INTRODUCTION
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BASIC SCIENCE

Excised outside-out patches from HEK293 cells stably transfected with the human (h) 5-HT(3A) receptor cDNA were used to determine the effects of cannabinoid receptor ligands on the 5-HT-induced current using the patch clamp technique. In addition, binding studies with radioligands for 5-HT(3) as well as for cannabinoid CB(1) and CB(2) receptors were carried out. 2 The 5-HT-induced current was inhibited by the following cannabinoid receptor agonists (at decreasing order of potency): Delta(9)-THC, WIN55,212-2, anandamide, JWH-015 and CP55940. The WIN55,212-2-induced inhibition was not altered by SR141716A, a CB(1) receptor antagonist. WIN55,212-3, an enantiomer of WIN55,212-2, did not affect the 5-HT-induced current. 3 WIN55,212-2 did not change the EC(50) value of 5-HT in stimulating current, but reduced the maximum effect. 4 The CB(1) receptor ligand [(3)H]-SR141716A and the CB(1)/CB(2) receptor ligand [(3)H]-CP55940 did not specifically bind to parental HEK293 cells. In competition experiments on membranes of HEK293 cells transfected with the h5-HT(3A) receptor cDNA, WIN55,212-2, CP55940, anandamide and SR141716A did not affect [(3)H]-GR65630 binding, but 5-HT caused a concentration dependent-inhibition. 5 In conclusion, cannabinoids stereoselectively inhibit currents through recombinant h5-HT(3A) receptors independently of cannabinoid receptors. Probably the cannabinoids act allosterically at a modulatory site of the h5-HT(3A) receptor. Thus the functional state of the receptor can be controlled by the endogenous ligand anandamide. This site is a potential target for new analgesic and antiemetic drugs. British Journal of Pharmacology (2002) 137, 589-596.


The central cannabinoid receptor (CB(1)) antagonist, SR-141716A, has been used extensively to ascertain that cannabinoids interact with the CB(1) receptor. SR-141716A has been shown to produce effects opposite of cannabinoids when administered alone. It has been theorized that SR-141716A may act as an inverse agonist at the CB(1) receptor or by disinhibiting an endogenous cannabinoid tone. In an effort to ascertain the exact interaction between SR-141716A and the CB(1) receptor, we have conducted a structure-activity relationship study to compare CB(1) receptor affinity of SR-141716A analogs with their ability to produce an increase in locomotor activity. SR-141716A produced a significant increase in locomotor activity in mice within the first hour of administration. Twenty SR-141716A analogs from five different chemical series were also tested. Our data implicate particular regions of the SR-141716A molecule that may be involved in stimulation and depression of locomotor activity. When the K(I) of the analogs was plotted against the percent stimulation that each analog produced, it is evident that there is no correlation between the ability of the analogs to stimulate locomotor activity and their affinity for the CB(1) receptor. [35S]GTPgammaS binding data indicate that SR-141716A and five of the analogs are inverse agonists. However, none of the analogs demonstrating inverse agonism
produce stimulation of locomotor activity. It is therefore concluded that the SR-141716A-induced stimulation in locomotor activity is not the result of inverse agonist activity at the CB(1) receptor or by disinhibition of an endogenous tone.


Tolerance to the effects of the cannabinoid agonist Delta(9)-tetrahydrocannabinol (Delta(9)-THC) was characterized in rats responding under a multiple schedule of repeated acquisition and performance. During the acquisition component, subjects acquired a different three-response sequence each session, whereas in the performance component the sequence was the same each session. Responding was maintained under a second-order fixed-ratio 2 (FR2) schedule of food reinforcement. Acute doses of Delta(9)-THC (1-10 mg/kg) decreased rate and accuracy in both components, whereas doses of the cannabinoid (CB1) receptor antagonist N-(piperidin-1-yn)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716A; 0.32 and 1 mg/kg) were ineffective. While 5.6 mg/kg of Delta(9)-THC disrupted responding when administered acutely, tolerance to the rate-decreasing and error-increasing effects of this dose developed in both components after daily administration. When 1 mg/kg of SR141716A was substituted for Delta(9)-THC during chronic administration, this previously ineffective dose selectively increased within-session errors in the acquisition component of the multiple schedule. During the postchronic phase, subjects were generally less sensitive to the disruptive effects of Delta(9)-THC. In summary, these data demonstrated that tolerance to Delta(9)-THC developed across two different behavioral tasks and that learning was generally more sensitive than performance to the effects of SR141716A during chronic treatment with Delta(9)-THC.


Cannabinoids, the active components of marijuana, are presumed to affect memory by an action on long-term potentiation. However, these molecules also reduce hippocampal glutamatergic neurotransmission. To distinguish the two activities, we studied the effects of the synthetic cannabinoid (R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphtalenylmethanone (Win 55,212-2, 10 &mgr;M) on CA1 hippocampal responses generated by the activation of two independent pathways, one of which was potentiated with a tetanic stimulation. The results of the study show the following: (a) the drug does not affect long-term potentiation provided that the responses are compared to those obtained in the unpotentiated control pathway; (b) Win 55,212-2 increases post-tetanic potentiation.


Our earlier studies demonstrated that in the hippocampus, cannabinoids suppress inhibitory synaptic transmission via CB(1) cannabinoid receptors, whereas a novel cannabinoid-sensitive receptor modulates excitatory synapses (). The novel receptor does not correspond to CB(2), since this receptor type is not expressed in the brain (Munro, S. et al., Nature 365 (1993) 61). Recent binding experiments revealed that the synthetic cannabinoid WIN 55,212-2 binds with lower affinity to brain membranes of CB(1) receptor-knockout mice indicating that pharmacological differences exist between these two types of cannabinoid receptors in the hippocampus (). To analyze this difference in detail, we first determined the EC(50) values of WIN 55,212-2 for excitatory and inhibitory transmission in rat hippocampal slices using whole-cell patch-clamp recordings. The estimated EC(50) value for inhibitory postsynaptic currents (IPSC) evoked by electrical stimulation in CA1 pyramidal cells was 0.24 &mgr;mM, whereas for excitatory postsynaptic currents (EPSC) it was 2.01 &mgr;mM, respectively. The cannabinoid antagonist, AM251, blocked the WIN 55,212-2-induced inhibition of evoked IPSCs, but not of EPSCs, providing evidence for its selectivity for CB(1). We then tested the hypothesis of whether the cannabinoid effect on hippocampal excitatory neurotransmission is mediated via receptors with
an affinity for vanilloid ligands. Co-application of the vanilloid receptor antagonist capsazepine (10 &mgr;M) with cannabinoids (WIN55,212-2 or CP55,940) prevented the reduction of EPSCs, but not of IPSCs. The amplitude of evoked EPSCs was also suppressed by superfusion of the vanilloid receptor agonist capsaicin (10 &mgr;M), an effect which could also be antagonized by capsazepine. In contrast, capsaicin did not change the amplitude of evoked IPSCs. These results demonstrate that WIN 55,212-2 is an order of magnitude more potent in reducing GABAergic currents via CB(1) than in inhibiting glutamatergic transmission via the new CB receptor. The sensitivity of the new CB receptor (and EPSCs) to vanilloid ligands, but not to the cannabinoid antagonist AM251, represents another pharmacological tool to distinguish the two receptors, since CB(1) (and its effect on IPSCs) is not modulated by vanilloids, but is antagonized by AM251.


Agonists at cannabinoid-1 (CB-1) receptors stimulate feeding and particularly enhance the reward aspects of eating. To investigate whether endogenous cannabinoids might influence appetite for palatable food, we compared CB-1 receptor density in the forebrain and hypothalamus, between rats fed standard chow (n=8) and others given palatable food (n=8) for 10 weeks to induce dietary obesity. CB-1 receptor density was significantly decreased by 30-50% (P<0.05) in the hippocampus, cortex, nucleus accumbens and entopeduncular nucleus of diet-fed rats. Furthermore, CB-1 receptor density in the hippocampus, nucleus accumbens and entopeduncular nucleus was significantly inversely correlated with intake of palatable food (r(2)=0.25-0.35; all P<0.05). By contrast, CB-1 receptor binding in the hypothalamus was low and not altered in diet-fed rats. CB-1 receptor down-regulation is consistent with increased activation of these receptors by endogenous cannabinoids. Acting in areas such as the nucleus accumbens and hippocampus, which are involved in the hedonic aspects of eating, cannabinoids may therefore drive appetite for palatable food and thus determine total energy intake and the severity of diet-induced obesity. However, cannabinoids in the hypothalamus do not appear to influence this aspect of eating behaviour.


The endocannabinoid system (i.e., the cannabinoid receptors and their endogenous ligands) plays an important role in the physiological control of intestinal motility. However, its participation in intestinal pathological states is still poorly understood. In the present study, we investigated the possible role of the endocannabinoid system in the pathogenesis of paralytic ileus, a pathological state consisting of decreased intestinal motility following peritonitis, surgery, or other noxious situations. Ileus was induced by i.p. administration of acetic acid, and gastrointestinal propulsion was assessed by the charcoal method. Endocannabinoid levels were measured by isotope-dilution gas chromatography-mass spectrometry, whereas cannabinoid CB1 receptors were identified by immunohistochemistry. Acetic acid administration inhibited gastrointestinal transit (ileus), and this effect was accompanied by increased levels of the endocannabinoid anandamide compared with control mice and by overexpression of CB1 receptors in myenteric nerves. Furthermore, acetic acid-induced ileus was alleviated by the CB1 receptor antagonist SR141716A and worsened by VDM11, a selective inhibitor of anandamide cellular uptake (and hence inactivation). From these findings, it can be concluded that the intestinal hypomotility typical of paralytic ileus is due, at least in part, to the enhancement of anandamide levels and CB1 expression during this condition, and that selective, nonpsychotropic CB1 receptor antagonists could represent new drugs to treat this disorder.


Yawning is a reflex or event that is not fully understood. It is controlled by many neurotransmitters and neuropeptides and can be induced pharmacologically by cholinergic or
dopaminergic agonists. Amongst their many actions, cannabinoids acting on cannabinoid (CB(1) or CB(2)) receptors can alter cholinergic and/or dopaminergic activity. This study examined the effects of Delta(8)-tetrahydrocannabinol (Delta(8)-THC) administered acutely (2.5 mg/kg intraperitoneally [ip], 15 min before test) or chronically (5 mg/kg for 30 days followed by 24 h or 7 days of discontinuation) on yawning induced by pilocarpine, a cholinergic agonist (0, 1, 2, 4 or 8 mg/kg ip), or apomorphine, a dopaminergic agonist (0, 20, 40 or 80 &mgr;g/kg subcutaneously [sc]). Acute effects of different doses of Delta(9)-tetrahydrocannabinol (Delta(9)-THC; 0, 0.5, 1.25 or 2.5 mg/kg ip) on yawning induced by pilocarpine (2 mg/kg ip) or apomorphine (40 &mgr;g/kg sc) were also investigated. Both pilocarpine and apomorphine produced yawning in a dose-related manner. Acute administration of Delta(8)-THC and Delta(9)-THC significantly reduced yawning induced by both pilocarpine and apomorphine. Chronic administration of Delta(8)-THC did not change yawning induced by either agonist 24 h or 7 days after discontinuation of Delta(8)-THC. However, a high frequency of spontaneous yawning was observed 7 days after Delta(8)-THC discontinuation. These results suggest that cannabinoid agonists inhibited yawning induced by cholinergic or dopaminergic agonists. In addition, the increased frequency of spontaneous yawning following cessation of chronic administration of a cannabinoid agonist may be of importance as a withdrawal sign for these drugs.


The ether extract of the New Zealand liverwort Radula marginata afforded a new cannabinoid type bibenzyl compound named perrottetinenic acid, and two new bibenzyls, together with a known cannabinoid, perrottetinene. Their structures were established by two dimensional (2D) NMR spectral data. The structure of perrottetinenic acid was a similar to that of Delta(1)-tetrahydrocannabinol, a known hallucinogen. Cannabinoid type bibenzyls have been isolated from liverwort Radula perrottetii, though have not previously been reported from the liverwort R. marginata.

CLINICAL SCIENCE


RATIONALE. Although some aspects of memory functions are known to be acutely impaired by Delta(9)-tetrahydrocannabinol (Delta(9)-THC; the main active constituent of marijuana), effects on other aspects of memory are not known and the time course of functional impairments is unclear. OBJECTIVE. The present study aimed to detail the acute and residual cognitive effects of Delta(9)-THC in infrequent cannabis users. METHODS. A balanced, double-blind cross-over design was used to compare the effects of 7.5 mg and 15 mg Delta(9)-THC with matched placebo in 15 male volunteers. Participants were assessed pre and 1, 2, 4, 6, 8, 24 and 48 h post-drug. RESULTS. Delta(9)-THC 15 mg impaired performance on two explicit memory tasks at the time of peak plasma concentration (2 h post-drug). At the same time point, performance on an implicit memory task was preserved intact. The higher dose of Delta(9)-THC resulted in no learning whatsoever occurring over a three-trial selective reminding task at 2 h. Working memory was generally unaffected by Delta(9)-THC. In several tasks, Delta(9)-THC increased both speed and error rates, reflecting "riskier" speed-accuracy trade-offs. Subjective
METHODS. Twelve healthy subjects who regularly used both marijuana and alcohol completed nine test sessions in a counterbalanced within-subject design. Subjects drank a beverage (0, 0.25, or 0.5 g/kg alcohol) then smoked a cigarette (0, 1.75, or 3.33% THC). Testing began 2 min after smoking and was conducted within the ascending limb of the blood alcohol curve. RESULTS. The 0.5 g/kg alcohol dose significantly increased brake latency without affecting body sway. In contrast, the 3.3% THC dose increased body sway but did not affect brake latency. There were no additive drug effects on mood or behavior. CONCLUSIONS. Although field sobriety tests are often used to determine driving impairment, these results suggest that impaired balance following marijuana use may not coincide with slowed reaction time. Conversely, braking impairment from low doses of alcohol may not be revealed by tests of balance.

RESULTS. Bivariate correlations demonstrate associations between many risk and protective factor domains, shows that rurality of residence and rurality of county both strongly and independently increase the risk of trying smokeless tobacco. Rurality of county also increases the odds of having smoked cigarettes. However, it has a weak but significant protective effect with respect to lifetime use of alcohol. Neither measure of rurality was a significant risk or protective factor for lifetime use of marijuana. CONCLUSIONS: Findings suggest that it is inappropriate to discuss the relationship between rurality and ATOD use as if ATOD use is a unitary phenomenon. Patterns of use and the salience of risk and protective factors vary across substances. In addition, the findings reiterate the need for more gradations in measures of rurality than the metro/non-metro dichotomy reported in most government documents.

Conflicting predictions have been made to the influence of decriminalization on cannabis use. Prohibitionists forecast that decriminalization will lead to an increase in consumption of cannabis, while their opponents hypothesise that cannabis use will decline after decriminalization. Most probably cannabis use in the Netherlands so far evolved in two waves, with a first peak around 1970, a low during the late 1970s and early 1980s, and a second peak in the mid-1990s.

It is striking that this trend in cannabis use among youth in the Netherlands rather parallels four identified stages in the availability of cannabis. The number of cannabis users peaked when the cannabis was distributed through an underground market (late 1960s and early 1970s). Then the number decreased as house dealers were superseeding the underground market (1970s), and went up again after coffee shops took over the sale of cannabis (1980s), and stabilised or slightly decreased by the end of the 1990s when the number of coffee shops was reduced. Although changes in cannabis policy went along with changes in availability of cannabis and prevalence of cannabis use, it is questionable whether changes in cannabis policy were causally related to trends in cannabis use. Cannabis use also developed in waves in other European countries that did not decriminalize cannabis, as well as in the US. Consequently, trends in cannabis use seem to develop rather independently of cannabis policy.

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