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Cannabimimetic Activity in Rats and Pigeons of HU 210, a Potent Antiemetic Drug

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FERRARI, F., A. OTTANI AND D. GIULIANI. *Cannabimimetic activity in rats and pigeons of HU 210, a potent antiemetic drug.* PHARMACOL BIOCHEM BEHAV **62**(1) 75–80, 1999.—Preliminary behavioral experiments in rats with the cannabinoid agonist HU 210 (12.5–100 μg/kg IP) showed that it has a potent cannabimimetic profile similar to that of Δ^9THC; the drug dose dependently depressed locomotor activity, rearing, and grooming and elicited vocalization and circling at the highest doses. In subsequent studies on pigeons, HU 210 (12.5–50 μg/kg SC) confirmed its sedative effects; it also afforded protection against vomiting induced by cisplatin (7.5 mg/kg IV) and emetine (20 mg/kg SC) and emetine-induced head shake. © 1998 Elsevier Science Inc.

Cannabinoids HU 210 Emesis Cisplatin Emetine Sedation Vocalization Circling Head shake Rats Pigeons

MANY cannabinoids, the principal chemical entities of marijuana (13), display antinociceptive, anticonvulsant, hypothermic, and antiemetic properties (8,20), besides producing well-known psychotropic effects (6). However, it is difficult to separate their therapeutic activities from undesirable side effects (2), and this limits their potential clinical usefulness (19). At present, only Δ^9-tetrahydrocannabinol (Δ^9THC) and nabilone are in common use as antinauseants and antiemetics in patients treated with chemotherapy (20).

It is established that cannabinoid-induced behavioral and physiological effects are linked to changes in the function of neurotransmitters (1,23,26,27,29) and neuroendocrine (4,7,18) systems; recently, specific binding sites have been discovered in the brain and in periphery (3,5,15,16,22,24), and their activation seems to be primarily responsible for cannabinoid activity. In fact, experimental studies have demonstrated a high degree of correlation between the ability to bind to cannabinoid receptors and drug efficacy in producing in vivo effects (3,22). These findings have prompted researchers to synthesize and test many compounds with the aim of discovering novel cannabinoids with enhanced selectivity of pharmacological action (22). Because there are many similarities between the effects of cannabinoids in animals and in humans (2,22), the present work was undertaken to investigate, in laboratory animals, the antiemetic activity of HU 210, a potent synthetic cannabinoid agonist (4,21,25). Our experiments were performed on pigeons in which vomiting was induced by cisplatin (8,28,32) or emetine (32). To establish whether antiemesis would occur at doses similar to or lower than those inducing other cannabinoid effects, we evaluated, in rats, additional behavioral parameters, namely, sedation, rearing, grooming, vocalization, and circling (17), that fulfill the criteria for determining a cannabimimetic profile. HU 210 sedative effects were also investigated in pigeons.

METHOD

Animals and General Behavioral Procedure

The subjects were male SPF-Wistar rats (Harlan Nossan, Udine, Italy), weighing 200–230 g at the outset, and mixed-breed pigeons of both sexes (Morini, S. Polo d'Enza, RE, Italy), weighing 330–360 g. The animals were housed in groups of six with food and water ad lib, and on a 12-h light cycle, from 0700 to 1900 h, for at least 1 week prior to the start of the experiments. Rats and pigeons were denied food and water during the observation periods.

The experiments were performed between 0900 and 1400 h in a sound-proof, air-conditioned room, where the animals

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were monitored by trained observers unaware of the treatment schedule. The controls were handled in the same way as the treated animals and received vehicle injections.

Locomotor Aactivity, Grooming, Rearing, Vocalization, and Circling in Rats

Behavioral evaluations were carried out on groups of animals (three to four per group, homogeneous as regards treatment) placed in the middle of glass observation cages (40 × 30 × 34 cm) on the day of the experiment, 50 min after the intraperitoneal (IP) injection of HU 210 (12.5, 25, 50, or 100 μg/kg) or vehicle.

The test started as soon as the animals were in place in the observation cages. Locomotor activity was scored as described elsewhere (10), each rat being observed for 30 s at 5-min intervals and rated on a scale 0–2 where: 0 = absent, 1 = discontinuous exploratory behavior, and 2 = uninterrupted locomotor activity for at least 25 s. This evaluation, although simple, gives data in line with those obtained using an actimeter (10) and allows the contemporaneous assessment of other parameters, namely grooming and rearing.

Grooming was evaluated according to Gispen et al. (14). In brief, an observer recorded every 15 s whether or not each rat displayed the phenomenon defined as face and body washing, scratching, licking paws, or tail. If one of these signs was observed, a positive score was given.

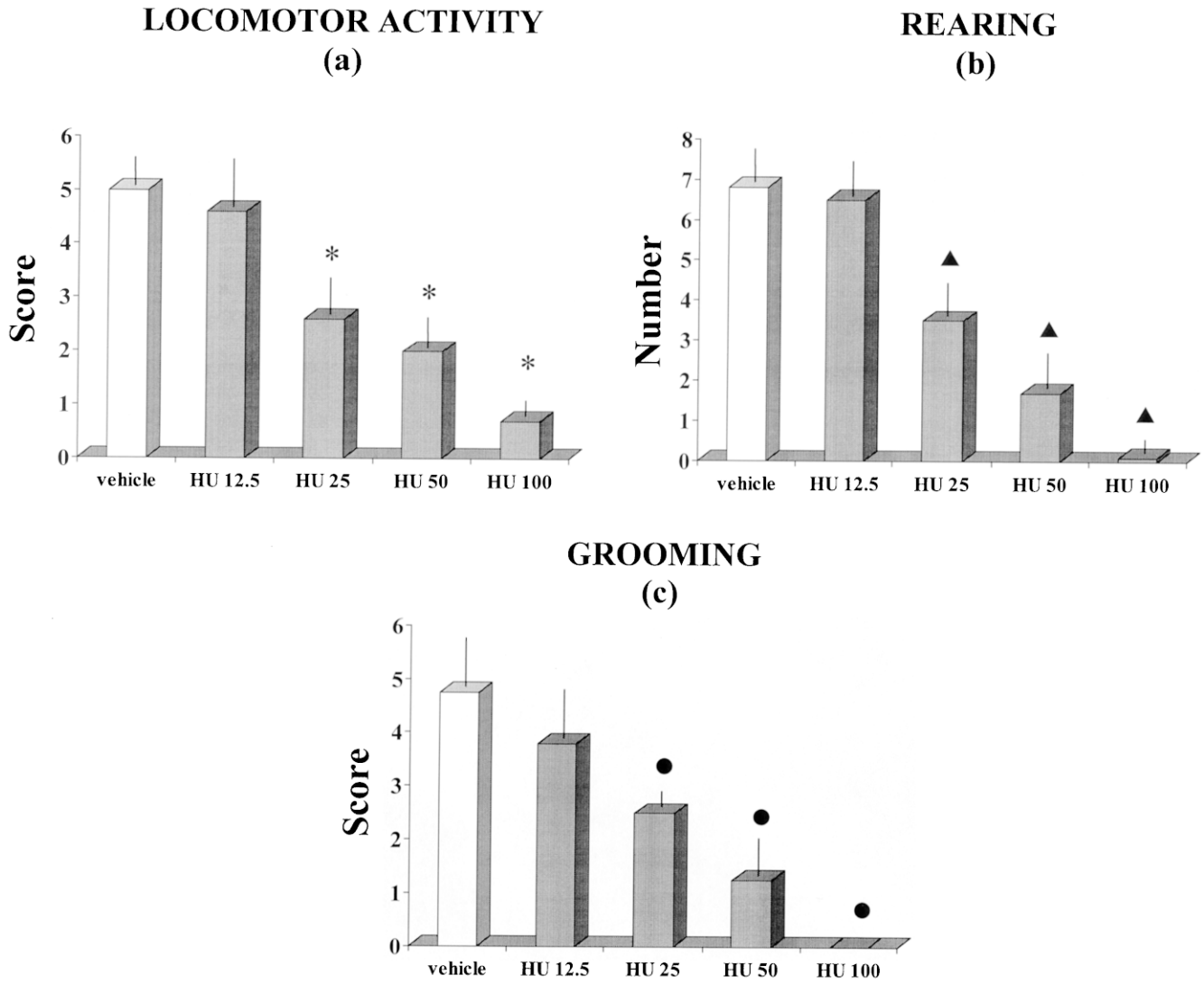

FIG. 1. Effect of HU 210 on locomotor activity, rearing, and grooming in rats. HU 210 (HU 12.5–100 μg/kg) or vehicle were injected IP 50 min before the observation period (30 min). Each histogram represents the mean ± SEM of the cumulative scores (a: locomotor activity; c: grooming) or the number of episodes (b: rearing) for each rat. Number of rats for treatment group: vehicle = 8; HU 12.5 = 8; HU25 = 8; HU 50 = 8; HU 100 = 6. ▲ Significantly different from controls (ANOVA followed by SNK test). *Significantly different from controls (Kruskal–Wallis: H = 25.3, followed by Mann–Whitney U-test: HU 25: T = 48; HU 50: T = 45.5; HU 100: T = 21.5). ● Significantly different from controls (Kruskal–Wallis: H = 27.4 followed by Mann–Whitney U-test: HU 25: T = 48; HU 50: T = 44; HU 100: T=21).

Rearing was scored as the number of times each animal stood up on its hind legs. Locomotor activity, grooming, and rearing values for each rat are the sum of all the scores or numbers attributed to the animal during the test period (30 min).

Subsequently, the same animals were tested for the presence or absence of vocalization and circling. Vocalization was evaluated by the experimenter gently pressing each rat with thumb and forefinger, two to four times bilaterally behind its forelimb on the ventral aspect of the frontal costal region (17). Circling was considered to be present if the animal turned at least 180 degrees around its vertical axis over a 5-min period (17).

Sedation in Pigeons

Behavioral evaluations were carried out on groups of animals which were transferred (three to four per group, homogeneous as regards treatment) to glass observation cages (40 × 30 × 34 cm) on the day of the experiment, 50 min after the subcutaneous (SC, in the breast) injection of HU 210 (12.5, 25, or 50 μg/kg) or vehicle.

The test started as soon as the animals were in place in the observation cages and lasted 30 min. At 15-s intervals an observer recorded whether or not each animal displayed sedation. Sedation scored 0 when the pigeon stood erect with an alert attitude; 1 when the bird, often perching, appeared completely immobile with hooded gaze and drooping wings; and 2 when its eyes were closed, its head bowed and its claws folded.

Cisplatin-Induced Vomiting in Pigeons

Experimentally naive pigeons were randomly assigned to various treatment groups. Immediately after cisplatin IV injection (7.5 mg/kg in the alar vein) each animal was placed in an individual observation cage (20 × 30 × 34 cm) and continuously observed for 3 h. The following parameters were scored: the onset of first retch, with or without vomiting (latency to emetic response), the number of episodes, and the weight of total vomitus expelled. Pretreatment with HU 210 (12.5, 25, or 50 μg/kg SC) or vehicle was performed 50 min before cisplatin.

Emetine-Induced Vomiting and Head Shake in Pigeons

Experimentally naive pigeons were randomly assigned to various treatment groups. Immediately after emetine injection (20 mg/kg SC) each animal was placed in an individual observation cage (20 × 30 × 34 cm) and continuously observed for 2 h. The following parameters were scored: the onset of first retch with or without vomiting (latency to emetic response), the number of episodes, the weight of total vomitus expelled, and the number of head shakes, as rapid and vigorous movements of the head. In preliminary experiments with emetine it was observed that this behavior often preceded vomiting. Pretreatment with HU 210 (12.5, 25, or 50 μg/kg SC) or vehicle was performed 50 min before emetine.

At the conclusion of the tests, the birds were euthanized.

All the behavioral procedures are in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Drugs and Treatment

HU 210 (Tocris-Cookson, Bristol, UK) was freshly prepared as a suspension containing a drop of Tween 80 (1%) and distilled water; cisplatin (Aldrich, Milan, Italy) was diluted in dimethylphormamide; emetine (Fluka, Milan, Italy) was dissolved in distilled water. All solutions were prepared at concentrations that allowed the injection of 1 ml/kg IP (rats), SC, or IV (pigeons).

Statistical Analysis

All data, except those regarding vocalization and circling, are presented as means ± SEM of the cumulative values obtained for each animal in the test period, and were analyzed using, as appropriate: ANOVA followed by Student–Newman–Keuls test (SNK test) and Kruskal–Wallis test followed by Mann–Whitney U-test (M-W test). Only the presence or

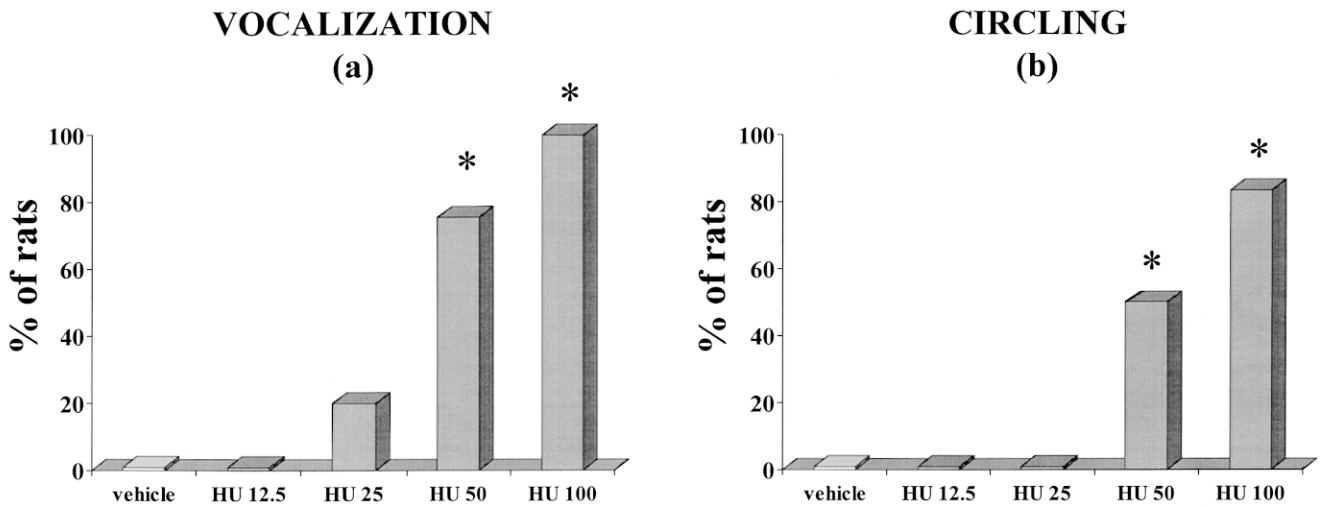

FIG. 2. Effect of HU 210 on vocalization and circling in rats. The animals tested 80 min after the injection of vehicle or HU 210 (HU, 12.5–100 μ g/kg), were the same as those used for locomotor activity, rearing, and grooming (see Fig. 1). Each histogram represents the percentage of animals displaying vocalization (a) or circling (b).*Significantly different from controls (Fisher's exact test).

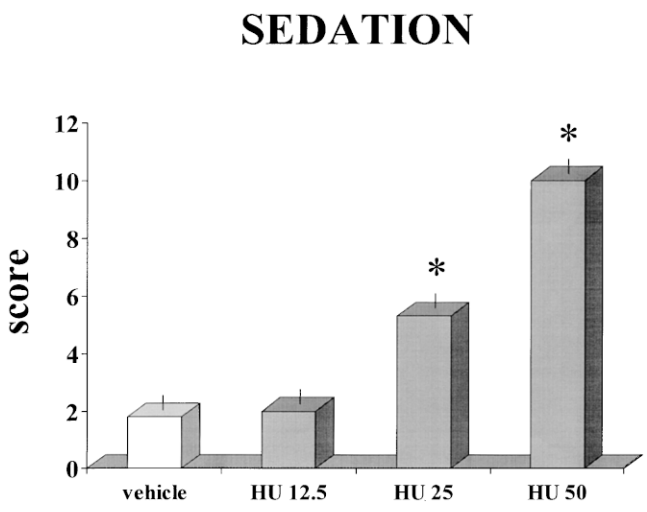

FIG. 3. Effect of HU 210 on sedation in pigeons. HU 210 (12.5–50 μg/kg) or vehicle were injected SC 50 min before the test (30 min). Each histogram represents the mean ± SEM of the cumulative scores attributed to each animal in the test period. Six pigeons were used in each treatment group. *Significantly different from controls (Kruskal–Wallis: $H = 21.8$, followed by Mann–Whitney U-test: HU 25: $T = 57$; HU 50: $T = 57$).

absence of vocalization and circling was recorded for the purposes of statistical evaluation, which was performed using Fisher's exact test. The level of significance was set at $p < 0.05$. At least six animals were used in each treatment group; the exact number of animals is reported in the figures and tables.

RESULTS

As shown in Fig. 1, the cannabinoid agonist HU 210 (12.5–100 μg/kg) dose dependently decreased rat locomotor activity (a) ($H = 25.3$, $p = 0.000$), rearing (b) $F(4, 35) = 5.4$, $p = 0.002$, and grooming (c) $H = 27.4$, $p = 0.000$, which are usually stimulated by a novel environment. All behavioral parameters changed significantly at doses of HU 210 25 μg/kg and above. The animals injected with the highest doses (50 and 100 μg/kg) showed a state of marked hypoactivity, alough being hypersensitive to tactile stimuli. In fact, when at the end of the test the animals were removed from the observational cages and gently pressed with the fingers, most of them vocalized strongly (Fig. 2a). Moreover, a certain percentage of rats treated at the same two doses, displayed circling (Fig. 2b).

The sedative effect of HU 210 was confirmed in pigeons where doses of 25 and 50 μg/kg increased sedation with respect to controls ($H = 21.8$, $p = 0.000$) (Fig. 3).

In all experimentally naive pigeons, cisplatin (7.5 mg/kg, IV) produced vomiting (Table 1). Over a 3-h observation period there was an average of 16.5 ± 5 emetic episodes per pigeon, with a very low onset (35.5 ± 6 min) and a consistent volume of vomitus expelled at the end of the test (1.8 ± 0.2 g). Pretreatment with HU 210 (12.5, 25, and 50 μg/kg SC) antagonized some aspects of the emetic response. Although latency was not noticeably affected, and the percentage of animals vomiting seemed to be modified only by the highest dose, bouts of vomiting and the amount of vomitus expelled were significantly reduced, $F(3, 20) = 4.9$, $p = 0.01$; $F(3, 16) = 48.1$, $p = 0.000$, respectively, at 12.5 μg/kg, a cannabinoid dose that did not induce sedation (Table 1).

HU 210 also displayed antiemetic activity in pigeons treated with emetine (20 mg/kg SC) (Table 2). The percentage of animals vomiting dose dependently decreased; latency to emetic response was significantly increased at 25 μg/kg, $F(2, 7) = 9$, $p = 0.01$, while the number of vomiting episodes and amount of vomitus expelled were already reduced at 12.5 μg/kg, $F(3, 20) = 20.7$, $p = 0.000$; $F(2, 7) = 66.5$, $p = 0.000$, respectively. Head shakes, which were numerous in emetine-treated animals, were abolished by the cannabinoid at all doses, $F(3, 20) = 29.4$, $p = 0.000$.

DISCUSSION

Our preliminary experiments on rats confirm and extend findings on the potent synthetic cannabinoid agonist HU 210 (4,21). As expected, acute injection of the drug dose dependently reduced locomotor activity, rearing, and grooming and, at the two highest doses tested (50 and 100 μg/kg), elicited vocalization and circling, which are considered behavioral pointers of cannabimimetic activity in rats (17). Although the chief effect of all cannabinoids is to induce central nervous system depression in animals (6), some of them, best typified by Δ^9THC, cause a particular concomitant stimulation, characterized by heightened reflexes (6,30). Vocalization in rats probably represents an enhanced irritative response associ-

TABLE 1

EFFECT OF HU 210 ON CISPLATIN-INDUCED EMESIS IN PIGEONS

Treatment (μg/kg, SC)	Vomiting Animals (No.)	Latency to Emetic Response (min)	Vomiting Episodes (No.)	Vomitus Expelled (g)
Vehicle	6/6	35.5 ± 6.0	16.5 ± 5.0	1.76 ± 0.17
HU 210, 12.5	5/6	54.6 ± 11.1	4.0 ± 1.7*	0.23 ± 0.04*
HU 210, 25	5/6	44.0 ± 6.6	5.2 ± 2.1*	0.17 ± 0.05*
HU 210, 50	4/6	59.2 ± 14.2	2.8 ± 1.1*	0.23 ± 0.12*

Emesis was induced by IV injection of a cisplatin solution 7.5 mg/kg (for details see the Methods section). Treatment with vehicle or HU 210 was performed 50 min before cisplatin. Animals were continuously observed for 3 h after last injection. Each value represents the mean ± SEM per animal; latency to emetic response and vomitus expelled were evaluated in animals vomiting.

*Significantly different from vehicle-treated pigeons (ANOVA followed by the SNK test).

TABLE 2

EFFECT OF HU 210 ON EMETINE-INDUCED EMESIS AND HEAD SHAKES IN PIGEONS

Treatment (μg/kg, SC)	Vomiting Animals (No.)	Latency to Emetic Response (min)	Vomiting Episodes (No.)	Vomitus Expelled (g)	Head Shakes (No.)
Vehicle	6/6	18.8 ± 2.3	9.1 ± 1.7	2.2 ± 0.1	25.5 ± 4.7
HU 210, 12.5	2/6†	35.5 ± 12.5	1 ± 0.6*	0.7 ± 0.2*	0*
HU 210, 25	2/6†	80.5 ± 29.5*	0.6 ± 0.5*	0.2 ± 0.1*	0*
HU 210, 50	0/6†	—	0*	—	0*

Emesis and head shakes were induced by SC injection of emetine (20 mg/kg). Treatment with vehicle or HU 210 was performed 50 min before emetine. Animals were continuously observed for 2 h after last injection. Each value represents the mean ± SEM per animal; latency to emetic response and vomitus expelled were evaluated in animals vomiting.

*Significantly different from vehicle-treated pigeons (ANOVA followed by the SNK test).

†Significantly different from vehicle-treated pigeons (Fisher's exact test).

ated with a fear- or stress-like state. A correlation between cannabinoids and stress has long been hypothesized (23) and recently supported by experimental data (4). This correlation would fit in with the potent Δ^9THC induced secretion of adrenocorticotropin hormone (ACTH) (6,7), which plays a key role in stress (14). As disphoria, anxiety, and panic have frequently been described in humans, mainly after high doses of cannabinoids (12,31,33), animal vocalization, as well as unpleasant human feelings, may be expressions of a similar underlying neurochemical mechanism. Although any comparison of the emotional effects in animals and humans is obviously highly speculative, a notable correspondence between the other pharmacological effects of cannabinoids, namely, sedation and antiemesis, has been established. The antinauseant and antiemetic properties of marijuana, Δ^9THC, and nabilone have been well documented in both species (8,20), and therapeutically exploited in patients treated with anticancer drugs. Unfortunately, the cannabinoid doses effective against vomiting need in general to be high and are, therefore, associated with the same disturbing side effects as seen in animals—namely, drowsiness, sedation, and/or anxiety (4,25,31,33).

Our findings in pigeons show that, in these animals too, acute HU 210 exerts predominantly sedative effects. A similarity between avians and rodents regarding drug-induced sedation has already been reported for central dopaminergic agonists at low doses (9,11). However, in pigeons, HU 210 counteracted cisplatin-induced vomiting even at a dose (12.5 μg/kg) lower than those interfering with the animals' normal behavioral pattern. Cisplatin, which is widely used as an antitumor agent, is one of the most potent emetogenics (8,28,32). It has already been reported that HU 211, a synthetic cannabinoid devoid of psychotropic effects, displays significant antiemetic efficacy at an optimal dose of 2.5 mg/kg in pigeons injected with cisplatin (10 mg/kg, IV) (8). It must be pointed out that our pigeons appeared to be particularly sensitive to cisplatin. In fact, although treated with a dose lower than that generally used (10 mg/kg), a high percentage of the animals vomited copiously and with a latency lower than that reported by several authors (8,32). At present, we cannot establish whether this effect is due to the relatively small size of our birds, their strain, and/or the vehicle used for cisplatin injection. The antiemetic activity of UH 210 was confirmed in emetine-treated pigeons; moreover, it was noted that the animals that had received pretreatment with the cannabinoid at the lowest dose (12.5 μg/kg), although not particularly sedated, did not exhibit head shake, which was potently stimulated by emetine. Our findings would suggest that head-shaking prior to vomiting may be considered a sign indicative of a state of animal discomfort, but we have as yet no assurance of this correlation because we have no data regarding its eventual occurrence after cisplatin. Experiments are being conducted to verify this hypothesis.

In conclusion, in our, as in other experiments, HU 210 mimicked the behavioral activity of Δ^9THC but proved to be much more potent. A certain distinction between the doses found to be antiemetic, sedative, and psychotropic—the latter deduced from the apperance of circling and vocalization in the rat—would suggest a potential clinical use for the compound.

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