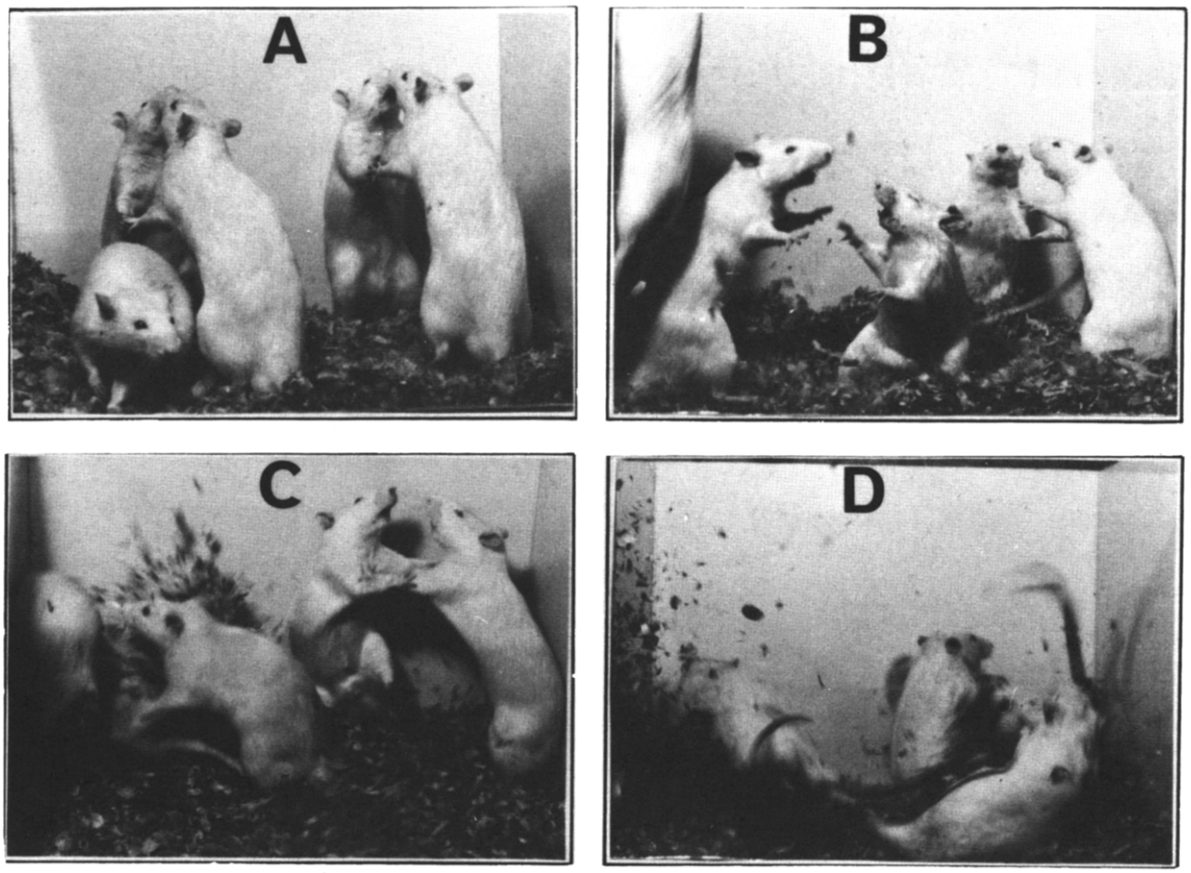

FIG. 1. THC-induced irritable aggression in 6-OHDA-treated rats, grouped together. After administration of THC 6 mg/kg IP, rats displayed mutual rearing accompanied by hissing (A) and even slight physical contact between cagemates elicited a sudden reflexive response of violent squealing and jumping (B, C). Subsequently, all five rats ran widely around the box (D).

injected successively into each of the lateral ventricles at an interval of 48 hr. Coordinates for the injection were AP −1.0 mm from bregma, ML±2.0 mm from midline, and DV −4.0 mm from the surface of the skull. The injection rate was 20 μl/min, with the cannula left in place for one additional minute to allow diffusion of the drug.

After surgery, 5 animals in each group were housed in plastic cages (30×35×17 cm) with free access to food and water and maintained on a 12 hr light-dark schedule (lights on 0700–1900 hr) at a temperature of 23±1°C.

Apparatus

The action analyzer (Kyushu Keisokuki, QAZ-502) used was newly designed to quantitatively and continuously record the behavior of the animals. A schematic diagram of the action analyzer is shown in Fig. 2. A minor-tremor pickup (MT pickup, Brüel and Kjoer, MT-3T) was installed in the center of the bottom of an acrylresin box (35×40×32 cm) in order to measure the vibrations of the box floor caused by violent activity of the rats. Activity is herein defined as hyperemotional behavior including fighting, jumping, struggling and running in the box, although the animals rarely exhibited attack behavior and biting. Squealing was measured using a microphone (SONY, EM-280) attached to the upper portion of the box. The entire action analyzer was housed within a sound-attenuated cubicle.

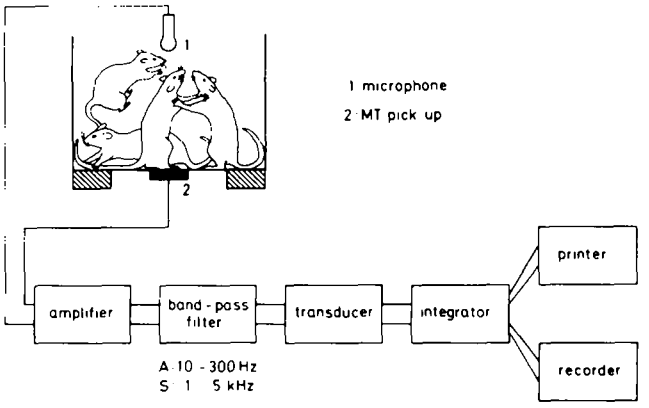

FIG. 2. Schematic diagram of action analyzer.

Impulses generated by activity and squealing of the rats via MT pickup and microphone, respectively, were amplified and passed through the band-pass filter. The frequency bands of activity and squealing were a 10–300 Hz and 1–5 kHz, respectively. Each output of the filter was transmitted to the transducer and, afterward, each integrated value of activity and squealing calculated by the integrator was recorded every 5 min as a digital and as an analog scale using a

printer (Nada, DP-102) and recorder (Watanabe Sokki, SR-6100). To avoid interference from any unrelated noise including locomotion, rearing, preening, grooming, head and body shaking etc. in the measurement of vibration of the box, the sensitivity of the action analyzer was regulated so that counts less than 100 per 5 min could not be detected even with five intact rats simultaneously exploring in the observation box. Similarly, in the measurement of squealing, sounds caused by exploration and contact with the walls of the box were not detected.

Preliminary frequency analysis showed that about 80% of squealing of rats was localized in a frequency range of 1500–2000Hz following administration of THC to 6-OHDA-treated rats which produced remarkable hyperirritability. Since the frequency range of squealing established in the present study was similar to that used by Gianutsos *et al.* [14], it was concluded that this range was a reliable measure of squealing when aggressive behavior appeared in aggregated rats [11].

Drugs

The drugs used in the experiment were THC, apomorphine hydrochloride (powder, Fujisawa) and methamphetamine hydrochloride (Philopon Powder, Dainippon). THC was isolated from the cannabis extract in the Department of Pharmacogosy, Kyushu University [19] and emulsified in a 1% Tween 80 solution. Apomorphine and methamphetamine were dissolved in distilled water. All drugs were adjusted to obtain a uniform dosage volume of 0.1 ml per 100 g body weight and administered IP except for apomorphine which was injected SC.

Procedure

Experiments were performed with five rats per cage. Before the administration of drugs, rats treated with 6-OHDA were placed in the observation box with five cagemates for 15 min in order to adapt to the experimental condition. The integrated values for activity and squealing were recorded of 2 sec intervals continuously during the adaptation period. Subsequently, each drug was administered to each rat and activity and squealing measures were take over 3 or 4 hr. THC was injected into the same 10 groups (composed of five rats each) at the assigned test time of 10, 30, 50, 70 and 100 days after treatment with the second injection of 6-OHDA. Furthermore, the first injection of THC was performed in the same rats 100 days after 6-OHDA treatment in order to compare these with rats who received their first injection 10 days after 6-OHDA. Apomorphine and methamphetamine were administered to 8 groups each (both composed of 5 rats each) 100 days after 6-OHDA-treatment. Non-lesioned rats, as the control group, were treated with each drug in the same manner as 6-OHDA-treated rats.

Assay of Catecholamine and Serotonin

Following completion of behavioral test, the brain contents of noradrenaline (NA), dopamine (DA) and serotonin (5-HT) was assayed to confirm the adequacy and pattern of amine depletions by 6-OHDA. Six intact rats and 5 rats administered the first 6 mg/kg dose of THC IP 100 days after 6-OHDA treatment were sacrificed by decapitation 10 days after THC treatment and the brains were quickly removed and placed on ice. Brains were dissected into the cortex striatum, thalamus + hypothalamus and midbrain excluding the subthalamus according to the method of Glowinski and Iversen [15]. NA and DA were extracted in 0.4 N perchloric acid, purified by modification of the alumina absorption method according to Anton and Sayre [1], and assayed by the trihydroxyindole method of Chang [5]. 5-HT was assayed by the method of Snyder *et al.* [21].

Statistical Analysis

The statistical significance of the data obtained was assessed by paired and Student's *t*-test (two-tailed). In those cases where there was unequal variance between groups the data were analyzed by Welch's *t*-test (two-tailed).

RESULTS

Ten days after 6-OHDA treatment, rats exhibited hyperirritability accompanied by squealing and violent activity when they were grasped by gloved hands. After that, rats placed in the observation box showed similar behavior to that of control rats in the absence of external stimulation. Even vibrations (activity) arising from violent movement involved in hypersexual behavior, such as mounting and mating, only resulted in about 300 counts/5 min. Moreover, rats treated with 6-OHDA alone did not exhibit squealing at all. In contrast, about 10 min after IP injection of 6 mg/kg of THC, even slight physical contact between cagemates elicited a reflexive response of violent squealing and jumping. All five rats ran randomly and rapidly around the box and subsequently displayed simultaneous rearing behvavior accompanied by hissing. Soon after episodes of rearing and hissing, the rats once again showed repeated occurrences of remarkable hyperirritability characterized by violent and sudden jumping. This bizzare aggressive behavior induced by THC in grouped rats treated with 6-OHDA, is shown in Fig. 1.

This hyperirritability was maximal 60 min after THC and at that time, activity increased to over 2,000 counts/5 min and squealing increased to over 1,500 counts/5 min. The aggression then diminished with the passage of time, and after 24 hr, the rats returned to a behavioral state similar to that before THC administration (Fig. 3A).

Table 1 compares the total number of integrated counts every two seconds obtained for activity and squealing during 2 hr periods following THC administration 10, 30, 50, 70 and 100 days after 6-OHDA treatment. Incidence of THC-induced aggression appeared topographically the same at each period after 6-OHDA treatment. However, the total number of activity counts and squeals over the 2 hr observation period decreased gradually from 30 days after 6-OHDA treatment, although there was no significant difference between the values obtained at any of the assigned testing intervals for either activity or squealing (Table 1).

When the first injection of THC (6 mg/kg IP) occurred 100 days after 6-OHDA treatment, rats also displayed aggressive behavior as described above. In this case, THC evoked aggression developed slower with respect to the peak time of effect and the number of activity counts and squeals tended to be smaller than the rats whose first THC injection was given 10 days after 6-OHDA treatment. Intact rats, on the other hand, when administered THC, lay prostrate and locomoted only with great difficulty, so that activity was about 50 to 100 counts/5 min at most and squealing was not manifested at all.

Two to 3 min after injection of 5 mg/kg of apomorphine SC to intact rats (group=6), increases in locomotor activity and signs of stereotyped behavior such as licking, gnawing

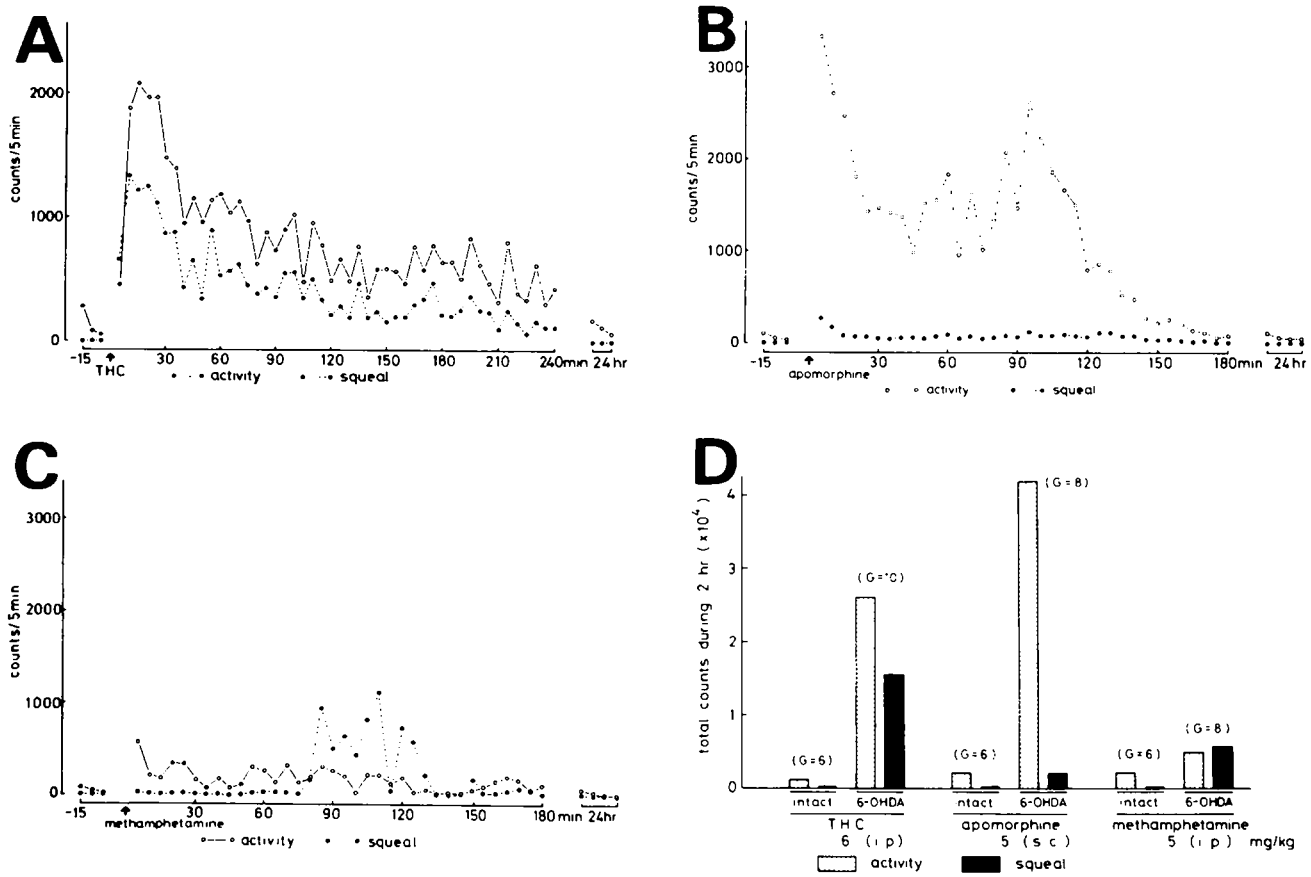

FIG. 3. Time course of aggressive behavior induced by (A) THC (6 mg/kg), (B) apomorphine (5 mg/kg) and (C) methamphetamine (5 mg/kg) in 6-OHDA-treated rats. Each point represents the average counts of activity (○ - ○) and squealing (● - ●) per 5 min. (D) Total counts during 2 hr of activity and squealing in intact rats and 6-OHDA-treated rats administered THC, apomorphine and methamphetamine.

TABLE 1

	No. of Group	Total Counts/2 hr Activity	Squealing
Intact	6	1222 ± 257	0 ± 0
6-OHDA Treated			
10 Days	10	36776 ± 11740	25512 ± 4810
30 Days	10	30629 ± 7010	24423 ± 3801
50 Days	10	25370 ± 6285	22399 ± 4294
70 Days	10	26780 ± 7418	17957 ± 4609
100 Days	10	26019 ± 6660	15369 ± 4163
First Injection 100 Days	10	14207 ± 1660	15645 ± 3245

THC-induced changes in activity and squealing at various intervals after 6-OHDA pretreatment. Total counts obtained for activity and squealing during 2 hr following IP injection of 6 mg/kg of THC at 10, 30, 50, 70 and 100 days after intraventricular administration of 6-OHDA (250 μg×2 times). Six and ten groups (composed of 5 rats each) were used for experiment of intact and THC injection, respectively. Values given represent the mean ± S.E.M.

and sniffing were observed. The response was most prominent after 30–60 min. Activity over 2 hr after drug administration was 2,123±499 counts/2 hr, whereas squealing was minimal at 36±8 counts/2 hr. In rats injected SC with 5 mg/kg of apomorphine 100 days after 6-OHDA treatment (group=8), a marked increase in locomotor activity and signs of aggression, such as biting and jumping, were manifested immediately. Activity at this time increased dramatically to 41,431±6,212 counts/2 hr. Squealing, however, measured only 1,967±400 counts/2 hr, much milder than that obtained after THC administration (Fig. 3B and D). Apomorphine-induced aggression was characterized by jumping attacks and "boxing" among cagemates and differed from THC-induced aggression in that 6-OHDA-treated rats remained in an upright posture after THC administration. As can be seen in Fig. 3B, the incidence of this behavior decreased 20 min after apomorphine, increased again about 90 min after injection and finally disappeared 2 hr after apomorphine administration.

In general, intraperitoneal injection of 5 mg/kg of methamphetamine to intact rats (group=6) produced an increase in locomotor activity (Fig. 3D). However, this effect almost completely disappeared 30 min after treatment and stereotyped behavior, including licking, head movement and

TABLE 2

	Control (n=6)	6-OHDA (n=5)	% of Control
5-HT (μg/g tissue)			
Cortex	0.42 ± 0.02	0.42 ± 0.03	100
Striatum	0.78 ± 0.02	0.79 ± 0.03	101
Thalamus + Hypothalamus	1.33 ± 0.08	1.43 ± 0.09	108
Midbrain	0.90 ± 0.06	0.82 ± 0.03	91
NA (μg/g tissue)			
Cortex	0.263 ± 0.012	0.004 ± 0.002*	1.5
Thalamus + Hypothalamus	0.80 ± 0.10	0.07 ± 0.02*	9
Midbrain	0.32 ± 0.01	0.04 ± 0.01*	13
DA (μg/g tissue)			
Striatum	9.33 ± 0.71	1.79 ± 0.16*	19

*Significantly different from controls ($p<0.001$).

Levels of serotonin (5-HT), noradrenaline (NA) and dopamine (DA) in rats' brain after intraventricular injection of 250 μg×2 6-hydroxydopamine (6-OHDA). Six of intact rats and five rats administered the first THC (6 mg/kg IP) 100 days after 6-OHDA treatment were used for assay. Values given represent the mean ± S.E.M.

sniffing, appeared. These stereotyped behaviors were not detected as activity in the measurement of vibration of the box, and also disappeared after 2 hr. Activity during this period was 2,131±278 counts/2 hr, but squealing was very low as 24±11 counts/2 hr.

On the other hand, immediately after administration of methamphetamine to 6-OHDA-treated rats (grouped=8), the animals exhibited mutual rearing and fighting to a mild degree. At the same time, stereotyped behavior, such as sniffing and licking, was observed while no changes in locomotor activity occurred and no squealing appeared. However, mutual rearing and fighting postures accompanied by squealing were observed around 90 min after methamphetamine injection (Fig. 3C). Methamphetamine-induced activity and squealing in 6-OHDA-treated rats were 4,878±2,259 counts/2 hr and 5,594±5,254 counts/2 hr, respectively (Fig. 3D).

Table 2 shows the regional concentrations of NA, DA and 5-HT in the brain of control rats and in rats injected with 6-OHDA 110 days prior to sacrifice. After treatment with two doses of 6-OHDA, NA and DA were severely depleted (2–20% of control) in all regions of the brain in which the amines were measured while 5-HT did not change.

DISCUSSION

Administration of THC to 6-OHDA-treated grouped rats produces fighting accompanied by hyperirritability from 10 to 100 days after the chemical lesions. In this experiment, it was shown that this bizarre aggression could be measured objectively by a newly designed action analyzer. This action analyzer appears to be very useful in recording this type of aggression because many indices, such as intensity and duration of effect, used for evaluating drug effects in grouped rats are obtained continuously and quantitatively.

The rats treated with only 6-OHDA were similar in appearance to intact rats as long as external stimulation such as handling or light tapping on the back was not applied. They did not show increased irritability or aggression between cagemates. Administration of THC alone to intact grouped rats produced sedation and catalepsy and the animals manifested squealing only when they were handled. However, when THC was administered to 6-OHDA-treated rats, physical contact between cagemates reflexively elicited violent squealing and the animals ran around the cage. This hyperirritability was not accompanied by biting among cagemates. Another characteristic feature was that this aggression could be readily induced by the sound of clapping or by gentle blowing a stream of air onto the rat.

In comparison to THC-induced hyperirritability, administration of apomorphine to 6-OHDA-treated rats produced combative behavior, including goal-directed biting until bleeding occurred between cagemates; squealing was not seen and only activity was markedly intensified. In this respect, apomorphine-induced aggression is qualitatively different from that induced by THC. Administration of methamphetamine to 6-OHDA-treated rats caused fighting accompanied by hyperactivity and stereotyped behavior and the occurrence of squealing. However, the degree of this increase was so slight that it could not be compared to the augmentation of activity and squealing evoked by THC. These results demonstrate that the effect of THC in 6-OHDA pretreated rats markedly differs from the action of apomorphine and methamphetamine.

It has been previously shown that administration of parachlorophenylalanine and 5,6-dihydroxytryptamine, which selectively reduce brain 5-HT, produced marked muricide and rod-attack behavior, and were enhanced by concomitant treatment with THC. However, no appreciable signs of irritable aggression appeared [9,11]. In this respect, the irritable aggression which was not accompanied by appreciable muricide or rod-attack behavior were not produced by THC

until rats were pretreated with 6-OHDA. On the other hand, it has been shown in both biochemical [7] and behavioral studies [23] that dopamine receptors in the striatum become supersensitive after nigro-striatal dopaminergic neurons were selectively lesioned by microinjection of 6-OHDA into the substantia nigra. In fact, the present experiment demonstrated that a relatively small dose of apomorphine (5 mg/kg) produced extensive fighting in rats treated with 6-OHDA. However, it has been reported that this form of fighting in intact rats was only induced by doses as high as 20 mg/kg of apomorphine [17]. Furthermore, a type of aggression similar to that observed in this study has been known to be produced by THC in rats made dependent upon morphine, a pharmacological state which may also induce supersensitivity in dopamine receptors [4, 6, 8]. Therefore, supersensitivity of catecholaminergic, especially dopaminergic receptors, is considered to be a necessary but not sufficient condition for the occurrence of THC aggression. The aggression induced by apomorphine and methamphetamine in 6-OHDA-treated rats was qualitatively different from THC-induced aggression. Therefore it must be considered that other factors in addition to the catecholaminergic mechanism participate in the appearance of THC-aggression.

There are many reports that THC causes an increase in the turnover rate of NA and DA without changing the basal levels [16]. Sofia *et al.* [20] reported that there was an increase in brain 5-HT with a concomitant decrease in synthesis rate, i.e., a decrease in the turnover rate of 5-HT following the injection of THC. Therefore, an imbalance in catecholaminergic and serotonergic activity in conjunction with hyperactivity in catecholaminergic receptors and hypoactivity in serotonergic neurons evoked by THC may play an important role in the occurrence of THC-aggression in 6-OHDA-treated rats.

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