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Cannabidiol: An Overview of Some Pharmacological Aspects

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Over the past few years, considerable attention has focused on cannabidiol (CBD), a major nonpsychotropic constituent of cannabis. The authors present a review on the chemistry of CBD and discuss the anticonvulsive, antianxiety, antipsychotic, antinausea, and antirheumatoid arthritic properties of CBD. CBD does not bind to the known cannabinoid receptors, and its mechanism of action is yet unknown. It is possible that, in part at least, its effects are due to its recently discovered inhibition of anandamide uptake and hydrolysis and to its antioxidative effect.

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Cannabidiol (CBD) was first isolated from the cannabis plant in the late 1930s and early 1940s, and its structure was elucidated in 1963. For an introduction to the chemistry of CBD, see Mechoulam and Hanus.[1] No pharmacological work was reported on CBD until the early 1970s, except the determination that it had no cannabis-like activity in vivo.[2,3] Over the next few years, some work was reported, particularly on its anticonvulsive effects. Later, antianxiety effects were noted, and some of its actions on the immune system were explored. More recently, its effects on nausea, as an antioxidant in biological systems and as an antirheumatoid arthritis drug, were reported. The present review summarizes these advances. Zuardi et al[4] have recently critically discussed the effects of CBD on some of these states. To avoid duplication, we emphasize in this review the antinausea and immune system effects, including rheumatoid arthritis, that are not evaluated by Zuardi et al.

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CBD: ANTICONVULSIVE EFFECTS

In the early 1970s, several groups found that CBD was active in reducing or blocking convulsions produced in experimental animals by a variety of procedures.[5-7] The CBD effects were comparable to those of diphenylhydantion (DPH) and other drugs, which are clinically effective in major seizures.[8] CBD was also found to enhance the anticonvulsant potency of DPH and phenobarbital.[8-9] Karler and Turkanis[10] compared the effects of CBD and THC in the maximal electroshock test in mice, which measures anticonvulsant activity. The ED_{50} of CBD (118 mg/kg) was close to that of Δ^9-THC (101 mg/kg). In frogs (*Rana pipiens*), both cannabinoids were about 1000 times more active, but only in the summer. In the winter, the frogs were not responsive to either cannabinoid, even at massive doses.[10] However, in another assay—the pentylene tetrazol minimal-seizure threshold test in mice—differences between the activities of CBD and THC were noted. It was assumed that THC and CBD act by different mechanisms, with CBD more closely resembling the well-established antiepileptics at that time (e.g., phenobarbital and DPH) than does Δ^9-THC. Indeed, when conformational energy maps were computed and compared for DPH and CBD, it was noted that the spatial relationship between the two rings in the two drugs was similar and close to the respective structures in the crystal. This was supported by ^{1}H and ^{13}C NMR measurements. It was also found that both compounds ful-

fill the stereochemical requirements suggested for anticonvulsant drug action.[11]

The early preclinical anticonvulsant work is well reviewed.[12,13] Consroe,[14] in a more recent review, has suggested that CBD is largely inactive in animal models of absence seizures produced by electroshock or chemoshock models. However, it is active against cortical focal seizures produced by topical application of convulsant metals or limbic seizures produced by electrical stimulation or kindling, as well as in generalized maximal (tonic-clonic) seizures produced by electroshock or GABA-inhibiting drugs.

Both CBD enantiomers are anticonvulsive.[15] It is quite possible that they act by different mechanisms. While the natural (–) CBD does not bind to the central cannabinoid receptor, CB1, the synthetic (+) CBD has recently been shown to bind to CB1.[16] The mechanism of (–) CBD anticonvulsive activity is unknown; however, it is reasonable to assume that (+) CBD, like THC, acts by activation of CB1. Recently, Wallace et al[17] compared the anticonvulsant effects of THC with those of CBD. The effects of THC could be blocked with a cannabinoid receptor antagonist, while those of CBD could not. The authors thus confirmed that the effects of CBD are not CB1 receptor mediated. These conclusions support the early observation by Karler and Turkanis.[10]

CBD has very low toxicity. LD_{50} on IV administration to the rhesus monkey was 212 mg/kg.[18] The oral LD_{50} could not be established, but it was pointed out that "the results obtained with prolonged oral CBD treatment should be viewed with the knowledge that the oral route requires 20-50 times larger cannabinoid dose than the i.v. route to initiate severe intoxication."[18] CBD did not elicit signs of CNS inhibition or stimulation and did not cause autonomic aberrations. Clinical measurements, eye examinations, and EKG recordings were normal. There were no significant alterations in growth rates.

The pharmacokinetics of CBD is quite complicated.[19] On IV administration, CBD is rapidly distributed, followed by prolonged elimination (terminal half-life = 9 h). CBD is barely absorbed after oral administration. The oral bioavailability ranges between 13% and 19%, which may be due to a first-pass effect. These observations may explain the results, described above, by Rosenkrantz et al.[18]

The essential lack of toxicity made possible an early anticonvulsive clinical trial.[20] After a phase I clinical trial in healthy volunteers, 15 patients suffering from secondary generalized epilepsy with temporal focus were randomly divided into two groups. Each patient received, in a double-blind procedure, 200 to 300 mg daily of CBD or placebo. The drugs were administered for as long as 4½ months. Clinical and laboratory examinations, EEG, and ECG were performed at 15- or 30-day intervals. Throughout the experiment, the patients continued to take the antiepileptic drugs prescribed before the experiment, although these drugs no longer controlled the signs of the disease. All patients and volunteers tolerated CBD very well, and no signs of toxicity or serious side effects were detected on examination. Four of the 8 CBD subjects remained almost free of convulsive crises throughout the experiment, and 3 other patients demonstrated partial improvement in their clinical condition. CBD was ineffective in 1 patient. The clinical condition of 7 placebo patients remained unchanged, whereas the condition of 1 patient clearly improved. Due to the huge amounts of drug required, this promising clinical trial was never continued.

CBD: SEDATIVE AND ANXIOLYTIC EFFECTS

In the early 1980s, several groups independently discovered that CBD has sedative and antianxiety properties, albeit at doses higher than those of the clinically used drugs at that time. Pickens[21] compared THC and CBD with chlorpromazine administered orally to mice and found that the sedative potency (SD_{50}) was 1.06 mg/kg for THC, 1.26 mg/kg for chlorpromazine, and 4.72 mg/kg for CBD.[21]

Musty[22] found that CBD improved avoidance learning in a stressful situation, decreased the occurrence of stress-induced ulcers in mice, and decreased response suppression in a punished response task. In a further work, Musty et al[23] showed that CBD affects conditioned anxiety-like behavior in a taste aversion model.

A Brazilian group, on the basis of initial studies in rats (unfortunately, some published in Portuguese and not generally available), undertook an evaluation of the action of CBD on anxiety and other effects produced by THC in normal subjects.[24] They found that CBD blocks the anxiety produced by THC. This effect also extended to other CNS effects caused by THC; however, not all THC effects were blocked. The effect of THC on pulse rate was unchanged. These observed effects support the widely held view that cannabis effects differ from those of THC alone, as the crude drug contains both CBD and THC. The same group later compared the anxiolytic effects of CBD with those of ipsapirone (a $5HT_{1A}$ partial agonist) and with diazepam in a double-blind study in a simulated public speaking test.[25] All three compounds were active, although the doses of CBD needed were considerably higher than those of the

two other drugs. No further human trials with CBD in anxiety have been reported, and there are no publications directly comparing the action of CBD, CBD/THC, or THC/cannabis in humans. However, the results in humans have been confirmed in animal studies. Guimaraes et al[26] showed that CBD in doses of 2.5, 5.0, and 10.0 mg/kg significantly increased the entry ratio (open/total number of entries) in the elevated plus-maze assay, an anxiolytic-like effect. CBD at a dose of 20.0 mg/kg was not effective. These results indicate that the anxiolytic effect of CBD in the elevated plus-maze, like many other effects of cannabinoids, is biphasic (cf. Sulcova et al[27]).

In a further publication by the same group, it was shown that the dimethylheptyl homolog of CBD (HU-219) is considerably more potent than CBD or diazepam in the same assay.[28]

Onaivi et al[29] also reported that, in contrast to effects seen with THC, mice treated with CBD spent a greater amount of time in the open arm of the elevated plus-maze, an effect similar to that produced by diazepam, the reference anxiolytic agent.

CBD: HYPNOTIC EFFECT

Monti[30] has reported that 20 mg/kg single doses of CBD decreased slow-wave sleep latency in rats, but higher doses caused an increase. However, wakefulness was decreased. This is another example of the biphasic action of CBD.

Carlini and Cunha[31] reported that relatively high doses of CBD (160 mg) caused significantly longer sleep in insomniacs than those on placebo.

CBD: ANTIPSYCHOTIC EFFECTS

Zuardi et al[32] have shown that CBD is active in animal models predictive of antipsychotic activity. Thus, CBD (15-480 mg/kg) reduced the occurrence of stereotype behavior induced by apomorphine and increased the doses of apomorphine needed to cause such behavior. The same effects were observed with haloperidol, albeit at much lower doses. However, haloperidol caused catalepsy at high doses, while CBD did not.

On the basis of these preclinical experiments and lack of toxicity (see above), a single case clinical trial was undertaken: a young 19-year-old black woman, diagnosed as schizophrenic, was administered CBD (up to 1.5 g/day). Improvement with CBD was observed in all items of the standard Brief Psychiatric Rating Scale (BPRS) and was essentially equivalent to that seen with haloperidol. The authors concluded that CBD may possess an atypical antipsychotic profile.[33]

A German group has looked into the effects of nabilone (a synthetic cannabinoid drug with THC-like properties) and CBD on binocular depth inversion. This visual phenomenon is a normal illusion of visual perception and is reduced in schizophrenic patients.[34] While nabilone caused impairment of binocular depth inversion, CBD reduced this impairment.[35] On this basis, the same group administered CBD to schizophrenic patients. Preliminary results, presented at a meeting, indicate positive results.[36] Is CBD, or a more potent derivative, going to become a new antischizophrenic drug?

CBD: ANTI-INFLAMMATORY EFFECTS

The pathogenesis involved in inflammatory reactions is complex and multifunctional. It is triggered and maintained by various intercellular mediators—the cytokines. One of these cytokines, tumor necrosis factor (TNF), is particularly important in triggering a cascade of other cytokines, which also participate in the inflammatory process. The rise and involvement of TNF in many pathological manifestations are well established. Recently, very encouraging results using anti-TNF therapy for rheumatoid arthritis and colitis were reported.[37] Potent suppression of the clinical manifestations of these chronic diseases was noted.

It is well established that stimulation causes a respiratory burst in phagocytes, characterized by a sharp increase in oxygen uptake. Reactive oxygen intermediates (ROI) are formed whose antimicrobial and antitumor activity is of major importance in the protection of body systems.[38]

Nitric oxide (NO) is an endogenous modulator with diverse biological functions.[39] It is produced by most mammalian cells and mediates multiple physiological and pathological processes. For example, it is a major endogenous regulator of vascular homeostasis and serves as a neurotransmitter in the brain and other parts of the body. NO has also been shown to possess antibacterial and antitumor activity[40] and affects various aspects of the inflammatory cascade.

It is well known, however, that many weapons of the immune system, which have the capacity to eliminate microbes and tumors, can also harm the host. For example, high levels of TNF, ROI, and NO can cause inflammation and damage cells and tissues and may also contribute to septic shock. Therefore, a primary therapeutic goal of using drugs acting on the immune system is to limit the effects of TNF, ROI, and NO.

A vast literature documents the immune-modulating effects of cannabinoids, mainly of Δ^9-THC, in vivo and

in vitro.[41] A partial list of in vitro effects of Δ^9-THC includes inhibition of the proliferative responses of T lymphocytes, inhibition of cytotoxic T cell activity, suppression of macrophage function and antigen presentation, and inhibition of NO production by macrophages. CBD has been reported to cause modulation of TNF, IL-1, and IFN-γ production by human peripheral blood mononuclear cells.[42,43] It suppresses chemokine production by a human B cell line.[44] These potentially anti-inflammatory properties of CBD, together with the lack of psychotropic effects and low toxicity, prompted Malfait et al[45] to test the potential of CBD as a therapeutic agent in collagen-induced arthritis (CIA).

CIA is a murine model for rheumatoid arthritis (RA). It is elicited by immunizing mice with type II collagen (CII) in complete Freund's adjuvant. The CII used is either bovine or murine, resulting in classical acute CIA or in chronic relapsing CIA, respectively. CBD was administered after onset of clinical symptoms, and in both models of arthritis, the treatment blocked progression of the disease.[45] CBD was effective when administered either i.p. or orally. The dose dependency showed a bell-shaped curve, with an optimal effect at 5 mg/kg per day i.p. or 25 mg/kg per day orally. Ex vivo, draining lymph node cells from CBD-treated mice showed diminished IFN-γ production, as well as decreased release of TNF by knee synovial cells. In vitro effects of CBD included a dose-dependent suppression of lymphocyte proliferation and the blockade of the Zymosan-triggered reactive oxygen burst generation by peritoneal granulocytes. CBD markedly lowered the production of TNF and NO in vitro by peritoneal macrophages (our unpublished data). It also suppressed mouse lymphocyte responses to mitogens and to allogenic stimuli and blocked the lipopolysaccharide-induced rise in serum TNF in mice. Taken together, these data show that CBD, through its combined immunosuppressive and anti-inflammatory actions, has a potent antiarthritic effect in CIA.[45]

CBD: ANTINAUSEA EFFECTS

The development of chemotherapy treatment has prolonged the lives of many cancer patients. However, use of these powerful drugs presents a serious challenge to both clinicians and patients. Significant side effects of cancer chemotherapy include nausea and vomiting, which may last for several days. These symptoms come to be dreaded by patients, often interfering with successful completion of treatment.

Although nausea often occurs prior to vomiting, each can occur independently. Nausea is a subjective phenomenon, an "unpleasant, but not painful, sensation associated with a heightened awareness of the upper gut, cold sweating and the feeling that vomiting is imminent."[46] In contrast, vomiting is a far more visible and easily recorded indictor of chemotherapy-induced side effects. In fact, vomiting is used in some antiemetic trials as the sole criterion of efficacy.[47] However, drugs effective against vomiting may not necessarily modify nausea, and drugs effective against nausea may not necessarily modify vomiting.

THC as an Antiemetic

Testimony of numerous patients, including the late Steven Jay Gould, indicates that marijuana reduces nausea and vomiting associated with chemotherapy, thereby maintaining the resolve to continue with therapy.[48] A survey of more than a thousand cancer specialists found that 44% had recommended THC or cannabis to at least one patient.[49]

Treatment of nausea is one of the few medical uses of a marijuana constituent that has been evaluated with clinical trials. The results of these trials, conducted primarily in the 1970s, indicated that pure Δ^9-THC and the synthetic cannabinoid nabilone (an analogue of THC) were as effective as any other antinausea agent available at the time.[50,51] For a review of clinical trials with Δ^9-THC (dronabinol), see Mechoulam et al.[52] There have been no animal or clinical trials that compare the effectiveness of cannabinoids with the powerful antiemetic HT_3 antagonists, nor have there been trials that evaluate cannabinoid use in combination with the serotonin antagonists.[53]

Recent experimental evidence that marijuana interferes with nausea and vomiting is limited. THC eliminates vomiting produced by cisplatin and the cannabinoid receptor antagonist SR 141716A.[54,55] The mechanism of action of the antinausea properties of THC is unknown; however, THC has been reported to reverse the effects of 5-HT_3 receptor agonists (which induce vomiting) in the nucleus tractus solitarii at the level of the area postrema, the chemoreceptor trigger zone for emetic reflexes.[56]

Conditioned Rejection Reactions as a Rat Model of Nausea

Animal models are essential to examine the efficacy and safety of agents used to treat the distressing side effects of both nausea and vomiting. Furthermore, animal models provide the opportunity to experimentally manipulate cues associated with chemotherapeutic

agents and to evaluate antiemetic treatment for anticipatory nausea and vomiting.

The phenomenon of nausea has been assessed exclusively by self-report in humans. However, there is considerable evidence (reviewed below) that nausea[57,58] and conditioned nausea[59,60] are displayed in rats as rejection reactions. The association between the flavor and activation of the emetic system results in altered affective reactions to the food or fluid. These altered affective reactions are called conditioned rejection reactions (gaping, chin rubbing, and paw treading in the taste reactivity test devised by Grill and Norgren[61]). Conditioned rejection reactions are exclusively elicited by emetic agents.[59,60,62-65]

Recent work indicates that conditioned rejection reactions in the taste reactivity test predict the emetic properties of an agent (in species that are capable of vomiting).[57,59-60] Since rats are incapable of vomiting, we have argued that these conditioned rejection reactions reflect nausea, based on the following evidence: (1) conditioned rejection reactions are selectively elicited by emetic treatments, such as lithium chloride, cyclophosphamide, high doses of nicotine, high doses of apomorphine, and full body rotation.[59,60,66] (2) Antiemetic treatments, including 5-HT antagonists and cannabinoid agonists, attenuate these conditioned rejection reactions.[67-70] (3) The literature on conditioned flavor avoidance learning has shown that flavor avoidance produced by drugs that elicit vomiting in other species is mediated by their action on the emetic systems of the midbrain and brainstem in rats. Ablation of the area postrema selectively eliminates taste avoidance and behavioral evidence of sickness produced by emetic agents.[71-74] (4) Ablation of the area postrema eliminates toxin-induced conditioned rejection reactions.[57,75] (5) Grundy[76] and his colleagues report that the vagal response to electrical and chemical stimulation by cytotoxic drugs in rats is similar to that of ferrets,[77-79] a species that vomits in response to these stimuli. This neural afferent reaction is disrupted by 5-HT_3 antagonists in both ferrets and rats.[75] These findings indicate that the gastrointestinal signals that precede vomiting in ferrets also occur in rats, suggesting that both species experience nausea.

Effect of Cannabinoids on Conditioned Rejection Reactions

We have recently reported that a low dose (0.5 mg/kg) of THC also attenuates conditioned rejection reactions,[68] although a much higher dose (2.5 mg/kg) is aversive to rats.[80] Limebeer and Parker[68] found that a dose of 0.5 mg/kg of THC eliminates the establishment of conditioned rejection reactions and the expression of previously established conditioned rejection reactions elicited by a cyclophosphamide-paired flavor. Cyclophosphamide is an agent used in chemotherapy treatment in humans. Rats administered THC during conditioning and during testing also displayed suppressed conditioned rejection reactions. Therefore, the decrement in responding at testing cannot be attributed to a change in state from conditioning to testing (i.e., our results cannot be attributed to state-dependent learning). These results demonstrate that THC interferes with cyclophosphamide-induced nausea in rats during conditioning and with conditioned nausea (anticipatory nausea) during testing.

CANNABIDIOL INTERFERES WITH NAUSEA IN RATS

Both THC (generic name dronabinol) and nabilone are clinically approved antinausea drugs for human patients, but as mentioned above, many users claim that marijuana suppresses nausea more effectively than oral THC.[48] In fact, the psychoactive effects of THC are disturbing to some patients, causing termination of use even though it may be effective against nausea.

Parker et al[70] evaluated the potential of CBD, which as mentioned above does not produce psychoactive effects, and its synthetic dimethylheptyl homolog (CBD-DMH) to suppress nausea in the conditioned rejection model. The potential of these nonpsychoactive cannabinoids to interfere with nausea was determined by administering them prior to lithium on the conditioning trial. In this trial, rats were injected with a low dose (5 mg/kg i.p.) of CBD, CBD-DMH, or vehicle 30 minutes prior to a pairing of saccharin solution and lithium chloride (20 ml/kg of 0.15 M LiCl) or saline. The potential of CBD and CBD-DMH to interfere with the expression of a previously established conditioned rejection (a model of anticipatory nausea) was evaluated by administering them prior to exposure on the taste reactivity test trial. On each of two tests, rats were injected with 5 mg/kg i.p. of the test drug (CBD, Experiment 1; CBD-DMH, Experiment 2) on one trial and with the vehicle on the other trial (in a counterbalanced order) 30 minutes prior to an intraoral infusion of saccharin solution. The rejection reactions (gapes, chin rubs, and paw treads) displayed by the rats during the infusion were videotaped.

Figure 1 presents the mean frequency of summed rejection reactions displayed during both the vehicle test trial and the drug test trial for each experiment. The pattern of results in both experiments was identical. Group vehicle lithium displayed conditioned rejection

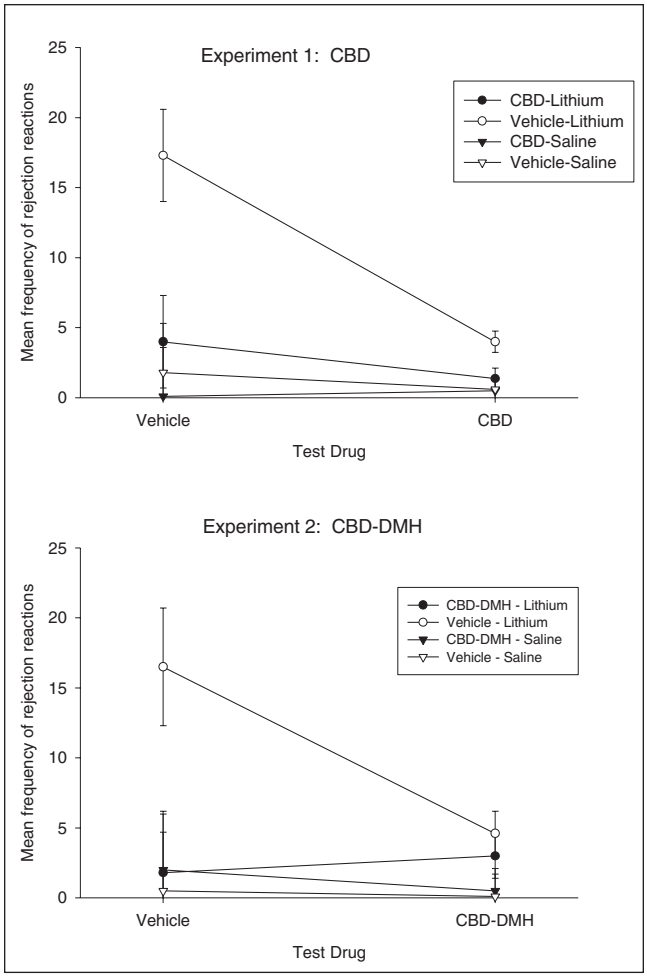

Figure 1. Mean (±SEM) frequency of conditioned rejection reactions displayed by groups pretreated with CBD (Experiment 1) or CBD-DMH (Experiment 2) during conditioning and testing. On the conditioning trial, independent groups received the cannabinoid or vehicle prior to receiving an intraoral infusion of saccharin solution, which was immediately followed by lithium or saline. On each of two test trials, rats were injected with the cannabinoid or vehicle (counterbalanced order) prior to receiving an intraoral infusion of saccharin solution.

reactions during the vehicle test only. When either CBD (Experiment 1) or CBD-DMH (Experiment 2) preceded lithium during conditioning, no rejection of saccharin solution occurred during the drug-free test (presumably because the drug interfered with lithium-induced nausea). Furthermore, when rats were administered either CBD or CBD-DMH prior to the test for conditioned rejection, these reactions were suppressed (presumably because the drug interfered with conditioned nausea).

These results suggest that the nonpsychoactive component of marijuana, CBD, and its synthetic homolog, CBD dimethylheptyl, interfere with nausea and conditioned nausea in rats. They provide promise for the development of an effective antinausea cannabinoid treatment for chemotherapy-induced nausea that is devoid of psychoactive side effects.

CBD: SPECULATIONS ON ITS MECHANISM OF ACTION

We have described above various effects caused by CBD. However, we are quite ignorant as to the biochemical or physiological mechanisms that are the basis of these activities. This situation contrasts sharply with that of THC, which mimics in many of its activities the endogenous cannabinoids. Cannabinoid receptors in the brain and the periphery bind THC but ignore CBD. Synthetic antagonists block THC (and endocannabinoid) action. None exist for the CBD effects. However, some recent observations may represent an opening toward elucidation of the CBD mechanism(s) of action.

Stereospecificity of CBD Action

As indicated above, both (–) and (+) CBD are anticonvulsive. Also, both (–) and (+) CBD similarly suppress TNF production by LPS-activated mouse macrophages (unpublished observations). On this basis, it was assumed that the actions of CBD are nonstereospecific. Recent data show that this is not the case, at least as regards binding to the cannabinoid receptors.[16] While (+) CBD and most of the (+) CBD analogs bind to both CB1 and CB2 receptors, (–) CBD and its analogs are essentially inactive. Obviously, CBD does not act through the known cannabinoid receptors, but the stereospecificity observed may indicate action through some other biochemical system (e.g., binding to another type of receptor). The existence of numerous, not well-characterized, new cannabinoid receptors has been suggested.[81-86] Is CBD a ligand to one of these? Indeed, evidence has been brought forward that suggests that CBD is an antagonist of an as-yet-unidentified endothelial receptor for anandamide.[86]

Inhibition of Anandamide Uptake

We have recently shown that CBD blocks anandamide uptake[16] and inhibits its enzymatic hydrolysis. If these effects are observed also in vivo, we may expect enhancement of endocannabinoid action, and at least

some of the CBD effects may in fact represent endocannabinoid actions.

Antioxidative Effect

CBD, like many other cannabinoids, is a potent antioxidative agent.[45,87] CBD was more protective against glutamate neurotoxicity than either ascorbate or α-tocopherol. The neuroprotection exhibited by CBD was unaffected by cannabinoid receptor antagonists. In view of its liposolubility, it may exert (nonspecific?) action both in the periphery and in the brain as it crosses the blood-brain barrier.

CONCLUSION

The nonpsychotropic CBD exhibits a plethora of effects, many of which may be of therapeutic importance or may serve as leads for pharmaceutical development.

It is unfortunate that the mechanism(s) of CBD action is still obscure; however, recent work on the stereospecificity of CBD action on its inhibition of anandamide uptake and hydrolysis, as well as on its antioxidative effects, may lead to elucidation of this longstanding enigma.

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