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HU 210: A Potent Tool for Investigations of the Cannabinoid System

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ABSTRACT

The synthetic compound HU 210 displays a multiplicity of biochemical, pharmacological, and behavioral effects, most of which have been demonstrated to be dependent on a selective agonistic activity at CB_1 and CB_2 cannabinoid receptors and to involve the main neurotransmitter systems. Results obtained in various studies suggest a potential clinical application of this highly potent drug (e.g., as antipyretic, antiinflammatory, analgesic, antiemetic, and antipsychotic agent) as well as its usefulness in research aimed to develop a better understanding of the involvement of the endogenous cannabinoid system in a number of physiopathological functions.

INTRODUCTION

Cannabis sativa derivatives are the most commonly used illicit drugs, but they have also been used for medicinal purposes by various cultures. Cannabinoid (CB) research (26), which has been performed primarly with the main psychoactive constituent of marijuana, Δ^9-tetrahydrocannabinol (THC), since its identification (45), has undergone a dramatic increase during the last decade (3,93,115) following the discovery of specific CB receptors (26,61,101) and their endogenous ligands, e.g., anandamide (ANA) and 2-arachidonylglycerol (27,93,139). To date, two different CB receptors have been characterized and cloned from mammalian tissues: the CB_1 receptor, which is found primarily in the central nervous system and testis (26), and the CB_2 receptor, which is located in the periphery, predominantly in the immune system (101).

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Studies on THC structure aided the identification of the structural features of CB compounds that are required for biological activity (91,144) and led to the synthesis of a number of high-affinity CB agonists (18), such as CP 55,940 (154), WIN 55,212-2 (74), and HU 210 (65), as well as antagonists, such as SR 141716A (120) and AM 251 (47).

MOLECULAR PHARMACOLOGY

The cloning of CB_1 (26) and CB_2 (101) receptors clearly established the molecular determinants of ligand binding and selectivity, as well as of their activation. CB receptors, which belong to the class of pertussis toxin-sensitive and G protein-coupled receptors, activate multiple intracellular signal transduction systems, such as inhibition of adenylate cyclase (34,134) and stimulation of the microtubule associated protein kinase (MAPK) cascade (8,9). The CB_1 receptor is also associated with the inhibition of ion channels (112), the mobilization of arachidonic acid, and the attenuation of cyclic adenosine monophosphate (cAMP) production (3). Depending on their chemical structures, CB agonists can be classified into at least four groups: classic CBs, bicyclic or nonclassic CBs, aminoalkylindoles, and fatty-acid amines and esters (18,74). HU 210 [(–)3–(1,1-dimethylheptyl)-(–)11-hydroxy-Δ^8-tetrahydrocannabinol] has been synthesized by Mechoulam's laboratory and belongs to the group of classic CBs, which present the tricyclic benzopyran structure as their skeletons (80,91). The marked lipophilic properties of HU 210 allow it to pass across the blood-brain barrier. It has been found to be much more potent than THC {(–)-trans-(6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-6H-dibenzo[b,d]pyran-1-o1} at binding to the neuronal CB_1 receptor and inhibiting adenylate cyclase (65,26). The potency ratio for inhibition of adenylate cyclase and accumulation of cAMP, observed for HU 210 to its (+)isomer [(+)3–(1,1-dimethylheptyl)-(–)11-hydroxy-Δ^8-tetrahydrocannabinol] (HU 211), exceeded 1000; as for CB_1 binding sites, the potency ratio for HU 210 to HU 211 was 1500 (65). This latter finding points to the relevance of enantioselectivity in the cannabimimetic activity (92). A lysine residue of the CB receptor is critical for receptor recognition by HU 210, as well as by CP 55,940 ((–)-*cis*-3-[(2-hydroxy-4-)(1,1-dimethylheptyl)phenyl]-*trans*-4-[3-hydroxypropyl]cyclohexanol) and ANA [(allZ)-N-(2-hydroxyethyl)-5,8,11,14-eicosatetraenamide] but not by WIN 55,212-2 ((*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone)(136). Studies on the ability of different CB agonists to activate G proteins in mouse brain membranes, as measured by binding assays, have demonstrated that, from a molecular point of view, HU 210 displays extremely high efficacy and potency (12). Evidence that CB agonists induce different conformations of the CB_1 receptor, which in turn can distinguish between different G proteins, would suggest that, therapeutically, this could provide a powerful mechanism to select for particular actions of CBs while avoiding some of the unwanted effects (7,55). It has been shown that HU 210 shares with other CBs the ability to regulate the Ca^{2+} channel, which is an important second messenger controlling the activity of numerous enzymes (106,112,134,146). A possible consequence of a modification in Ca^{2+} influx is interference in the various Ca^{2+}-dependent intracellular processes, including the synthesis of nitric oxide (NO) by neuronal NO synthase (NOS) (62). In the light of the widespread role of NO as a modulatory agent in the

brain, it is likely that NOS inhibition plays a role in the overall effects of HU 210 and other CBs on the brain functions (62). HU 210, as well as THC, produces a CB_1-receptor-mediated increase in glucose metabolism in primary astrocytes, the major class of glial cells in mammalian brain, by a mechanism which seems to be related to MAPK stimulation (130). These data indicate that HU 210 may perturb the homeostatic functions of the astroglia.

In view of the neuronal distribution of CB receptors in the adult rat brain (83), a great deal of research has been carried out in an attempt to characterize the relationship between CBs and other neurotransmitter systems. Modulation of acetylcholine (ACh) (48,50), dopamine (DA) (46,49,96,128), norepinephrine (NE) (107,132), serotonin (5-HT) (16,72, 104), opioids (105), and γ-aminobutyric acid (GABA) (84,126) in specific brain regions known to possess a high density of CB_1 receptors, such as the basal ganglia, hippocampus, and cerebellum (26,83,89), has been well documented.

ENDOCRINOLOGY

In laboratory animals, HU 210 induces a set of endocrine alterations, closely related to those described for natural CBs, such as THC (29,66,72,73,137), but at doses 50 to 200 times lower than those required for the main psychoactive constituent of marijuana (88). HU 210 administration in adult rats results in a dose-dependent inhibition of plasma growth hormone, follicle stimulating hormone, and luteinizing hormone; modifications of plasma adrenocorticotropic hormone (ACTH) and corticosterone levels reveal a dose-dependent action on the pituitary-adrenal axis after acute exposure (88). This finding is in line with the hypothesis that the endocrine effects of THC are mediated by alterations in the hypothalamic mechanisms controlling pituitary hormone synthesis (118). The anxiogenic responses elicited by high doses of HU 210 in rats have been found to be associated with a dose-dependent increase in plasma corticosterone levels and probably involve endogenous corticotropin releasing factor (CRF) as it is attenuated by pretreatment with the potent CRF antagonist D-phe-$CRF_{(12–41)}$ (123). Increases in CRF have also been found in the limbic system during withdrawal elicited by SR 141716A in rats chronically exposed to HU 210 (124).

HU 210 affects rat plasma prolactin levels in a biphasic fashion, with low and high doses increasing and decreasing this hormone, respectively (88). Interestingly, the inhibitory effects of HU 210 on plasma prolactin are concomitant with a decrease in the medium basal hypothalamic contents of DA, the proposed prolactin-inhibiting factor, as well as with an increase in the L-3,4-dihydroxyphenylacetic acid/DA ratio, an index of DAergic activity.

IMMUNE SYSTEM AND CANCER

CB addiction has been associated with suppression of the immune function (70,71), and a number of studies would suggest that endocannabinoids are also immunosuppressive (14,30,77). Most of the research into CB effects on animals has led to results con-

sistent with dose-dependent immunosuppression; this activity has been largely attributed to activation of CB_2 receptors, which are expressed almost exclusively on peripheral immune cells, such as lymphocytes, macrophages, and mast cells (33,44,131). Interference with the immune response is also potently displayed by HU 210 but not by its nonpsychotropic (+) enantiomer HU 211 (143). These data support the hypothesis that HU 210 suppresses the productive phase of the primary humoral immune response by impairing B cells macromolecular synthesis, which is chirally dependent (69,143).

HU 210 has been found to inhibit the activity of macrophages (13,14), which are important for the immune response because of their capacity as antigen-presenting cells, as producers of positive and negative modulatory proteins (64,147), and as cytotoxic effectors against tumor cells, protozoa, and virus-infected cells (32,39).

Recent data, however, indicate that the general view, namely that CBs induce immunosuppression, should be reassessed. In fact, when the metabolic response of spleen lymphocytes to HU 210 and THC was investigated in mice, the two CBs, at low physiologically relevant doses, induced metabolic stimulation of lymphocytes, as recorded by an increase in the rate of glucose oxidation to CO_2 and glucose incorporation into phospholipids and glycogen (129). These findings are consistent with those showing that low doses of CBs display a receptor-dependent growth-enhancing activity on human B cells (25). A biphasic effect of HU 210 is not surprising for it is well known that many CBs exert stimulant or inhibitory activity at low or high doses, respectively; moreover, it opens new perspectives for the therapeutic potential of CBs as modulators of the immune response (129).

A further benefical use of CBs has been suggested by evidence that HU 210 shares with ANA an inhibitory activity on cell proliferation *in vitro* on prostate and human breast cancer; in this case, suppression of prolactin receptor synthesis and, therefore, of prolactin action (66), may represent the underlying mechanisms (23,94).

PERINATAL EXPOSURE

Perinatal exposure to marijuana and other CBs alters neurochemical development in the rodent brain, markedly affecting the maturation of several neurotransmitter systems, in particular those of the endogenous opioids and DA (121,149,150,153). Again, THC or cannabinol interfered with the development of male reproductive functions in mice by acting on fetal testis, the pituitary, and the hypothalamus (22). When rats were exposed to HU 210 during gestation and lactation and the ensuing effects on several endocrine and immune parameters of the adult male offspring were analyzed (24), the results revealed that maternal exposure to HU 210 results in minor changes in the development of the immune system but induces long lasting alterations in the functional status of the hypothalamic-pituitary-adrenal axis, as in the case of exposure to THC (127).

BEHAVIORAL PHARMACOLOGY

HU 210 behaves, in most cases, quite similarly to THC in its pharmacological effects; however, it was found to be between 80 and 1100 times more potent according to the *in*

vivo effects examined. HU 210, like most CBs, exerts a multiplicity of behavioral effects that seem to occur in concert with modifications of several neurotransmitter systems (84,113,126).

Motor Activity

When psychotomimetic CBs were tested in a number of laboratories for their effects on animals and man, the overall result was a decrease in psychomotor function (29,125); HU 210-induced sedation was observed in pigeons (35) and in rats (36,88,123) whose locomotion, shaking, and rearing (35,36,125), as well as exploratory behavior in the X maze apparatus (53), were dose-dependently depressed by acute HU 210. At high doses, the CB agonist induced unilateral rotational activity (circling) (35) and a cataleptic state (88,122), which was further enhanced in rats chronically treated with the dopamine receptor agonist SKF 38393 (122).

Tolerance, more or less complete, to HU 210-induced sedation was demonstrated (36,53) as it was for most of the pharmacological effects of CBs (29,122). Acute, but not subchronic (once daily for 7 days), administration of HU 210 potently counteracted acute and subchronic cocaine-induced hyperlocomotion and enhanced rearing (36). Similarly, the CB agonist, when acutely injected, inhibited locomotor activity, stereotyped behavior, and shaking elicited by the D_1/D_2 agonist CQP 201 403, while a subchronic treatment (once daily for 7 days) enhanced CQP 201 403 induced locomotor activity and potently stimulated escape attempts from observation cages (36). Awareness of the involvement of DA in the effects exerted by CBs has been greatly increased by the discovery of the colocalization of CB_1 and DA receptors in specific brain areas of several mammalian species (3,26,61,83,103). Since: 1) motor hyperactivity and stereotyped behavior elicited by cocaine and D_1/D_2 receptor agonists have been adopted for the study of the DAergic function associated with psychotic states, and 2) HU 210 shares with all neuroleptics the ability to antagonize these DA induced abnormal behaviors, it has been suggested that CBs might rather alleviate than worsen certain aspects of psychosis (36). A neuroleptic-like profile would be confirmed by the potent antiemetic properties displayed by HU 210 in pigeons (35) and the reported induced catalepsy (122).

The proposed neural substrates of CB/DA receptor interaction are the medium-spiny GABAergic neurones of the striatum which project to the globus pallidus and substantia nigra, and also to striatal cholinergic neurons (122). The activation of CB receptors located on striatonigral GABAergic neurons has been found to be accompanied by a reduction in neurotransmitter uptake, thus prolonging the presence of GABA in the synaptic cleft (126). This mechanism might explain the CB-induced motor inhibition through the potentiation of GABA function.

The observation that no relevant motor impairment is produced by HU 210 in rat swimming performance in a water maze task (37) needs further investigation to identify the reasons for the differential motor effects exerted by the compound depending on the experimental model adopted.

Cognitive Functions

CBs have long been known to impair learning, memory, and attention, as demonstrated in a variety of tasks in rodents, nonhuman primates, and humans (19). It is now well rec-

ognized that CB receptors are mainly localized in brain areas (61,83) that are directly involved in the control of cognitive processes and which contain ACh as a key neurotransmitter (6). HU 210, THC, WIN 55,212-2, and endogenous ligands have been found to inhibit hippocampal and medial prefrontal cortex long-term potentiation (LTP) (17,138, 140), a synaptic change suggested to be a neural mechanism for information storage in the brain (142). CB-mediated blockade of LTP in sectioned rat hippocampus was not displayed by the nonpsychoactive (+) isomer HU 211 and was prevented by the CB_1 antagonist SR 141716A (17,141). Again, recent *in vitro* and *in vivo* animal studies have demonstrated that ACh release and choline uptake, in the medial prefrontal cortex and hippocampus, are inhibited by different CB agonists and potentiated by the CB antagonist SR 141716A (49–51,79).

Experiments with rats subjected to a water maze task showed that HU 210 interfered with learning processes in a time- and dose-dependent manner; this finding is consistent with the neurochemical and electrophysiological hippocampal changes described above (37,110). On the whole, all data indicate that HU 210, like most CB agonists, produces disruptions of learning, although some studies suggest that CB system is not tonically involved in cognitive processes. In fact, little or no effect when administered alone was reported when SR 141716A was administered alone (11,85). It must be pointed out that, in humans, cannabis-induced impairment of cognitive functioning is questionable (82).

Emotional Responses

Dysphoria, anxiety, and panic have been described in humans, particularly after high doses and long-term exposure of marijuana and hashish (40,98,157); likewise, an anxiety-like state has been found in CB-treated rodents subjected to different behavioral procedures (29,109,123). Despite a state of marked sedation, rats injected with high doses of HU 210 were hypersensitive to tactile stimuli and vocalized strongly when touched (35,37). This unique mixture of depressant and stimulatory effects is typically induced by CBs (29). Vocalization is also considered a pointer of cannabimimetic activity (60) and was elicited by HU 210 at doses much lower than those of THC (35,37). This sign might reflect heightened emotionality associated with a state of fear, and the same anthropomorphic interpretation has been made with regard to aggressive reactions observed in rats after HU 210 (123) and other CBs (29). The correlation between CBs and stress has been long proposed (29) and supported by biochemical findings on animals, where, as already reported, CBs induce a potent secretion of ACTH (28) and CRF (123), which play a key role in stress (31,52). ACTH and CRF markedly enhance rat grooming (52,100), which probably represents a response to a state similar to psychological human mild stress since it manifests itself as stereotyped behavior in different stressful situations. While grooming is dose-dependently diminished by acute injection of HU 210 (35) and other CBs (125), it is increased by subchronic (once daily for 7 days) treatment with HU 210 at high doses (53). The drug provokes other behavioral patterns that seem to point to an anxiogenic activity; it enhances the rat's natural aversion for open spaces in the X maze test (53) as well as "wall hugging" (37). It has been hypothesized that the marked anxiety-like state induced by HU 210 at high doses may partially contribute to the disruptive effects exerted in most of the behaviors examined (35–38).

Sexual Behavior

Despite some anecdotal reports of the aphrodisiac effects of marijuana and others that describe cannabis-induced human sexual dysfunction (5,98), there are few properly controlled studies relating CB effects to sexual performance (29,42,108). A modification of this behavior would be amply justified because one of the main neurotransmitters involved in CB activity is DA which, as is well known, exerts a key role in modulating sexual behavior (95). Acute administration of THC interferes with rat copulatory behavior (97), decreasing the percentage of copulating animals and increasing the latency periods to mount and intromission (102). Likewise, HU 210 has been found to exert sexual inhibition in sexually active male rats (38). Impairment in the mating tests involved both the precopulatory phase, most commonly measured by latencies to mount and intromission, and the consummatory phase, mainly represented by the frequency of intromission and the latency to the first ejaculation (95). This effect was long lasting and ejaculatory mechanisms seemed to recover before sexual arousal, when the drug was discontinued. As the negative influence exerted by THC in male rat copulation was found to be associated with modified neuroendocrine responses (102), it is quite possible that the complex set of hormonal changes provoked by HU 210 (88) similarly plays a crucial role in mating impairment. HU 210 also inhibited female rat sexual behavior, potently interfering with lordosis and proceptive behaviors (e.g., ear wiggling and hopping) as indexes of sexual responsiveness (38).

Ingestive Behavior and Body Weight

Historical records support a role for the central CB system in feeding regulation. Since one of the most common effects of marijuana or hashish intoxication in humans is increased appetite (1,41,59,90), THC and dronabinol are used to promote overconsumption in patients with acquired immunodeficiency syndrome (AIDS) (4), Alzheimer's disease (152), and cancer (117). However, the modulation of feeding by the CB system is not well established, and considerable discrepancies emerge from the studies of CB influence on animal ingestive behavior as increases (145,155), decreases (29), or no effects (58) have been reported.

HU 210, subchronically administered in rats (once daily for 4 days), produces a dose- and time-dependent loss of body weight which, at high doses, is marked and is not regained for a long time after the drug is discontinued. These data are consistent with the anorexic effect displayed by the CB at high doses (54). Facilitation of ingestive behavior is not seen at any dose, as would be expected from the studies showing a biphasic modulation by THC of rodent eating (56).

DEPENDENCE

Although the neural substrate of the addictive effects of marijuana is still not well defined, considerable advances in this field have been made during the last years. Experimental evidence indicates that the facilitation of mesolimbic DA neurotransmission is the common neural substrate for the motivational and rewarding properties of drugs of abuse,

such as morphine, alcohol, and nicotine, and the same mechanism is now well recognized for CBs (46,49,96).

Brain CRF has also been implicated in the mediation of the stress-like symptoms observed during withdrawal of CBs and many drugs of abuse (124). As for CBs, a clear cut abstinence syndrome has rarely been reported, presumably because of their long life. Recent studies have demonstrated that in mice made tolerant to THC, the administration of SR 141716A promptly precipitates a profound withdrawal syndrome (20). Similar symptomatology is obtained in rats chronically treated with HU 210 and injected with the CB_1 antagonist (123,124). Enhanced withdrawal responses are found to be associated with an increased release of CRF in the limbic system, where maximal levels correspond to the maximal behavioral signs (123,124).

A link between the endogenous brain CB and opioid systems has been demonstrated; SR 141716A induces an opiate-like withdrawal in morphine-dependent rats and the same occurs when naloxone is injected in rats made CB-dependent by repeated administration of HU 210 (105). Despite the lack of influence of naloxone on the acute effects of THC (78,86), the suggestion that the CB_1 receptor may play a role in the neuroadaptive processes associated with opiate dependence (149,150) seems to be plausible, in view of the co-localisation of CB_1 and μ receptors in several brain areas (i.e., nucleus accumbens, septum, dorsal striatum, the central amygdaloid nucleus and the habenular complex) (105).

HYPOTHERMIC, ANALGESIC, AND ANTIINFLAMMATORY ACTIVITY

There are conflicting reports in the literature regarding the activity of "old" CBs in a number of animal assays for antiinflammatory, mild analgesic, and antipyretic effects (29). In general, HU 210 has been found to be 100–500 times more potent than THC in the induction of analgesia and hypothermia in rats (88,111). However, Zimmer et al. (1999) found that in knockout mice THC, but not HU 210, induced analgesia in the tail flick test. Hypothermia, which can be antagonized by adrenergic agonists and enhanced by adrenergic antagonists, does not seem to be related to prostaglandin synthesis, and it is probably dependent on HU 210 activity in the preoptic area (111). When examined for its influence on lipopolysaccharide-induced cytokines in Corynebacterium parvum primed and unprimed mice, HU 210 decreased production of inflammatory cytokines while increasing antiinflammatory interleukin-10 (135). The same effects were exerted by WIN 55,212-2, thus suggesting a role for the CB_1 receptor subtype in cytokine modulation by CB ligands (135). Antinociception by HU 210 (as well as that of WIN 55,212-2) was demonstrated in the tail-flick test, which was performed after microinjection in the rostral ventromedial medulla of rats (87). These data, along with those reporting that ANA was also analgesic (103), while the main CB_1 antagonist SR 141716A produced hyperalgesia (119), indicate that the CB receptor system participates in the control of nociception and suggest the possibility that CBs modulate nociceptive responsiveness (68,87).

CARDIOVASCULAR PHARMACOLOGY

Recreational use of marijuana or hashish in humans influences a number of physiological functions, including cardiovascular variables (3,29); moreover, there is growing evidence that endocannabinoids may have important cardiovascular actions (81,116). In animals, endocannabinoids, THC, and HU 210 induce hypotension and bradycardia *in vivo* and vasorelaxation *in vitro* (114,148,151,158), thus mimicking the effects observed in humans. Although some studies with the selective CB_1 receptor antagonist SR 141716A would implicate the CB_1 receptor subtype in CB-induced hypotension and bradycardia (75,148), a conclusion confirmed by the use of mice deficient in CB_1 receptors (76), other studies have found no antagonism of CB-induced vasorelaxation by SR 141716A (114). At present, there are many discordant findings regarding CB modulation of the cardiovascular system, probably due to the different species and arterial beds used (15). Again, the precise molecular site of the cardiovascular effects of CBs is unknown (63), although the involvement of several mechanisms has been proposed (67): 1) presynaptic inhibition of NE release from peripheral sympathetic nerve terminals; 2) centrally mediated sympathoinhibition; 3) direct activity on CB_1 receptors; 4) cross-talk between CB_1 and imidazoline receptors (99), which have been demonstrated to be inhibitory in animal and human blood vessels and heart (43,57); and 5) release of NO, which in turn inhibits NE release (2,133).

The possibility that HU 210 plays a role as a platelet aggregating agent, arising from a study showing ANA-induced rabbit platelet activation, has been discarded (10).

CONCLUSIONS

HU 210 has been found to be effective, when systemically administered to animals, at doses from 4 to 100 μg/kg, depending on the experimental models used. All in all, the results obtained in a great number of studies embracing various fields of physiology, biochemistry, and pharmacology indicate that this drug is one of the most potent and selective CB agonists available for research in the CB system. However, in the absence of demonstrated selectivity of action, many of the effects displayed by HU 210 may not be necessarily specific. Some pharmacological properties, such as antipyretic, antiinflammatory, analgesic, antiemetic and antipsychotic effects, as well as the modulation of immune function, support the potential clinical use of old and novel CBs.

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