INTRODUCTION

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BASIC SCIENCE


Cannabinoids are powerful hypotensives and vasodilators. However, their mode of action is controversial. This study is the first to investigate the distribution of vascular CB1 receptor protein expression in situ. We used double-fluorescence and chromogenic immunohistochemistry to investigate patterns of CB1 protein expression in cerebrovascular tissue in rat brain sections. We found a layer of intense CB1 labeling immediately adjacent to the internal elastic lamina, consistent with myointimal and vascular smooth muscle cells, and diffuse labeling adventitial to this layer. We concluded that CB1 receptor are most intensely expressed in the vascular smooth muscle layer in cerebral arteries, and are likely to be chiefly responsible for the potent vasodilatory effect of cannabinoids.


Cannabinoid receptors type 1 (CB1) play a central role in both short-term and long-term extinction of auditory-cued fear memory. The molecular mechanisms underlying this function remain to be clarified. Several studies indicated extracellular signal-regulated kinases (ERKs), the phosphatidylinositol 3-kinase with its downstream effector AKT, and the phosphatase calcineurin as potential molecular substrates of extinction behavior. To test the involvement of these kinase and phosphatase activities in CB1-dependent extinction of conditioned fear behavior, conditioned CB1-deficient mice (CB1(-/-)) and wild-type littermates (CB1(+/+)) were sacrificed 30 min after recall of fear memory, and activation of ERKs, AKT, and calcineurin was examined by Western blot analysis in different brain regions. As compared with CB1(+/+), the nonreinforced tone presentation 24 h after auditory-cued fear conditioning led to lower levels of phosphorylated ERKs and/or calcineurin in the basolateral amygdala complex, ventromedial prefrontal cortex, dorsal hippocampus, and ventral hippocampus of CB1(-/-). In contrast, higher levels of phosphorylated p44 ERK and calcineurin were observed in the central nucleus of the amygdala of CB1(-/-). Phosphorylation of AKT was more pronounced in the basolateral amygdala complex and the dorsal hippocampus of CB1(-/-). We propose that the endogenous cannabinoid system modulates extinction of aversive memories, at least in part via regulation of the activity of kinases and phosphatases in a brain structure-dependent manner.


The endocannabinoid system consists of several endogenous lipids, including anandamide and 2-arachidonoyl-glycerol (2-AG), and constitute a retrograde signalling system, which modulates neurotransmitter release and synaptic plasticity. Specific brain-type cannabinoid receptors (CB(1)) are widely distributed in the central nervous system, and are localized presynaptically. Mounting evidence, reviewed here, indicates that cannabinoids can act to
increase food consumption, and cannabinoid CB(1) receptor antagonists/inverse agonists reduce food intake and suppress operant responding for food rewards. Hence, endocannabinoids provide the first example of a retrograde signalling system, which is strongly implicated in the control of food intake. Benzodiazepine and opioid palatability-dependent appetite are well-established processes supported by several sources of convergent evidence; they provide pharmacological benchmarks against which to evaluate the endocannabinoids. To date, evidence that endocannabinoids specifically modulate palatability as an affective evaluative process is insufficient and not compelling. Endocannabinoids may have important clinical utility in the treatment of human obesity and forms of eating disorders.


The effects of Rimonabant (SR141716), an antagonist at cannabinoid CB1 receptors, were evaluated in animal models for subjective and rewarding effects of nicotine. Acute administration of 1 or 3 mg/kg SR141716 blocked expression of nicotine-induced conditioned place preferences. SR141716 (0.3-3 mg/kg) was also studied in rats trained to discriminate nicotine from saline under a fixed-ratio schedule of food delivery. In contrast to nicotine replacement therapy and bupropion, SR141716 did not have nicotine-like discriminative effects and did not alter the dose-response curve for nicotine discrimination. These findings support the proposed use of SR141716 for smoking cessation and indicate that it would selectively reduce the influence of environmental stimuli that contribute to persistent smoking behavior, without affecting subjective responses to nicotine.


Recent research suggests that the endogenous cannabinoids ("endocannabinoids") and their cannabinoid receptors have a major influence during pre- and postnatal development. First, high levels of the endocannabinoid anandamide and cannabinoid receptors are present in the preimplantation embryo and in the uterus, while a temporary reduction of anandamide levels is essential for embryonal implantation. In women accordingly, an inverse association has been reported between fatty acid amide hydrolase (the anandamide degrading enzyme) in human lymphocytes and miscarriage. Second, CB(1) receptors display a transient presence in white matter areas of the pre- and postnatal nervous system, suggesting a role for CB(1) receptors in brain development. Third, endocannabinoids have been detected in maternal milk and activation of CB(1) receptors appears to be critical for milk sucking by newborn mice, apparently activating oral-motor musculature. Fourth, anandamide has neuroprotectant properties in the developing postnatal brain. Finally, prenatal exposure to the active constituent of marihuana (Delta(9)-tetrahydrocannabinol) or to anandamide affects prefrontal cortical functions, memory and motor and addictive behaviors, suggesting a role for the endocannabinoid CB(1) receptor system in the brain structures which control these functions. Further observations suggest that children may be less prone to psychoactive side effects of Delta(9)-tetrahydrocannabinol or endocannabinoids than adults. The medical implications of these novel developments are far reaching and suggest a promising future for cannabinoids in pediatric medicine for conditions including "non-organic failure-to-thrive" and cystic fibrosis.


The pharmacology of monoacylglycerol lipase (MAGL) is not well understood. In consequence, the abilities of a series of analogues of 2-arachidonoylglycerol (2-AG) to inhibit cytosolic 2-oleoylglycerol and membrane-bound anandamide hydolysis by MAGL and fatty acid amide hydrolase (FAAH), respectively, have been investigated. 2-AG and its 1-regioisomer (1-AG) interacted with MAGL with similar affinities (IC50 values 13 and 17 microM, respectively). Shorter homologues of 2-AG (2-linoleoylglycerol and 2-oleoylglycerol) had affinities for MAGL
similar to 2-AG. This pattern was also seen when the arachidonoyl side chain of arachidonoyl trifluoromethylketone was replaced by an oleoyl side chain. Arachidonoyl serinol (IC50 value 73 microM) was a weaker inhibitor of MAGL than 2-AG. The IC50 values of noladin ether towards MAGL and FAAH were 36 and 3 microM, respectively. Arachidonoyl glycine interacted with FAAH (IC50 value 4.9 microM) but only weakly interacted with MAGL (IC50 value >100 microM). alpha-Methyl-1-AG had similar potencies towards MAGL and FAAH (IC50 values of 11 and 33 microM, respectively). O-2203 (1-(20-cyano-16,16-dimethyl-eicosa-5,8,11,14-tetraenoyl) glycerol) and O-2204 (2-(20-hydroxy-16,16-dimethyl-eicosa-5,8,11,14-tetraenoyl) glycerol) were slightly less potent, but again affected both enzymes equally. alpha-Methyl-1-AG, O-2203 and O-2204 interacted only weakly with cannabinoid CB1 receptors expressed in CHO cells (Ki values 1.8, 3.7 and 3.2 microM, respectively, compared with 0.24 microM for 1-AG) and showed no evidence of central cannabinoid receptor activation in vivo at doses up to 30 mg kg(-1) i.v. It is concluded that compounds like alpha-Methyl-1-AG, O-2203 and O-2204 may be useful as leads for the discovery of selective MAGL inhibitors that lack direct effects upon cannabinoid receptors.


Delta9-Tetrahydrocannabinol, a major psychoactive constituent of marijuana, interacts with specific receptors, i.e., the cannabinoid receptors, thereby eliciting a variety of pharmacological responses. To date, two types of cannabinoid receptors have been identified: the CB 1 receptor, which is abundantly expressed in the nervous system, and the CB 2 receptor, which is predominantly expressed in the immune system. Previously, we investigated in detail the structure-activity relationship of various cannabinoid receptor ligands and found that 2-arachidonoylglycerol is the most efficacious agonist. We have proposed that 2-arachidonoylglycerol is the true natural ligand for both the CB 1 and CB 2 receptors. Despite the potential physiological importance of 2-arachidonoylglycerol, not much information is available concerning its biological activities toward mammalian tissues and cells. In this study, we examined the effect of 2-arachidonoylglycerol on morphology as well as the actin filament system in differentiated HL-60 cells which express the CB 2 receptor. We found that 2-arachidonoylglycerol induces rapid morphological changes such as the extension of pseudopods. We also found that it provokes a rapid actin polymerization in these cells. The actin polymerization induced by 2-arachidonoylglycerol was abolished when cells were treated with SR144528, a CB2 receptor antagonist, and pertussis toxin, suggesting that the response was mediated by the CB 2 receptor and Gi/o. A phosphatidylinositol 3-kinase, Rho family small G proteins and a tyrosine kinase were also suggested to be involved. Reorganization of the actin filament system is known to be indispensable for a variety of cellular events; it is possible that 2-AG plays physiologically essential roles in various inflammatory cells and immune-competent cells by inducing a rapid actin rearrangement.


Affinities and efficacies of several reference cannabinoid ligands were investigated at central and peripheral cannabinoid receptors in three different species (rat, mouse, and human). The tested compounds belong to different chemical classes such as classical and non-classical terpene derivatives (Delta(8)-THC, Delta(9)-THC, HU 210, CP 55,940, CP 55,244, CP 55,243 and CP 47,947), aminoalkylindole (WIN 55,212-2, WIN 55,212-3) and diarylpyrazole cannabinoids (SR 141716A, SR 144528). As cannabinoid receptors have been shown to be mainly coupled to Gi/o type G-proteins, and by using the [(35)S]-GTPgammaS nucleotide binding modulation, we characterized the functional activity of these ligands which can act as agonists (positive intrinsic activity), partial agonists (partial positive intrinsic activity), antagonists (no intrinsic activity), or inverse agonists (negative intrinsic activity). To our knowledge, some derivatives (Delta(8)-THC, WIN 55,212-3, CP 55,243 and CP 47,947) have never been characterized in [(35)S]-GTPgammaS binding assays and up to now, this study represents the
largest survey of reference cannabinoids performed in unique experimental conditions and in the same laboratory.


In recent years, it has been demonstrated that high circulating levels of the endogenous cannabinoid anandamide, resulting from low expression of its metabolizing enzyme fatty acid amide hydrolase (FAAH), may contribute to spontaneous miscarriage and poor outcome in women undergoing in vitro fertilization. The site of action of this compound, however, has not been determined. In this study, we examined the distribution of the cannabinoid receptors, CB1 and CB2, and the endocannabinoid-metabolizing enzyme FAAH in first trimester human placenta. Here, we show that FAAH is expressed throughout the human first trimester placenta, in extravillous trophoblast columns, villous cytotrophoblasts, syncytiotrophoblasts, and macrophages. Furthermore, FAAH mRNA levels appear to be regulated during gestation, with levels peaking at 11 wk before declining again. The immune system-associated cannabinoid CB2 receptors were localized only to placental macrophages. Interestingly, the cannabinoid receptor CB1 was not identified in first trimester placenta despite having previously been shown to be present in placental tissues at term. These findings suggest that the placenta may form a barrier preventing maternal-fetal transfer of anandamide and/or modulate local levels of anandamide by regulation of FAAH expression with gestation.


Cannabinoids induce the expression of the cyclooxygenase-2 (COX-2) isoenzyme in H4 human neuroglioma cells via a pathway independent of cannabinoid- or vanilloid receptor activation. The underlying mechanism was recently shown to involve increased synthesis of ceramide, which in turn leads to activation of p38 and p42/44 mitogen-activated protein kinases (MAPKs). The present study investigates a possible contribution of membrane lipid rafts to cannabinoid-induced COX-2 expression. To address this issue, we tested the influence of methyl-beta-cyclodextrin (MCD), a membrane cholesterol depletor, on COX-2 expression by the endocannabinoid analogue R(+)-methanandamide (R(+)-MA). Incubation of H4 cells with MCD was associated with a loss of lipid raft integrity and a substantial inhibition of R(+)-MA-induced COX-2 expression and subsequent formation of prostaglandin E(2). Moreover, MCD was shown to suppress signal transduction steps upstream to COX-2 induction by R(+)-MA. Accordingly, the cholesterol depletor suppressed R(+)-MA-induced formation of ceramide as well as phosphorylation of p38 and p42/44 MAPKs. Together, our results suggest that R(+)-MA induces COX-2 expression in human neuroglioma cells via a pathway linked to lipid raft microdomains.


Delta(9)-Tetrahydrocannabinol from Cannabis sativa is mimicked by cannabimimetic analogs such as CP55940 and WIN55212-2, and antagonized by rimonabant and SR144528, through G-protein-coupled receptors, CB(1) in the brain, and CB(2) in the immune system. Eicosanoids anandamide and 2-arachidonoylglycerol are the "endocannabinoid" agonists for these receptors. CB(1) receptors are abundant in basal ganglia, hippocampus and cerebellum, and their functional activity can be mapped during behaviors using cerebral metabolism as the neuroimaging tool. CB(1) receptors couple to G(i/o) to inhibit cAMP production, decrease Ca(2+) conductance, increase K(+) conductance, and increase mitogen-activated protein kinase activity. Functional activation of G-proteins can be imaged by [35S]GTPgammaS autoradiography. Post-synaptically generated endocannabinoids form the basis of a retrograde signaling mechanism referred to as depolarization-induced suppression of inhibition (DSI) or excitation (DSE). Under circumstances of sufficient intracellular Ca(2+) (e.g., burst activity in seizures), synthesis of endocannabinoids releases a diffusible retrograde messenger to stimulate presynaptic CB(1) receptors. This results in suppression of gamma-aminobutyric acid (GABA) release, thereby relieving the post-synaptic inhibition. Tolerance develops as neurons adjust both receptor number
and cellular signal transduction to the chronic administration of cannabinoid drugs. Future therapeutic drug design can progress based upon our current understanding of the physiology and pharmacology of CB(1), CB(2) and related receptors. One very important role for CB(1) antagonists will be in the treatment of craving in the disease of substance abuse.


(-)-Adamantyl-Delta-tetrahydrocannabinol (AM-411) is a 'classical' tricyclic cannabinoid CB1 receptor agonist in which the C-3 alkyl side-chain has been replaced with an adamantyl group. The compound is cannabinoid CB1 receptor subtype selective (CB1Ki=6.86 nmol/l, CB2Ki=52.0 nmol/l). We examined the effects of AM-411 alone and in combination with the cannabinoid CB1 receptor antagonist/inverse agonist, SR-141716, on open-field behaviors of rats. The lowest effective dose of AM-411, 3 mg/kg, suppressed ambulation (horizontal activity) and rearing (vertical activity) and increased circling frequency compared to vehicle control levels. Co-administration of SR-141716 normalized these changes. SR-141716 (3 and 5.6 mg/kg) also produced significant increases in scratching and grooming (both frequency and duration), effects that were not eliminated in the presence of AM-411. Coupled with previous drug discrimination data, the open-field profile of AM-411 suggests that this high-affinity CB1 cannabinoid receptor agonist induces behavioral effects similar to the natural cannabinoid Delta-tetrahydrocannabinol and different from (R)-methanandamide, a chiral analog of the endogenous ligand anandamide.


AIMS: The cannabinoid CB1 receptor antagonist, SR141716A, differentially affects the ethanol preference of chronically alcoholized rats when administered during cycles of ethanol exposure and withdrawal. In this study, ethanol preference was investigated in chronically alcoholized rats that underwent regular withdrawal periods during which the brain cannabinoid CB1 receptor antagonist, SR141716A, was administered. METHODS: The cannabinoid receptor antagonist SR141716A, 3 or 10 mg/kg/day, was administered i.p. to Wistar rats at the conclusion of a 4-week period of chronic alcoholization, as they commenced a cycle of alcohol withdrawal for 10 days followed by a period of 10 days chronic ethanol exposure. In a second set of experiments, an additional cycle of ethanol withdrawal and re-exposure was given. Preference for ethanol versus water started at the end of the first or second chronic ethanol re-exposure for a period of at least 30 days. RESULTS: In rats pretreated with the higher dose of SR141716A, ethanol preference during free choice was significantly increased after two ethanol re-exposures. In contrast, pretreatment with the lower SR141716A dose induced no significant change in ethanol intake during the free choice followed by either one or two ethanol re-exposures. CONCLUSIONS: SR141716A, 10 mg/kg/day dose, induced a significant increase in ethanol preference which was dependent on both the number of ethanol withdrawals and chronic ethanol re-exposures, while 3 mg/kg/day had no significant effect on ethanol preference.


Recent studies implicate a protective role for the endogenous cannabinoids against ischaemia-reperfusion (I/R) injury in the heat-shock (HS) preconditioned heart. The aim of this study was to elucidate the effect of HS pretreatment on myocardial Ca(2+) (i) homeostasis in the isolated, perfused rat heart during an I/R insult. The Ca(2+)(i) transients were detected by surface fluorimetry. The results show that the endocannabinoid anandamide (ANA) is upregulated by HS pretreatment with a concomitant reduction in Ca(2+)(i) overload during I/R. Our results may suggest a causative relationship between upregulation of ANA and protection against Ca(2+)(i) overload.

Functionality of the endogenous cannabinoid system undergoes relevant changes in reward-related brain areas in animal models of opiate addiction. By using a limited access heroin self-administration paradigm we show that cannabinoid CB(1) receptor antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716A, 0.03-3.0 mg/kg) suppresses heroin self-administration only in opiate-dependent rats but not in non-dependent animals. These results further support the study of cannabinoid CB(1) receptor antagonists for the treatment of opiate addiction.


The effects of cannabinoid receptor ligands including 2-arachidonoylglycerol, R-methanandamide, Delta(9)-THC (Delta(9)-tetrahydrocannabinol), WIN 55,212-2 [4,5-dihydro-2-methyl-4-(4-morpholinylmethyl)-1-(1-naphthalenylcarbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one, CP 55,940 ([1alpha,2beta-(R)-5alpha]-(-)-5-(1,1-dimethyl)-2-[5-hydroxy-2-(3-hydroxypropyl)cyclohexyl-phenol]) and a series of fatty acids on depolarization-induced Ca(2+) effluxes mediated by voltage-dependent Ca(2+) channels were investigated comparatively in transverse tubule membrane vesicles from rabbit skeletal muscle. Vesicles were loaded with (45)Ca(2+) and membrane potentials were generated by establishing potassium gradients across the vesicle using the ionophore valinomy cin. Endocannabinoids, 2-arachidonoylglycerol and R-methanandamide (all 10^{-4}mol L^{-1}), inhibited depolarization-induced Ca(2+) effluxes and specific binding of [(3)H]PN 200-110 (isradipine) to transverse tubule membranes. On the other hand, synthetic cannabinoids, including CP 55,940, WIN 55,212-2, and Delta(9)-THC (all 10^{-4}mol L^{-1}), were ineffective. Additional experiments using endocannabinoid metabolites suggested that whereas ethanolamine and glycerol were ineffective, arachidonic acid inhibited Ca(2+) effluxes and specific binding of [(3)H]PN 200-110. Further studies indicated that only those fatty acids containing two or more double bonds were effective in inhibiting depolarization-induced Ca(2+) effluxes and specific binding of [(3)H]PN 200-110. These results indicate that endocannabinoids, but not synthetic cannabinoids, directly inhibit the function of voltage-dependent calcium channels (VDCCs) and modulate the specific binding of calcium channel ligands of the dihydropyridine (DHP) class.


The effects of Delta(-9)-tetrahydrocannabinol (Delta(-9)-THC) on locomotor activities and related basal ganglia neural responses were investigated in rats. A multiple-channel, single unit recording method was used to record neuronal activity in the dorsal lateral striatum, the globus pallidus, the subthalamic nucleus, and the substantia nigra pars reticulata simultaneously during spontaneous movement and treadmill locomotion. Delta(-9)-THC treatment (0.05-2.0 mg/kg, i.p.) dose-dependently decreased spontaneous motor activity and altered walking patterns in treadmill locomotion in that stance time was increased and step number was decreased. In parallel with the behavioral effects, Delta(-9)-THC treatment inhibited neural activity across all four basal ganglia areas recorded during both motor tests. Further, this inhibition of basal ganglia neural activity was behavioral context-dependent. Greater inhibition was found during resting than during walking periods in the treadmill locomotion test. Delta(-9)-THC treatment also changed firing patterns in the striatum and globus pallidus. More neurons in these regions discharged in an oscillatory pattern during treadmill walking with Delta(-9)-THC, and the oscillatory frequency was similar to that of the step cycle. Synchronized firing patterns were found in few basal ganglia neurons in the control condition (approximately 1%). Synchronized firing patterns increased during the treadmill resting phase after Delta(-9)-THC treatment, but still represented a very small proportion of the total neural population (1.9%). The drug treatment did not change neural responses to the tone cue proceeding treadmill locomotion. This study demonstrates dose-dependent inhibitory effects of cannabinoid injection on motor activity. This effect may be related
to the behavioral context-dependent inhibition observed in the basal ganglia system where CB1 receptors are densely distributed. Synapse 55:1-16, 2005. (c) 2004 Wiley-Liss, Inc.


The present study compared the effects of the cannabinoid receptor antagonist SR 141716 on morphine-induced locomotor sensitization (Experiment 1) and conditioned place preference (CPP, Experiment 2) in male albino Wistar rats. In Experiment 1, rats received seven consecutive daily treatments with morphine (10 mg/kg, SC) in combination with either SR 141716 (0, 0.1, 0.5 or 3.0 mg/kg, IP), or naloxone (10 mg/kg, IP). Three days later, all rats were challenged with a lower dose of morphine (5 mg/kg, SC). Rats pre-treated with morphine showed significantly elevated locomotor activity during the challenge session compared to vehicle-pre-treated animals indicating behavioural sensitization. Prior naloxone, but not SR 141716, co-administration with morphine, significantly attenuated the locomotor sensitization observed. In Experiment 2A, SR 141716 (0.1 mg/kg, IP), co-administered during conditioning, significantly attenuated the place preference produced by morphine (4 mg/kg, SC) in a standard unbiased two compartment place conditioning task. In Experiment 2B, the timing of drug administration and drug doses used were altered to be similar to Experiment 1, such that a comparison between the sensitization and CPP paradigms could be made. Thus, rats were conditioned with morphine (10 mg/kg, SC) combined with SR 141716 (0, 0.1, 0.5 or 3.0 mg/kg, IP) and tested for place preference under the influence of morphine (5 mg/kg, SC). SR 141716 attenuated morphine place preference at a dose (3.0 mg/kg) that did not itself affect place conditioning. Morphine also induced locomotor sensitization in the drug-paired compartment in Experiment 2B which was not blocked by any dose of SR 141716. We conclude that CB(1) receptor antagonism modulates the rewarding value of opioids, but not the behavioural sensitization induced by chronic opioid administration.


To develop an approach to obtain milligram quantities of purified isotope-labeled seven transmembrane G-protein coupled cannabinoid (CB) receptor for NMR structural analysis, we chose a truncated CB receptor fragment, CB2(180-233), spanning from the fifth transmembrane domain (TM5) to the associated loop regions of cannabinoid CB2 receptor. This highly hydrophobic membrane protein fragment was pursued for developmental studies of membrane proteins through expression and purification in Escherichia coli. The target peptide was cloned and over-expressed in a preparative scale as a fusion protein with a modified TrpDeltaLE1413 (TrpLE) leader sequence and a nine-histidine tag at its N-terminal. An experimental protocol for enzyme cleavage was developed by using Factor Xa to remove the TrpLE tag from the fusion protein. A purification process was also established using a nickel affinity column and reverse-phase HPLC, and then monitored by SDS-PAGE and MS. This expression level is one of the highest reported for a G-protein coupled receptor and fragments in E. Coli, and provided a sufficient amount of purified protein for further biophysical studies.

**CLINICAL SCIENCE**


**BACKGROUND AND AIMS:** To explore the association between chronic cannabis abuse and a cyclical vomiting illness that presented in a series of cases in South Australia. METHODS: Nineteen patients were identified with chronic cannabis abuse and a cyclical vomiting illness. For legal and ethical reasons, all patients were counselled to cease all cannabis abuse. Follow up was provided with serial urine drug screen analysis and regular clinical consultation to chart the clinical course. Of the 19 patients, five refused consent and were lost to follow up and five were excluded on the basis of confounders. The remaining nine cases are presented here and compared with a published case of psychogenic vomiting. RESULTS: In all cases, including the published case, chronic cannabis abuse predated the onset of the cyclical vomiting illness.
Cessation of cannabis abuse led to cessation of the cyclical vomiting illness in seven cases. Three cases, including the published case, did not abstain and continued to have recurrent episodes of vomiting. Three cases rechallenged themselves after a period of abstinence and suffered a return to illness. Two of these cases abstained again, and became and remain well. The third case did not and remains ill. A novel finding was that nine of the 10 patients, including the previously published case, displayed an abnormal washing behaviour during episodes of active illness. CONCLUSIONS: We conclude that chronic cannabis abuse was the cause of the cyclical vomiting illness in all cases, including the previously described case of psychogenic vomiting.


BACKGROUND: The long-term treatment of Parkinson disease (PD) may be complicated by the development of levodopa-induced dyskinesia. Clinical and animal model data support the view that modulation of cannabinoid function may exert an antidyskinetic effect. The authors conducted a randomized, double-blind, placebo-controlled crossover trial to examine the hypothesis that cannabis may have a beneficial effect on dyskinesia in PD. METHODS: A 4-week dose escalation study was performed to assess the safety and tolerability of cannabis in six PD patients with levodopa-induced dyskinesia. Then a randomized placebo-controlled crossover study (RCT) was performed, in which 19 PD patients were randomized to receive oral cannabis extract followed by placebo or vice versa. Each treatment phase lasted for 4 weeks with an intervening 2-week washout phase. The primary outcome measure was a change in Unified Parkinson's Disease Rating Scale (UPDRS) (items 32 to 34) dyskinesia score. Secondary outcome measures included the Rush scale, Bain scale, table arm drawing task, and total UPDRS score following a levodopa challenge, as well as patient-completed measures of a dyskinesia activities of daily living (ADL) scale, the PDQ-39, on-off diaries, and a range of category rating scales. RESULTS: Seventeen patients completed the RCT. Cannabis was well tolerated, and had no pro- or antiparkinsonian action. There was no evidence for a treatment effect on levodopa-induced dyskinesia as assessed by the UPDRS, or any of the secondary outcome measures. CONCLUSIONS: Orally administered cannabis extract resulted in no objective or subjective improvement in dyskinesias or parkinsonism.


Abstract: Background: Endocannabinoids may participate in the homeostasis of arterial pressure. Recently, anandamide, the most extensively studied endocannabinoid, has been proposed as a key mediator in the peripheral arterial vasodilation of cirrhosis. Objectives: To determine if circulating levels of anandamide are related to the extent of the peripheral arterial vasodilation, the severity of portal hypertension and the degree of liver and renal dysfunction of patients with cirrhosis. Methods: Plasma levels of anandamide and several systemic, portal and renal hemodynamic parameters were determined in 18 patients with cirrhosis and eight healthy subjects (control group). Results: Plasma levels of anandamide were elevated in patients compared to the control group (P<0.05), nevertheless, no differences between patients with ascites and well-compensated patients were found. There was no correlation between anandamide concentration and arterial pressure, cardiac output and systemic vascular resistance, Child-Pugh's score, portal pressure, renal vascular resistance, plasma renin activity or
plasma aldosterone concentration. Conclusions: Circulating levels of anandamide are increased in cirrhotic patients. However, this elevation was unrelated to the extent of arterial vasodilation, the severity of portal hypertension or the degree of hepatic and renal dysfunction. Although a local hormonal action cannot be excluded, our results do not support a relevant contribution of this system in the hemodynamic disturbance of cirrhosis.


RATIONALE. The primary psychoactive constituent of marijuana, Delta(9)-THC, activates cannabinoid receptors, which are especially abundant in the frontal cortex and hippocampus. Acute marijuana smoking can disrupt working memory (WM) and episodic memory (EM) functions that are known to rely on these regions. However, the effects of marijuana on the brain activity accompanying such cognitive processes remain largely unexplored. OBJECTIVES. To examine such effects on performance and neurophysiological signals of these functions, EEG recordings were obtained from ten subjects (5M, 5F) performing cognitive tasks before and after smoking marijuana (3.45% Delta(9)-THC) or a placebo. WM was assessed with a spatial N-back task, and EM was evaluated with a test requiring recognition of words after a 5-10 min delay between study and test. RESULTS. Marijuana increased heart rate and decreased global theta band EEG power, consistent with increased autonomic arousal. Responses in the WM task were slower and less accurate after smoking marijuana, accompanied by reduced alpha band EEG reactivity in response to increased task difficulty. In the EM task, marijuana was associated with an increased tendency to erroneously identify distracter words as having been previously studied. In both tasks, marijuana attenuated stimulus-locked event-related potentials (ERPs). CONCLUSIONS. The results suggest that marijuana disrupted both sustained and transient attention processes resulting in impaired memory task performance. In subjects most affected by marijuana a pronounced ERP difference between previously studied words and new distracter words was also reduced, suggesting disruption of neural mechanisms underlying memory for recent study episodes.


BEHAVIOURAL SCIENCE


This article presents the main outcome findings from two inter-related randomized trials conducted at four sites to evaluate the effectiveness and cost-effectiveness of five short-term outpatient interventions for adolescents with cannabis use disorders. Trial 1 compared five sessions of Motivational Enhancement Therapy plus Cognitive Behavioral Therapy (MET/CBT) with a 12-session regimen of MET and CBT (MET/CBT12) and another that included family education and therapy components (Family Support Network [FSN]). Trial II compared the five-session MET/CBT with the Adolescent Community Reinforcement Approach (ACRA) and Multidimensional Family Therapy (MDFT). The 600 cannabis users were predominately white

**Background.** This study identified similarities and differences in risk factors for marijuana use initiation from grades 7 to 8, grades 8 to 9, and grades 9 to 10, and examined differences between earlier initiates, later initiates, and nonusers on various problem behaviors at grade 10.

**Method.** Longitudinal data were used to examine predictors and outcomes associated with marijuana initiation from grade 7 (N = 1,955) to grade 10 (N = 909). Participants completed yearly surveys to assess problem behaviors, social influences, and marijuana-related attitudes and behavior.

**Results.** Earlier initiates were more likely than later initiates to exhibit problem-related marijuana use, hard drug use, polydrug use, poor grades, and low academic intentions at grade 10. Across ages, initiation was predicted by smoking, frequency of marijuana offers, and poor grades.

Results provided some evidence for a shift from familial to peer influence on marijuana initiation with increasing age. Marijuana-related beliefs were relatively weak predictors of initiation at all ages after controlling for pro-marijuana social influences and engagement in other types of substance use and delinquent behavior.

**Conclusions.** Results emphasize the importance of early intervention and identify a wide range of potentially modifiable risk factors that may be targeted.


**Abuse of the stimulant drug methamphetamine is associated with neural injury and neuropsychological (NP) deficits, while the residual effects of marijuana use remain uncertain.** We sought to determine if methamphetamine dependent persons who also met criteria for marijuana abuse or dependence evidenced different NP performance than those with dependence for methamphetamine alone. We examined three groups that did not differ significantly on important demographic factors: (1) subjects with a history of methamphetamine dependence and history of marijuana abuse/dependence (METH+/MJ+, n = 27); (2) methamphetamine dependent subjects without history of marijuana abuse/dependence (METH+/MJ-, n = 26); (3) a control group with minimal or no drug use (n = 41). A comprehensive NP battery was administered and performance was quantified for five cognitive ability areas. The METH+/MJ- group generally demonstrated the greatest NP impairment, with statistically significant differences observed between the METH+/MJ- and control group in learning, retention/retrieval, and a summary score of global NP performance. The METH+/MJ+ group did not differ significantly from the control or METH+/MJ- group on any NP ability. However, there was a significant linear trend in the global NP score suggesting that the METH+/MJ+ performed intermediate to the control and METH+/MJ- groups. Based on these findings, we cannot conclude that there is a protective effect of marijuana use in methamphetamine users; however, marijuana use clearly did not appear to exacerbate methamphetamine neurotoxicity. Further investigations are needed to determine if the emerging literature, suggesting that certain cannabinoids might have neuroprotective actions, is generalizable to community-dwelling substance abusers.


**Neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are critically implicated in development and maintenance of function of neurons.**
Neurodevelopment is reported to be impaired in schizophrenia and vulnerable schizophrenic brains may be more sensitive to toxic influences. Thus, cannabis as a neurotoxin, may be more harmful to schizophrenic brains than to non-schizophrenic brains when used chronically. And neurotoxic events may promote disease-onset and lead to exaggerated release of neurotrophins. We investigated 157 drug-naive first-episode schizophrenic patients and found significantly elevated BDNF serum concentrations (by up to 34%) in patients with chronic cannabis abuse (n = 35, p < 0.001) or multiple substance abuse (n = 20, p < 0.001) prior to disease onset. Drug-naive schizophrenic patients without cannabis consumption showed similar results to normal controls and cannabis controls without schizophrenia. Thus, raised BDNF serum levels are not related to schizophrenia and/or substance abuse itself but may reflect a cannabis-related idiosyncratic damage of the schizophrenic brain. In line with this hypothesis, disease onset was 5.2 years earlier in the cannabis-consuming group (p = 0.0111).


BACKGROUND: Previous research has reported both a moderate degree of comorbidity between cannabis dependence and major depressive disorder (MDD) and that early-onset cannabis use is associated with increased risks for MDD. OBJECTIVE: To examine whether associations between both lifetime cannabis dependence and early cannabis use and measures of MDD, suicidal ideation, and suicide attempt persist after controlling for genetic and/or shared environmental influences. DESIGN: Cross-sectional survey of twin pairs discordant for lifetime cannabis dependence and those discordant for early cannabis use. SETTING: General population sample of twins (median age, 30 years). PARTICIPANTS: Two hundred seventy-seven same-sex twin pairs discordant for cannabis dependence and 311 pairs discordant for early-onset cannabis use (before age 17 years). MAIN OUTCOME MEASURES: Self-report measures of DSM-IV-defined lifetime MDD, suicidal ideation, and suicide attempt. RESULTS: Individuals who were cannabis dependent had odds of suicidal ideation and suicide attempt that were 2.5 to 2.9 times higher than those of their non-cannabis-dependent co-twin. Additionally, cannabis dependence was associated with elevated risks of MDD in dizygotic but not in monozygotic twins. Those who initiated cannabis use before age 17 years had elevated rates of subsequent suicide attempt (odds ratio, 3.5 [95% confidence interval, 1.4-8.6]) but not of MDD or suicidal ideation. Early MDD and suicidal ideation were significantly associated with subsequent risks of cannabis dependence in discordant dizygotic pairs but not in discordant monozygotic pairs. CONCLUSIONS: Comorbidity between cannabis dependence and MDD likely arises through shared genetic and environmental vulnerabilities predisposing to both outcomes. In contrast, associations between cannabis dependence and suicidal behaviors cannot be entirely explained by common predisposing genetic and/or shared environmental predispositions. Previously reported associations between early-onset cannabis use and subsequent MDD likely reflect shared genetic and environmental vulnerabilities, although it remains possible that early-onset cannabis use may predispose to suicide attempt.


A clinic-referred sample of 109 children with attention-deficit/hyperactivity disorder (ADHD) was followed into adolescence for the ascertainment of alcohol and other drug use and abuse. Learning disability (reading or math) in childhood was examined as a predictor of adolescent substance use and substance use disorder for alcohol and marijuana. No statistically significant group differences for children with LD versus those without LD emerged even after using different methods to compute LD. IQ/achievement discrepancy scores were similarly not predictive of later use or abuse. However, children with ADHD who had higher IQs and higher levels of academic achievement in childhood were more likely to try cigarettes, to smoke daily, and to have their first drink of alcohol or first cigarette at an early age. Children with ADHD who had higher reading achievement scores were less likely to have later alcohol use disorder. Although these findings are necessarily preliminary, due to the small number of children interviewed, the pattern of results suggests that level of cognitive functioning--rather than
discrepancy between IQ and achievement--is important for the prediction of later substance use and abuse, at least in this clinic-referred sample of children with ADHD. Further, different mechanisms of risk related to cognitive functioning may be operating for experimentation with legal drugs such as alcohol and tobacco, regular cigarette smoking, and problematic alcohol use.


The active principle of marijuana, Delta(9)-tetrahydrocannabinol (Delta(9)-THC), exerts its pharmacological effects by binding to selective receptors present on the membranes of neurons and other cells. These cannabinoid receptors are normally engaged by a family of lipid mediators, called endocannabinoids, which are thought to participate in the regulation of a diversity of brain functions, including pain, mood, appetite and memory. Marijuana use may lead to adaptive changes in endocannabinoid signaling, and these changes might contribute to effects of marijuana as well as to the establishment of marijuana dependence. In the present article, I outline current views on how endocannabinoid substances are produced, released, and deactivated in the brain. In addition, I review recent progress on the development of pharmacological agents that interfere with endocannabinoid deactivation and discuss their potential utility in the treatment of marijuana dependence and other aspects of drug abuse.

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