

Neuroleptic-like profile of the cannabinoid agonist, HU 210, on rodent behavioural models

Alessandra Ottani, Francesca Ferrari, Daniela Giuliani*

Department of Biomedical Sciences, Division of Pharmacology, University of Modena and Reggio Emilia, Via G. Campi 287, I-4110 Modena, Italy

Abstract

(1) The present study was performed to assess the effects exerted by the cannabinoid (CB) agonist, (–)11-hydroxy- Δ^8 -tetrahydrocannabinol-dimethylheptyl (HU 210; 12.5–50 $\mu\text{g/kg}$ ip), on rodent behavioural tests involving dopamine (DA) transmission; in comparison, the DA D_2 antagonist, *S*(–)-3-chloro-5-ethyl-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-6-hydroxy-2-methoxy-benzamide hydrochloride ((–)eticlopride; 50 $\mu\text{g/kg}$ sc), was used. (2) In rats, HU 210, at all doses, potently antagonized penile erection (PE) and stretching–yawning (SY) typically elicited by the DA D_2/D_3 agonists, 6-allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo-[4,5-*d*]-azepine (B-HT 920) and $\pm$ 7-hydroxy-*N,N*-di-*n*-propylaminotetralin hydrobromide (7-OH-DPAT) both at 100 $\mu\text{g/kg}$ ip. (3) In nonreserpinized mice, HU 210 impaired motor ability assessed by means of a motor test battery, and B-HT 920 (1 mg/kg ip) worsened the phenomenon. (4) In reserpinized mice, HU 210 at 50 $\mu\text{g/kg}$ counteracted the amelioration exerted by B-HT 920 (1 mg/kg ip) on reserpine-induced akinesia. (5) As all these effects were similarly displayed by (–)eticlopride (50 $\mu\text{g/kg}$ sc), our data suggest a neuroleptic-like profile of acute HU 210 in animal behavioural tests. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Behaviour; Dopamine agonists and antagonists; HU 210; Rodents; SR 141716A

1. Introduction

The colocalisation of cannabinoid (CB) and dopamine (DA) receptors in those brain areas (Herkenham et al., 1991) that have a pivotal role in regulating motor and emotional responses, and whose dysfunction is associated to several pathologies (Albin et al., 1989) has stimulated research into the cross-talk between CBs and DA for the modulation of behaviour.

It is well established that natural and synthetic CBs, as well as the main endogenous ligand, anandamide (Devane et al., 1992; Di Marzo, 2000), impair motor function in animals (Dewey 1986; Romero et al., 1995; Ferrari et al., 1999a,b) and this effect seems to be mediated by a selective agonistic activity in the basal ganglia (Herkenham et al., 1991). Recent studies have demonstrated that CBs interfere with DA D_1 and D_2 receptor-mediated effects (Rodriguez De Fonseca et al., 1994; Romero et al., 1995; Anderson et al., 1996; Maneuf et al., 1997). In particular, it has been reported

that the synthetic CB agonist, HU 210, when acutely injected in rats, potently antagonized motor hyperactivity and stereotyped behaviour, elicited by cocaine and the DA D_1/D_2 receptor agonist CQP 201–403, respectively (Ferrari et al., 1999c). The synthetic compound HU 210 was found to be seven-fold more potent than Δ^9 -tetrahydrocannabinol, the main psychoactive component of cannabis, at binding to the neuronal CB $_1$ receptor (Howlett et al., 1990) and a high degree of correlation exists between this property and the efficacy in producing *in vivo* effects (Little et al., 1989).

The purpose of present work was to investigate the influence exerted by an acute treatment with HU 210 on several behavioural tests that may be considered specific for DA D_2/D_3 receptor activity (Ferrari, 1985; Ferrari and Giuliani, 1996a). To this aim, we evaluated: (1) the typical pattern induced in rats by two selective DA D_2/D_3 receptor agonists, B-HT 920 and 7-OH-DPAT, namely, sedation, penile erection (PE) and stretching–yawning (SY) (Ferrari, 1985; Ferrari and Giuliani, 1996b); (2) the motor effects provoked by B-HT 920 in nonreserpinized (Anden et al., 1982) or reserpinized mice (Hinzen et al., 1986). It is known that B-HT 920 displays differential activity in normal or denervated animals, for it decreases or increases motor function, respectively, these effects being ascribable to

Abbreviations: CB, cannabinoid; DA, dopamine; g, grams; h, hour/s; min, minute; PE, penile erection; s, seconds; SY, stretching–yawning

* Corresponding author. Tel.: +39-59-205-5374; fax: +39-59-205-5376.

E-mail address: giuliani.daniela@unimo.it (D. Giuliani).

stimulation of DA D₂/D₃ presynaptic or supersensitive postsynaptic D₂ receptors (Hinzen et al., 1986). In our studies, (–)eticlopride or *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (SR 141716A) were used as specific antagonists of DA D₂/D₃ (Köhler et al., 1986; Ferrari and Giuliani, 1994, 1996b) or CB₁ receptors (Rinaldi-Carmona et al., 1994; Compton et al., 1996), respectively.

2. Materials and methods

2.1. Animals

The subjects were male albino Swiss mice and Wistar rats (Harlan Nossan, Udine, Italy) weighing 25–30 or 230–250 g, respectively, at the outset. They were housed in groups of three to four, with food and water ad libitum and on a 12-h light cycle, from 07:00 to 19:00 h, for at least 1 week prior to the start of the experiments. Tests were performed between 09:00 and 14:00 h in a soundproof, air-conditioned room (temperature 20±2 °C), with normal lighting conditions, where the animals were monitored by trained observers unaware of the treatment schedule. Controls were handled in the same way as treated animals and received vehicle injections. The regulations in force on the care of animals for scientific purposes (CEE Council 86/609, Italian D.L. 27/01/92 no. 116) were strictly complied with.

2.2. Drugs

(–)11-Hydroxy-Δ⁸-tetrahydrocannabinol-dimethylheptyl (HU 210; Tocris-Cookson, Bristol, UK) and *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (SR 141716A; Sanofi Recherche, Montpellier, France) were freshly prepared as suspensions containing a drop of Tween 80 (0.1%) and distilled water. Reserpine (Sigma, Milano, Italy) was prepared as a suspension containing a drop of acetic acid (0.1%) and distilled water. 6-Allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo-[4,5-*d*]-azepine (B-HT 920; Boehringer Ingelheim, Ingelheim am Rhein, Germany), ±7-hydroxy-*N,N*-di-*n*-propylaminotetralin hydrobromide (7-OH-DPAT) and *S*(–)-3-chloro-5-ethyl-*N*-[(1-ethyl-2-pyrrolidinyl)-methyl]-6-hydroxy-2-methoxy-benzamide hydrochloride ((–)eticlopride; RBI, Natick, MA, USA) were dissolved in distilled water. The doses of the drugs and the pretreatment times were chosen on the basis of previous experiments. Drugs were intraperitoneally given, apart from (–)eticlopride that was subcutaneously injected, and all substances were administered at 1 ml/kg.

2.3. Experiments in rats

On the day of experiments, the rats were randomly assigned to different treatment groups (*n*=6). Pretreatments

with (–)eticlopride (at 50 µg/kg) or HU 210 (at 12.5 and 50 µg/kg) were performed 30 or 50 min, before the DA agonists B-HT 920 or 7-OH-DPAT (both at 100 µg/kg), respectively. Immediately after the last injection, the animals were transferred, in groups of three, homogeneous as regards treatment, to glass observation cages (40×30×34 cm), where they were continuously observed for 30 min, after a 5 min adaptation period. The following behavioural aspects were taken into account: SY, PE and sedation. Each episode of SY and PE was scored up for each animal exhibiting it. Sedation was evaluated every 5 min, observing each animal for 30 s, and rated on a scale of 0–2: 0=absent; 1=immobility of the animal, for at least 25 s, with open eyes; 2=immobility of the animal, for at least 25 s, with closed eyes (Ferrari and Giuliani, 1994). SY, PE and sedation values were represented by the sum of all the numbers of episodes or the scores attributed to each rat during the test period.

2.4. Experiments in mice: motor test battery

A motor test battery was performed to assess drug influence on mice motor activity. The test was modified from that described by Björklund et al. (1980) to evaluate motor orientation and coordinated limb use on each side of the body; the response in each test was rated on a three-point scale. Initially, each animal was observed unrestrained on the bench for 2 min to ascertain *general posture asymmetry*, as inclination, more or less marked, of the head (0=absent, 1=weak and 2=strong) and *hypokinesia*, as animal's exploring behaviour (0=normal exploration, 1=reduced exploration, 2=no exploration). Subsequently, limb reflexes and coordinated limb use were assessed. *Forelimb placement*: the animal was grasped around the abdomen and slowly head first towards the surface of the bench, any inaccuracy or lack of coordination in the reflex placement of the forelimbs being rated on a scale 0–2, where 0=symmetrical landing, 1=the animal lands with only one paw, 2=asymmetrical landing involving the body. *Forelimb suspension*: the animal was left hanging from a wooden bar and the inability with which it pulled itself up was rated as follows: 0=the animal rises, 1=the animal hangs up, 2=the animal falls down. *Climbing grid*: the animal was placed on a vertical wire grid with horizontal grills (a removable cage floor clamped vertically by its upper edge to the bench surface) and its climbing inability rated on the same scale as before. *Pyramidal signs*: the animal was placed at the edge of the bench, with an hindpaw hanging on to the vertical side; the speed with which it retracted its paw was rated, during a 5-s observation period, as follows: 0=rapid retraction (within 1 s); 1=slow retraction (more than 1 s), 2=no retraction; since the evaluation was performed for each hindpaw the maximal score was 4. *Catalepsy*: the animal was placed with its forepaws on an horizontal bar and the time to resume a four-paw posture was evaluated during a 30-s period; the

Table 1

Effect of (–)eticlopride on B-HT 920-or 7-OH-DPAT-induced sedation, penile erection and stretching–yawning

Pretreatments ($\mu\text{g/kg}$)	Treatments ($\mu\text{g/kg}$)	Sedation (score)	PE (n°)	SY (n°)
Saline	Saline	1.5 ± 0.4	0.2 ± 0.2	0.7 ± 0.3
Saline	B-HT 920, 100	9.8 ± 0.7^a	2.7 ± 0.4^b	20.8 ± 1.5^b
Saline	7-OH-DPAT, 100	9.1 ± 1.1^a	2.8 ± 0.5^b	21.2 ± 3.7^b
Eti, 50	Saline	6.3 ± 0.9^a	0	0.2 ± 0.2
Eti, 50	B-HT 920, 100	10.5 ± 1.1^a	0.5 ± 0.3^c	2.5 ± 1.3^c
Eti, 50	7-OH-DPAT, 100	11.3 ± 0.7^a	0.7 ± 0.3^c	4.5 ± 1.8^c

PE=penile erection; SY=stretching–yawning. (–)Eticlopride (Eti) was administered 30 min before the DA agonists. Test period=30 min. Values are the means $\pm$ S.E.M. of the scores or of the numbers for each treatment group ($n=6$).

^a Significantly different from saline+saline (Friedman's test followed by Mann–Whitney *U* test).

^b Significantly different from saline+saline. (ANOVA followed by Student–Newman–Keuls' test).

^c Significantly different from respective controls (ANOVA followed by Student–Newman–Keuls' test).

following scores were given: 0=0–15 s, 1=15–30 s, 2=more than 30 s. At the end of the test battery, a cumulative score (as sum of the rating scores across tests) was given to each animal (maximal score=16).

2.4.1. Nonreserpinized mice

Four motor tests were performed on forty-eight experimentally naive mice that were randomly divided into six groups ($n=8$); all subjects received an injection of vehicle and, 24 h later, they were submitted to Test 1. Subsequently, the groups were treated as follows: (1) vehicle+vehicle, (2) vehicle+HU 210 at 12.5 $\mu\text{g/kg}$, (3) vehicle+HU 210 at 50 $\mu\text{g/kg}$, (4) vehicle+(–)eticlopride at 50 $\mu\text{g/kg}$, (5) SR 141716A at 3 mg/kg+vehicle, (6) SR 141716A at 3 mg/kg+HU 210 at 50 $\mu\text{g/kg}$. Vehicle or SR 141716A was administered 30 min before HU 210 or vehicle. Test 2 was performed 1 h after the last treatment; immediately thereafter, all groups were injected with B-HT 920 at 1 mg/kg and were submitted to Test 3 and 4, 20 min and 24 h later, respectively.

2.4.2. Reserpinized mice

Six groups of naive mice ($n=10$ for each group) were treated with reserpine (5 mg/kg) and 24 h later were

submitted to the same experimental procedure as nonreserpinized mice.

2.5. Statistical analysis

Data, for rats, are presented as means ($\pm$ S.E.M.) and analysed using ANOVA followed by Student–Newman–Keuls test (SNK test) or Friedman's test followed by Mann–Whitney *U* test, where appropriate. Data, for mice, are presented as cumulative score for each treatment group and were analyzed using Friedman's test followed by Mann–Whitney *U* test.

The level of significance was set at $P<.05$.

3. Results

3.1. Experiments in rats

As expected, on the basis of our previous experiments (Ferrari, 1985; Ferrari and Giuliani, 1996a), B-HT 920 and 7-OH-DPAT, both at 100 $\mu\text{g/kg}$, elicited sedation, PE and SY, and the pretreatment with (–)eticlopride at 50 $\mu\text{g/kg}$

Table 2

Effect of HU 210 on B-HT 920-or 7-OH-DPAT-induced sedation, penile erection and stretching–yawning

Pretreatments ($\mu\text{g/kg}$)	Treatments ($\mu\text{g/kg}$)	Sedation (score)	PE (n°)	SY (n°)
Saline	Saline	1.5 ± 0.4	0.2 ± 0.2	0.7 ± 0.3
Saline	B-HT 920, 100	9.8 ± 0.7^a	2.7 ± 0.4^c	20.8 ± 1.5^c
Saline	7-OH-DPAT, 100	9.1 ± 1.1^a	2.8 ± 0.5^c	21.2 ± 3.7^c
HU, 12.5	Saline	2 ± 0.4	0.3 ± 0.3	0.3 ± 0.2
HU, 25	Saline	4.7 ± 0.6^a	0	0.2 ± 0.2
HU, 50	Saline	8.3 ± 0.8^a	0	0
HU, 12.5	B-HT 920, 100	9.8 ± 0.8	0.7 ± 0.5^d	10 ± 1.5^d
HU, 25	B-HT 920, 100	10.2 ± 0.6	0.5 ± 0.3^d	3.3 ± 1.3^d
HU, 50	B-HT 920, 100	12.5 ± 0.6^b	0.8 ± 0.5^d	2.7 ± 1.5^d
HU, 12.5	7-OH-DPAT, 100	10.3 ± 1.1	1.8 ± 0.4^d	8.7 ± 1.9^d
HU, 50	7-OH-DPAT, 100	12.3 ± 0.7^b	0.5 ± 0.3^d	3.3 ± 1.9^d

PE=penile erection; SY=stretching–yawning. HU 210 (HU) was administered 50 min before the DA agonists. Test period=30 min. Values are the means $\pm$ S.E.M. of the scores or of the numbers for each treatment group ($n=6$).

^a Significantly different from saline+saline. (Friedman's test followed by Mann–Whitney *U* test).

^b Significantly different from respective controls (Friedman's test followed by Mann–Whitney *U* test).

^c Significantly different from saline+saline. (ANOVA followed by Student–Newman–Keuls' test).

^d Significantly different from respective controls (ANOVA followed by Student–Newman–Keuls' test).

significantly counteracted this phenomenon, whereas it increased sedation (Table 1).

Table 2 shows that HU 210, at all doses (12.5–50 $\mu\text{g/kg}$) potently antagonized B-HT 920- and 7-OH-DPAT-induced PE and SY. Sedation provoked by the two DA agonists was increased by HU 210 at 50 $\mu\text{g/kg}$.

3.2. Experiments in mice

3.2.1. Nonreserpinized mice

Acute injection of HU 210 at 50 $\mu\text{g/kg}$ and (–)eticlopride similarly impaired motor ability in animals; pre-treatment with the CB antagonist SR 141716A significantly counteracted the effect exerted by HU 210 (Fig. 1, Test 2). In Test 3, B-HT 920 worsened motor dysfunction in all groups, apart from that of mice treated with SR 141716A+HU 210 at 50 $\mu\text{g/kg}$, which significantly differed with respect to vehicle- or HU 210 (50 $\mu\text{g/kg}$)-treated groups in the same test. Twenty-four hours after B-HT 920 (Test 4), motor function of all groups restored, apart from that of mice injected with HU 210 at 50 $\mu\text{g/kg}$.

3.2.2. Reserpinized mice

Fig. 2 shows that all mice differed with respect to non-reserpinized animals (Fig. 1), for they exhibited a high motor impairment (Test 1); any treatment did affect the behavioural pattern provoked by reserpine (Test 2). When the DA D_2 agonist, B-HT 920, was administered to the various treatment groups (Test 3), motor ability was improved with respect to Tests 1 and 2 only in mice injected with vehicle or with HU 210 at 12.5 $\mu\text{g/kg}$. Twenty-four hours later (Test 4), B-HT 920-induced amelioration in vehicle- or

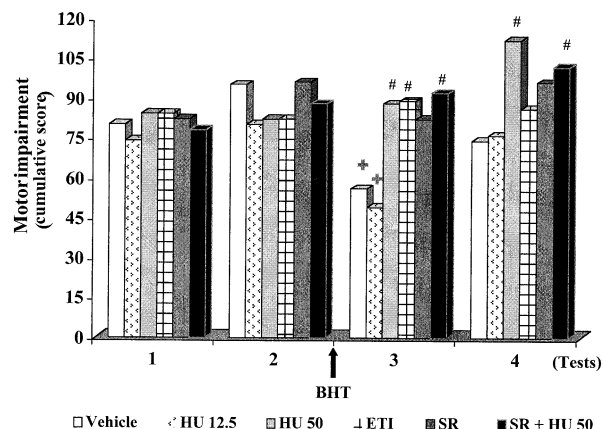


Fig. 2. Effect of HU 210 on motor test battery in reserpinized mice. The animals were injected with reserpine (5 mg/kg ip) 24 h before Test 1. For treatments, see Section 2. Each histogram is the cumulative score for treatment group ($n=10$). BHT=B-HT 920 at 1 mg/kg; HU 12.5 or 50=HU 210 at 12.5 or at 50 $\mu\text{g/kg}$; ETI=(–)eticlopride at 50 $\mu\text{g/kg}$; SR=SR 141716A at 3 mg/kg. Significantly different from: + the same group in Tests 1 and 2, # vehicle in the same test (Friedman's test followed by Mann–Whitney U test).

HU 210 (12.5 $\mu\text{g/kg}$)-treated mice disappeared. Animals injected with HU 210 at 50 $\mu\text{g/kg}$ or SR 141716A+HU 210 at 50 $\mu\text{g/kg}$ exhibited a motor dysfunction significantly higher than that of vehicle-treated group in the same test.

4. Discussion

It is generally recognized that DA plays a key role in biochemical defects underlying psychoses (Berger et al., 1978); accordingly, most preclinical investigations into the mechanism of potential antipsychotic agents focus attention on the interactions of these drugs with the DA function (Carlsson, 1978). Present experiments extend findings on the neuroleptic-like effects induced by the potent synthetic CB agonist, HU 210, when acutely injected in animals (Ferrari et al., 1999c). It has been reported that this compound shares with other CB agonists and DA antagonists the ability to induce sedation and, at high doses, a cataleptic state (Rodriguez De Fonseca et al., 1994), beside exerting a potent antiemetic effect (Dewey, 1986; Ferrari et al., 1999a).

The similarity between HU 210 and neuroleptics was confirmed by means of the other behavioural tests here considered. In rats, HU 210, like (–)eticlopride, potently counteracted PE and SY typically elicited by two DA agonists and attributed to a selective agonism on DA D_2/D_3 receptors (Ferrari, 1985; Ferrari and Giuliani, 1996a). It is noteworthy that HU 210-induced effect was displayed already at a dose (12.5 $\mu\text{g/kg}$) which is unable to modify rat normal behaviour, thus, excluding that it is simply ascribable to an specific dampening of general motor activity.

In nonreserpinized mice, the acute injection of HU 210, like (–)eticlopride, only impaired motor ability. In reserpi-

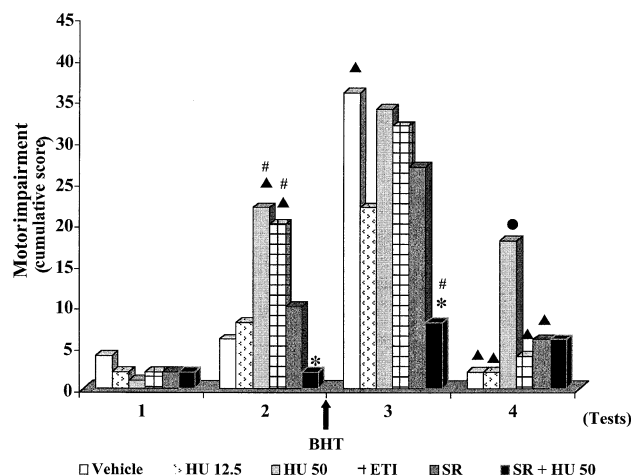


Fig. 1. Effect of HU 210 on motor test battery in nonreserpinized mice. For treatments, see Section 2. Each histogram is the cumulative score for treatment group ($n=8$). BHT=B-HT 920 at 1 mg/kg; HU 12.5 or 50=HU 210 at 12.5 or 50 $\mu\text{g/kg}$; ETI=(–)eticlopride at 50 $\mu\text{g/kg}$; SR=SR 141716A at 3 mg/kg. Significantly different from: # vehicle in the same test, * HU 210 at 50 $\mu\text{g/kg}$ in the same test, ● all other groups in the same test; ▲ the same group in the previous test (Friedman's test followed by Mann–Whitney U test).

nized mice, that have been widely employed to assess the potential usefulness or injury of DAergic drugs in Parkinson's disease (Hinzen et al., 1986; Ahlenius and Salmi, 1994; Maneuf et al., 1997), the CB agonist and the DA antagonist did not change the behavioural pattern but prevented the amelioration elicited by B-HT 920, which is due to stimulation of "denervated" supersensitive post-synaptic DA D₂ receptors (Hinzen et al., 1986).

These data are in line with those reporting an alleviation of reserpine-induced akinesia by the DA agonist, quinpirole, and a reduction of this effect by the CB receptor agonist, WIN 55,212-2 (Maneuf et al., 1997). However, in our experiments, while SR 141716A strongly inhibited HU 210-induced effect in nonreserpinized mice, surprisingly, and in disaccordance with Maneuf et al. (1997), it worsened the damage produced by the CB agonist in reserpinized animals.

Despite of this lack of antagonism, that remains to be clarified for a single dose was used in present study, our results further show that the CB agonist, HU 210, behaves very similarly to classical neuroleptics in several animal models involving DA transmission, only differing for a more pronounced and prolonged action.

5. Conclusions

While acknowledging that any comparison between experimental and clinical findings is a matter of speculation, our data suggest a potential effect of HU 210, when acutely administered, in those pathologies responsive to neuroleptics.

Acknowledgments

A special thanks to Sanofi Recherche (France) for the generous gift of SR 141716A. This work was supported by grants from Ministero della Pubblica Istruzione and by CNR.

References

- Ahlenius, S., Salmi, P., 1994. Behavioral and biochemical effects of dopamine D₃ receptor-selective ligand, 7-OH-DPAT, in the normal and the reserpine-treated rat. *Eur. J. Pharmacol.* 260, 177–181.
- Albin, R.L., Hwang, A.B., Penney, J.B., 1989. The functional anatomy of basal ganglia disorders. *Trends Neurosci.* 12, 366–375.
- Andén, N.E., Golembiowska-Nikitin, K., Thornstrom, U., 1982. Selective stimulation of dopamine and noradrenaline autoreceptors by B-HT 920 and B-HT 933, respectively. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 321, 100–104.
- Anderson, J.J., Kask, A.M., Chase, T.N., 1996. Effects of cannabinoid receptor stimulation and blockade on catalepsy produced by dopamine receptor antagonists. *Eur. J. Pharmacol.* 295, 163–168.
- Berger, P.A., Elliott, G.R., Barchas, J.D., 1978. Neuroregulators and schizophrenia. In: Lipton, M.A., DiMascio, A., Killam, K.F. (Eds.), *Psychopharmacology: A Generation of Progress*. Raven Press, New York, pp. 1070–1082.
- Bjorklund, A., Dunnett, S.B., Stenevi, U., Lewis, M.E., Iversen, S.D., 1980. Reinnervation of the denervated striatum by substantia nigra transplants: functional consequence as revealed by pharmacological and sensorimotor testing. *Brain Res.* 199, 307–333.
- Carlsson, A., 1978. Mechanism of action of neuroleptic drugs. In: Lipton, M.A., Carlsson, A., DiMascio, A., Killam, K.F. (Eds.), *Psychopharmacology: A Generation of Progress*. Raven Press, New York, pp. 1057–1070.
- Compton, D.R., Aceto, M.D., Lowe, J., Martin, B.R., 1996. In vivo characterization of a specific cannabinoid receptor antagonist (SR 141716A): inhibition of Δ^9 -tetrahydrocannabinol-induced responses and apparent agonist activity. *J. Pharmacol. Exp. Ther.* 277, 586–594.
- Devane, W.A., Hanus, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., Mechoulam, R., 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *J. Med. Chem.* 258, 1946–1949.
- Dewey, W.L., 1986. Cannabinoid pharmacology. *Pharmacol. Rev.* 38, 151–178.
- Di Marzo, V., 2000. Regulation of endocannabinoid levels under physiological and pathological conditions. A mini-review. *Pharm. Pharmacol. Commun.* 6, 235–241.
- Ferrari, F., 1985. Sexual excitement and stretching–yawning induced by B-HT 920. *Pharmacol. Res. Commun.* 17, 557–563.
- Ferrari, F., Giuliani, D., 1994. The selective D₂ dopamine receptor antagonist eticlopride counteracts the ejaculatio praecox induced by the selective D₂ dopamine agonist SND 919 in the rat. *Life Sci.* 55, 1155–1162.
- Ferrari, F., Giuliani, D., 1996. Behavioral effects induced by the dopamine D₃ agonist 7-OH-DPAT in sexually active and inactive male rats. *Neuropharmacology* 35, 279–284.
- Ferrari, F., Giuliani, D., 1996. Influence of eticlopride on cocaine- and DA D₂ agonist-induced behavioral effects in rats. *Pharmacol., Biochem. Behav.* 53, 525–530.
- Ferrari, F., Ottani, A., Giuliani, D., 1999. Cannabinoid activity in rats and pigeons of HU 210, a potent anti-emetic drug. *Pharmacol., Biochem. Behav.* 62, 75–80.
- Ferrari, F., Ottani, A., Vivoli, R., Giuliani, D., 1999. Learning impairment produced in rat by the cannabinoid agonist HU 210 in a water maze task. *Pharmacol., Biochem. Behav.* 64, 555–561.
- Ferrari, F., Ottani, A., Giuliani, D., 1999. Influence of the cannabinoid agonist HU 210 on cocaine- and CQP 201–403-induced behavioural effects in rat. *Life Sci.* 65, 823–831.
- Herkenham, M., Lynn, A.B., Johnson, M.R., Melvin, L.S., De Costa, B.R., Rice, K.C., 1991. Characterization and localisation of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J. Neurosci.* 11, 563–583.
- Hinzen, D., Hornykiewicz, O., Kobinger, W., Pichler, L., Pifl, C., Schingnitz, G., 1986. The dopamine autoreceptor agonist B-HT 920 stimulates denervated postsynaptic brain dopamine receptors in rodents and primate models of Parkinson's disease: a novel approach to treatment. *Eur. J. Pharmacol.* 131, 75–86.
- Howlett, A.C., Champion, T.M., Wilken, G.H., Mechoulam, R., 1990. Stereochemical effects of 11-OH- Δ^8 -tetrahydrocannabinol-dimethylheptyl to inhibit adenylate cyclase and bind to the cannabinoid receptor. *Neuropharmacology* 29, 161–165.
- Kohler, C., Hall, H., Gawell, L., 1986. Regional in vivo binding of the substituted benzamide [³H]eticlopride in the rat brain: evidence for selective labelling of dopamine receptors. *Eur. J. Pharmacol.* 120, 217–226.
- Little, P.J., Compton, D.R., Mechoulam, R., Martin, B.R., 1989. Stereochemical effects of 11-OH- Δ^8 -THC-dimethyleptyl in mice and dogs. *Pharmacol., Biochem. Behav.* 32, 61–66.
- Maneuf, Y.P., Crossman, A.R., Brothie, J.M., 1997. The cannabinoid receptor agonist WIN 55,212-2 reduces D₂ but not D₁ dopamine receptor-mediated alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease. *Exp. Neurol.* 148, 265–270.

- Rinaldi-Carmona, M., Barth, F., Heaulme, M., Shire, D., Calandra, B., Congy, C., Martinez, S., Maruani, J., Neiliat, G., Caput, D., Ferrara, P., Soubri , P., Breliere, J.C., Le Fur, G., 1994. SR 141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett.* 350, 240–244.
- Rodr guez De Fonseca, F., Martin-Calderon, J.L., Mechoulam, R., Navarro, M., 1994. Repeated stimulation of D₁ dopamine receptors enhances (–)-11-hydroxy-D8-tetrahydrocannabinol-dimethylheptil-induced catalepsy in male rats. *NeuroReport* 5, 761–765.
- Romero, J., Garcia, L., Cebeira, M., Zadrozny, D., Fernandez-Ruiz, J.J., Ramos, J.A., 1995. The endogenous cannabinoid receptor ligand, anandamide, inhibits the motor behaviour: role of nigrostriatal dopaminergic neurons. *Life Sci.* 56, 2033–2040.