INTRODUCTION

Here is the latest summary of research abstracts. A reminder that the 2005 Symposium on the Cannabinoids to be held June 24th - 27th, 2005 at the Hilton Clearwater Beach Resort in Clearwater, Florida USA; registration details are available at http://CannabinoidSociety.org/. In addition a workshop entitled “Cannabinoids: developing clinically useful analgesics” has been announced at the International Association for the Study of Pain (IASP) meeting in Sydney Australia to be held on August 21-26th 2005. Details are available at http://www.iasp-pain.org/05Cong.html.

BASIC SCIENCE


Previous studies have revealed that cannabinoid (CB)-receptor agonists inhibit gastric acid secretion stimulated by indirectly acting agents, but not by histamine. Aiming to investigate whether central or peripheral mechanisms are involved, the effects of the synthetic CB-receptor agonists WIN55,212-2 and HU-210, administered either intracerebroventricularly (i.c.v.) or intravenously (i.v.) to the anesthetized rat with lumen-perfused stomach, against gastric acid secretion induced by pentagastrin were tested. Injected i.c.v., both WIN55,212-2 (50 and 100μg/kg) and HU-210 (25, 50 and 100μg/kg) were ineffective on either basal secretion or acid output induced by pentagastrin (7.7μg/kg, i.v.). By contrast, i.v. injections of WIN55,212-2 (100 and 1000μg/kg) or HU-210 (10-100μg/kg) significantly inhibited pentagastrin-induced acid secretion, maximal reductions being 75.70 and 82.24% for WIN55,212-2 and HU-210, respectively. The gastric antisecretory effect of HU-210 was prevented by administration of the selective CB(1)-receptor antagonist SR141716A (100μg/kg, i.v.). These results show that CB(1)-receptors mediating inhibition of gastric acid secretion in the rat are mainly peripherally located.


CRH receptor 1 (CRHR1) and the cannabinoid receptor 1 (CB1) are both G protein-coupled receptors. Activation of CRHR1 leads to increases in cAMP production and phosphorylation of the transcription factor cAMP response element-binding protein (CREB). In contrast, CB1 is negatively coupled to the cAMP signaling cascade. In this study we analyzed a putative interaction between these two systems focusing on the regulation of the expression of brain-derived neurotrophic factor (BDNF), a CREB-regulated gene. In situ hybridization revealed co-expression of CRHR1 and CB1 receptors in the granular layer of the cerebellum. Therefore, we analyzed the effects of CRH and the CB1 agonist WIN-55,212-2 on BDNF expression in primary cerebellar neurons from rats and mice. We observed that application of CRH for 48 h led to an increase in BDNF mRNA and protein levels. This effect was inhibited by WIN-55,212-2. At the level of intracellular signaling, short-term application of WIN-55,212-2 inhibited CRH-induced cAMP accumulation and CREB phosphorylation. Pharmacological analysis demonstrated that the CRHR1 antagonist R121919, the protein kinase A (PKA) inhibitor H89 and the calcium chelator...
BAPTA-AM inhibited CRH-mediated BDNF expression. Moreover, depolarization-induced BDNF synthesis was also inhibited by long-term application of WIN-55,212-2 in wild-type, but not CB1-deficient mice. Thus, these data highlight an interaction between the CRH and the cannabinoid system in the regulation of BDNF expression by influencing cAMP and Ca(2+) signaling pathways.


On the basis of contradictory findings on the rewarding effects of Delta(9)-tetrahydrocannabinol (Delta(9)-THC) in laboratory animals, the effect of the compound on conditioned place preference and intracerebroventricular (i.c.v.) self-administration in a free-choice procedure, using a wide range of doses (0.015-6 mg/kg for conditioned place preference test and 0.01-1 mug/2 mul/infusion for i.c.v. self-administration), was studied in Wistar rats. The present results showed that Delta(9)-THC induced reward in both tests, but only at the lowest tested doses (0.075-0.75 mg/kg i.p. for conditioned place preference test and 0.01-0.02 mug/infusion for i.c.v. self-administration). This effect was fully antagonised by i.p. pretreatment with the cannabinoid CB(1) receptor antagonist, SR 141716A [N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4 methyl pyrazole 3-carboxamide] (0.25-1 mg/kg), and the opiate receptor antagonist, naloxone (0.5-2 mg/kg), suggesting the involvement of both endocannabinoid and opioid systems. In conclusion, these findings demonstrate, for the first time, that low doses of Delta(9)-THC can act as an effective reinforcer in Wistar rats providing a reliable animal model of human marijuana abuse.


The complete 1H- and 13C-NMR assignments of the major Cannabis constituents, delta9-tetrahydrocannabinol, tetrahydrocannabinolic acid, delta8-tetrahydrocannabinol, cannabinerol, cannabinol, cannabinoids, cannabidiolic acid, cannflavin A and cannflavin B have been determined on the basis of one- and two-dimensional NMR spectra including 1H- and 13C-NMR, 1H-1H-COSY, HMQC and HMBC. The substitution of carboxylic acid on the cannabinoid nucleus (as in tetrahydrocannabinolic acid and cannabidiolic acid) has a large effect on the chemical shift of H-1" of the C5 side chain and 2'-OH. It was also observed that carboxylic acid substitution reduces intermolecular hydrogen bonding resulting in a sharpening of the H-5' signal in cannabionic acid in deuterated chloroform. The additional aromaticity of cannabinol causes the two angular methyl groups (H-8 and H-9) to show identical 1H-NMR shifts, which indicates that the two aromatic rings are in one plane in contrast to the other cannabinoids. For the cannabiflavonoids, the unambiguous assignments of C-3' and C-4' of cannflavin A and B were determined by HMBC spectra.


Promising therapeutic uses and a great variety of pharmacological effects are the leading forces that focus actual cannabinoid research. Cannabinoid and opioid systems share neuroanatomical, neurochemical, and phaharmacological features. This fact supports the notion that actions induced by each one of these types of drugs involved an interaction between the endogenous opioid and endocannabinoid neuronal systems. Over the last decade our group and others have investigated cannabinoid/opioid crosstalk in the central nervous system by studying the mechanisms underlying pharmacological and biochemical interactions between the two systems in experimental paradigms of antinociception, drug reinforcement, and anxiety. The goal of this review is to revise the latest work done on this subject, with special emphasis on the research done with genetically modified animals. Whereas clinical progress is going ahead slowly, basic research in this area is progressing rapidly. Clinical applications derived from the cannabinoid/opioid crosstalk and based tightly on medical evidence are yet to come, but it is hoped that knowledge of this central messenger interaction will help to develop new alternatives for the treatment of some pathological states.

The role of anandamide in the development of inflammatory hyperalgesia and visceral hyperreflexia was studied in the rat urinary bladder. Animals were given intraperitoneal cyclophosphamide injection, which evokes painful hemorrhagic cystitis accompanied by increased bladder reflex activity. The vanilloid receptor 1 [transient receptor potential vanilloid 1 (TRPV1)] antagonist capsazepine, applied onto the serosal surface of bladders, significantly reduced the hyperreflexia. Mass spectrometric analysis revealed that cyclophosphamide injection significantly and persistently increased the anandamide content of bladder tissues. The increase in the anandamide content paralleled the development of reflex hyperactivity. Anandamide (1-100 microm), applied onto the serosal surface of naive bladders, increased the reflex activity in a concentration-dependent manner. Repeated anandamide applications did not produce desensitization of the response. The anandamide-evoked effect was blocked by capsazepine or by instillation of resiniferatoxin, the ultrapotent TRPV1 agonist, into the bladders 24 hr before the anandamide challenge. The cannabinoid 1 receptor antagonist SR141716A [N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide] significantly increased the potency of anandamide in enhancing bladder reflex activity in naive but not in cyclophosphamide-injected animals. Application of the fatty amide hydrolase inhibitor palmitoylisopropylamine onto the serosal surface of bladders also increased the reflex activity both in naive and cyclophosphamide-injected rats. This latter effect in naive animals was blocked by capsazepine and by resiniferatoxin pretreatment. Finally, intravesical instillation of anandamide (50 microm) increased c-fos expression in the spinal cord, which was reduced by capsazepine or by resiniferatoxin pretreatment. These results suggest that anandamide, through activating TRPV1, contributes to the development of hyperreflexia and hyperalgesia during cystitis.


Cannabinoid receptors in the brain (CB(1)) take part in modulation of learning, and are particularly important for working and short-term memory. Here, we employed a delayed-matching-to-place (DMTP) task in the open-field water maze and examined the effects of cannabis plant extracts rich in either Delta(9)-tetrahydrocannabinol (Delta(9)-THC), or rich in cannabidiol (CBD), on spatial working and short-term memory formation in rats. Delta(9)-THC-rich extracts impaired performance in the memory trial (trial 2) of the DMTP task in a dose-dependent but delay-independent manner. Deficits appeared at doses of 2 or 5 mg/kg (i.p.) at both 30 s and 4 h delays and were similar in severity compared with synthetic Delta(9)-THC. Despite considerable amounts of Delta(9)-THC present, CBD-rich extracts had no effect on spatial working/short-term memory, even at doses of up to 50 mg/kg. When given concomitantly, CBD-rich extracts did not reverse memory deficits of the additional Delta(9)-THC-rich extract. CBD-rich extracts also did not alter Delta(9)-THC-rich extract-induced catalepsy as revealed by the bar test. It appears that spatial working/short-term memory is not sensitive to CBD-rich extracts and that potentiation and antagonism of Delta(9)-THC-induced spatial memory deficits is dependent on the ratio between CBD and Delta(9)-THC.


There is currently substantial evidence that Cannabis sativa derivates act on brain reward in a way very similar to other drugs of abuse and exert numerous pharmacological effects through their interaction with various neurotransmitters and neuromodulators. Among them, the endogenous opioids seem to play an important role in modulating the addictive properties of cannabinoids. Given the plethora of research activity on such a topic, this brief review is necessarily focused on cannabinoid/opioid interaction in reward-related events and restricted to the recent literature. Recent findings from our and other laboratories concerning cannabinoid reinforcing effects as revealed by behavioral animal models of addiction are here summarized. Evidence is then provided demonstrating a functional cross-talk between the cannabinoid and...
opioid systems in the mutual modulation of the addictive behavior; accordingly, very recent data from transgenic mice lacking either the cannabinoid CB1 or opioid receptors are also presented. Finally, the role of the endogenous cannabinoid system in relapse to opioids is investigated by means of extinction/reinstatement animal models following a period, even prolonged, of drug abstinence. Altogether, the reviewed studies provided a better understanding of the neurobiological mechanisms involved in cannabinoid actions and revealed a bidirectional interaction between the endogenous cannabinoid and opioid systems in reward that extends to central mechanisms underlying relapsing phenomena. Challenges for the future involve elucidation of the neuroanatomical substrates of cannabinoids action, even in light of the therapeutic potential of these compounds.


Fatty-acid amide hydrolase (FAAH) is an intracellular serine enzyme that catalyzes the hydrolysis of bioactive fatty-acid ethanolamides such as anandamide and oleylethanolamide (OEA). Genetic deletion of the faah gene in mice elevates brain anandamide levels and amplifies the effects of this endogenous cannabinoid agonist (Cravatt et al., 2001). Here, we show that systemic administration of the selective FAAH inhibitor URB597 (cyclohexyl carbamic acid 3'-carbamoyl-biphenyl-3-yl ester; 0.3 mg/kg, intraperitoneal, i.p.) increases anandamide levels in the brain of rats and wild-type mice (Kathuria et al., 2003), but has no such effect in FAAH-null mutants. Moreover, URB597 enhances the hypothermic actions of anandamide (5 mg/kg, i.p.) in wild-type mice, but not in FAAH-null mice. In contrast, the FAAH inhibitor does not affect anandamide or OEA levels in the rat duodenum at doses that completely inhibit FAAH activity. In addition, URB597 does not alter the hypophagic response elicited by OEA (5, 10 mg/kg, i.p.), which is mediated by activation of peroxisome proliferator-activated receptor type-alpha (PPAR-alpha) (Rodriguez de Fonseca et al., 2001; Fu et al., 2003). Finally, exogenously administered OEA (5 mg/kg, i.p.) was eliminated at comparable rates in wild-type and FAAH(-/-) mice. Our results indicate that URB597 increases brain anandamide levels and magnifies anandamide responses by inhibiting intracellular FAAH activity. The results also suggest that an enzyme distinct from FAAH catalyzes OEA hydrolysis in the duodenum, where this lipid substance acts as a local satiety factor (Rodriguez de Fonseca et al., 2001; Fu et al., 2003).


The cannabinergic system is present in a variety of organs and tissues that perform a wide range of essential physiologic functions making it an inherently important therapeutic target for drug discovery. In order to augment our knowledge regarding the interactions between cannabinoid receptors (CBs) and their ligands, efficient and effective tools are essential for robust expression and purification of these membrane-bound proteins. In this report, we describe a suitable method for purification of the human cannabinoid receptor 2 (CB2) to a qualitative and quantitative level sufficient for mass spectral analysis. We utilized a baculovirus expression system, incorporating several epitope tags to facilitate purification and to ameliorate the effect the tags have on CB2 expression and function. Expressed protein encoded by a carboxy (C)-terminal His-tagged CB2 construct displayed a B(max) value of 9.3 pmol/mg with a K(D) of 7.30 nm using [3(H)]CP-55(940), a standard cannabinoid radioligand, and was selected for subsequent purification experiments. Western blot analysis of purified membrane protein yielded several forms of CB2, the most abundant being a 41 kDa peptide. A second protein species was observed with an apparent molecular weight of 46 kDa representing a glycosylated form of CB2. In addition, a CB2 homodimer was also identified. The purified receptor was subjected to mass spectroscopic analysis to confirm its identity and purity. Mass spectra corresponding to the intracellular, extracellular and transmembrane domains were obtained. These experiments exemplify the importance of high-level expression systems when developing membrane-bound protein purification strategies. This work will aid in the identification of receptor-ligand binding sites, the characterization of molecular features involved in receptor activation, and the elucidation of the CB2 receptor tertiary structure.

Delta(9)-Tetrahydrocannabinol (Delta(9)-THC) and (-)-cannabidiol are major constituents of the Cannabis sativa plant with different pharmacological profiles: (-)-Delta(9)-tetrahydrocannabinol, but not (-)-cannabidiol, activates cannabinoid CB(1) and CB(2) receptors and induces psychoactive and peripheral effects. We have tested a series of (+)-cannabidiol derivatives, namely, (+)-7-OH-DMH (DMH-1,1-dimethylheptyl), (+)-7-OH-cannabidiol-DMH, (+)-7-COOH- cannabidiol, and (+)-7-COOH-cannabidiol-DMH, for central and peripheral (intestinal, antiinflammatory and peripheral pain) effects in mice. Although all (+)-cannabidiols bind to cannabinoid CB(1) and CB(2) receptors, only (+)-7-OH-cannabidiol-DMH was centrally active, while all (+)-cannabidiol analogues completely arrested defecation. The effects of (+)-cannabidiol-DMH and (+)-7-OH-cannabidiol-DMH were partially antagonized by the cannabinoid CB(1) receptor antagonist N-(piperidiny-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (SR141716), but not by the cannabinoid CB(2) receptor antagonist N-[(-1S)-endo-1,3,3-trimethyl bicyclo[2.2.1]heptan-2-yl-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carb oxamide (SR144528), and had no effect on CB(1)(-/-) receptor knockout mice. (+)-Cannabidiol-DMH inhibited the peripheral pain response and arachidonic-acid-induced inflammation of the ear. We conclude that centrally inactive (+)-cannabidiol analogues should be further developed as antidiarrheal, antiinflammatory and analgesic drugs for gastrointestinal and other peripheral conditions.


Delta(9)-Tetrahydrocannabinol (Delta(9)-THC), the major psychoactive component of marijuana, induces catalepsy-like immobilization and impairment of spatial memory in rats. Delta(9)-THC also induces aggressive behavior in isolated housing stress. These abnormal behaviors could be counteracted by SR141716A, a CB(1) cannabinoid receptor antagonist. Also Delta(9)-THC inhibited release of glutamate in the dorsal hippocampus, but this inhibition could be antagonized by SR141716A in an in vivo microdialysis study. Moreover, NMDA and AMPA-type glutamate receptor enhancers improved the Delta(9)-THC-induced impairment of spatial memory. On the other hand, Delta(9)-THC markedly inhibited the neurodegeneration in experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis and reduced the elevated glutamate level of cerebrospinal fluid induced by EAE. These therapeutic effects on EAE were reversed by SR141716A. Taken together, our results demonstrate that the inhibition of glutamate release via activation of the CB(1)-cannabinoid receptor is one mechanism involved in Delta(9)-THC-induced impairment of spatial memory, and the therapeutic effect of Delta(9)-THC on EAE, and a Delta(9)-THC analog might provide an effective treatment for psychosis and neurodegenerative diseases.


A possible involvement of endocannabinoids in a chronic model of endotoxemia was assessed by measuring the regional (renal, mesenteric, hindquarters) hemodynamic responses to continuous, 24 h lipopolysaccharide (LPS) infusion (150 microg/kg/h) in conscious, male Sprague-Dawley rats, in the absence or presence of the cannabinoid (CB1) receptor antagonist, AM 251 (3 mg/kg). AM 251 inhibited the tachycardic and hindquarters vasodilator effects of LPS, but did not influence the other hemodynamic changes. In subsequent experiments it was shown that the tachycardic and hindquarters vasodilator effects of LPS were also inhibited by the non-selective beta-adrenoceptor antagonist, propranolol. In addition, the late (at 24 h) hindquarters vasodilator effects of LPS were inhibited by the beta2-adrenoceptor antagonist, ICI 118551. Against the background of our previous work showing beta-adrenoceptor involvement in the cardiovascular effects of exogenous cannabinoids, we conclude that AM 251 may have been inhibiting endocannabinoid-modulated, sympathoadrenal-mediated activation of vasodilator beta-
adrenoceptors in LPS-infused rats, rather than suppressing a direct vasodilator action of endocannabinoids.


Endocannabinoids and CB1 receptors have been implicated in endotoxin (LPS)-induced hypotension: LPS stimulates the synthesis of anandamide in macrophages, and the CB1 antagonist SR-141716 inhibits the hypotension induced by treatment of rats with LPS or LPS-treated macrophages. Recent evidence indicates the existence of cannabinoid receptors distinct from CB1 or CB2 that are inhibited by SR-141716 but not by other CB1 antagonists such as AM251. In pentobarbital-anesthetized rats, intravenous injection of 10 mg/kg LPS elicited hypotension associated with profound decreases in cardiac contractility, moderate tachycardia, and an increase in lower body vascular resistance. Pretreatment with 3 mg/kg SR-141716 prevented the hypotension and decrease in cardiac contractility, slightly attenuated the increase in peripheral resistance, and had no effect on the tachycardia caused by LPS, whereas pretreatment with 3 mg/kg AM251 did not affect any of these responses. SR-141716 also elicited an acute reversal of the hypotension and decreased contractility when administered after the response to LPS had fully developed. The LPS-induced hypotension and its inhibition by SR-141716 were similar in pentobarbital-anesthetized wild-type, CB1(-/-), and CB1(-/-)/CB2(-/-) mice. We conclude that SR-141716 inhibits the acute hemodynamic effects of LPS by interacting with a cardiac receptor distinct from CB1 or CB2 that mediates negative inotropy and may be activated by anandamide or a related endocannabinoid released during endotoxemia.


AIMS: The present study investigated the effect of the newly synthesized cannabinoid CB1 receptor antagonist, SR147778, on alcohol intake and the motivational properties of alcohol in selectively bred Sardinian alcohol-preferring (sP) rats. METHODS AND RESULTS: In Experiment 1, the repeated administration of SR147778 (0.3-3 mg/kg twice daily, i.p.) specifically suppressed the acquisition of alcohol drinking behaviour in alcohol-naive rats exposed to the two-bottle 'alcohol vs water' choice regimen for 24 h/day. In Experiment 2, an acute administration of SR147778 (2.5-10 mg/kg, i.p.) specifically reduced alcohol intake in alcohol-experienced rats that were given alcohol and water under the two-bottle choice regimen in daily sessions of 4 h. In Experiment 3, an acute administration of SR147778 (0.3-3 mg/kg, i.p.) suppressed the 'alcohol deprivation effect', i.e. the extra-intake of alcohol occurring after a period of alcohol abstinence. In Experiment 4, an acute administration of SR147778 (0.3-3 mg/kg, i.p.) specifically suppressed the extinction responding for alcohol, i.e. the maximal number of lever responses reached in the absence of alcohol in rats trained to lever-press for alcohol (measure of the motivational properties of alcohol). In Experiment 5, the combination of 3 mg/kg of SR147778 (i.p.) and 0.5 g/kg of alcohol (i.p.), a dose comparable with those usually consumed by sP rats in each drinking binge, failed to induce any conditioned taste aversion. CONCLUSION: Taken together, these results extend to SR147778 the anti-alcohol profile of the prototype cannabinoid CB1 receptor antagonist, rimonabant (SR141716), and strengthen the hypothesis that the cannabinoid CB1 receptor is part of the neural substrate mediating alcohol intake and the motivational properties of alcohol.


In an effort to improve indole-based CB(2) cannabinoid receptor ligands and also to develop SAR for both the CB(1) and CB(2) receptors, 47 indole derivatives were prepared and their CB(1) and CB(2) receptor affinities were determined. The indole derivatives include 1-propyl- and 1-pentyl-3-(1-naphthoyl)indoles both with and without a 2-methyl substituent. Naphthoyl substituents include 4- and 7-alkyl groups as well as 2-, 4-, 6-, 7-methoxy and 4-ethoxy
groups. The effects of these substituents on receptor affinities are discussed and structure-activity relationships are presented. In the course of this work three new highly selective CB(2) receptor agonists were identified, 1-propyl-3-(4-methyl-1-naphthoylindole (JWH-120), 1-propyl-2-methyl-3-(6-methoxy-1-naphthyindole (JWH-151), and 1-pentyl-3-(2-methoxy-1-naphthylindole (JWH-267). GTGp gammaS assays indicated that JWH-151 is a full agonist at CB(2), while JWH-120 and JWH-267 are partial agonists. Molecular modeling and receptor docking studies were carried out on a set of 3-(4-propyl-1-naphthoyl)indoles, a set of 3-(6-methoxy-1-naphthoyl)indoles and the pair of N-pentyl-3-(2-methoxy-1-naphthyl)indoles. Docking studies indicated that the CB(1) receptor affinities of these compounds were consistent with their aromatic stacking interactions in the aromatic microdomain of the CB(1) receptor.


The role of cannabinoid receptor I (CBR-1) in the induction of decidualization was examined using decidual fibroblasts and human endometrial stromal cells as model systems. Decidual fibroblasts decidualized in vitro for 3 and 6 days in the presence of the CBR-1 agonist R(+)-WIN 55,212-2 mesylate (WIN, 0.1-10muM) expressed less of the decidualization-specific markers prolactin, CBR-1, forkhead (FKHR), TIMP-3, laminin, endometrial bleeding associated factor (EBAF), decorin and insulin-like growth factor binding protein-1 (IGFBP-1) mRNA levels compared to control cells. The maximal decrease for each transcript was in the range of 50-99%. In contrast, cells exposed to the CBR-1 inhibitor AM-251 (1muM) expressed about two-fold higher levels of the decidualization-specific marker gene mRNAs. The WIN-exposed cells showed a marked decrease in intracellular cAMP levels and a progressive, concentration-dependent increase in DNA fragmentation (TUNEL assay) and caspase 3 levels during decidualization compared to control cells. These studies strongly suggest that activation of CBR-1 inhibits human decidualization and stimulates apoptosis by a cAMP-dependent mechanism.


The endogenous cannabinoid system is a relatively novel discovered system consisting of cannabinoid CB1 receptors, which are expressed both in the periphery and in the central nervous system, peripheral cannabinoid CB2 receptors and endogenous cannabinoids, which are anandamide and 2-arachidonyl glycerol. The cannabinoid CB1 receptors have recently been implicated in rewarding aspects of not only the cannabinoid drug Delta(9)-tetrahydrocannabinol (Delta(9)-THC), but also of other drugs of abuse, including cocaine. The present study was designed to further investigate the role of CB1 receptors in reward-related effects of cocaine. Using the CB1 receptor selective antagonist SR141716A, the involvement of CB1 receptors in cocaine reinforcement was determined by intravenous cocaine self-administration. In addition, the effects of the CB1 receptor selective antagonist SR141716A upon the development of cocaine-induced behavioural sensitization were investigated. SR141716A did not affect cocaine reinforcement nor did it affect the development of behavioural sensitization to the locomotor stimulant effects of cocaine. These findings suggest that CB1 receptors are not involved in acute cocaine reinforcement nor in cocaine-induced behavioural sensitization.

were not modified. Although ineffective in wild-type mice, treatment of ob/ob mice with leptin re-established endocannabinoid levels and enzyme activities back to the values observed in wild-type littermates. Finally, treatment of ob/ob females with the CB1 receptor antagonist SR141716A did not improve their fertility, and inhibition of endocannabinoid inactivation with the endocannabinoid uptake inhibitor OMDM-1 in wild-type females did not result in impaired fertility.


Loss of cannabinoid receptors (CB1) occurs prior to neurodegeneration in Huntington's disease (HD). The levels and distribution of CB1 RNA were equivalent in 3-week-old mice regardless of genotype demonstrating that the specific factors and appropriate chromatin structure that lead to the transcription of CB1 were present in the striatum of young R6/2 and R6/1 transgenic HD mice. The expression of the mutant HD transgene led progressively to decreased steady-state levels of CB1 mRNA in neurons of the lateral striatum, which was dependent on the size of the CAG repeat and relative expression of the gene encoding mutant huntingtin (HD). Although it is known that the coding region of CB1 is contained within a single exon in mice, rats and humans, the 5'-untranslated region of the mouse gene remained to be defined. CB1 mRNA is encoded by two exons separated by an 18.4-kb intron. Transcription of CB1 occurred at multiple sites within a GC-rich promoter region upstream of exon 1 encoding the 5'-UTR of CB1. There was no difference in the selection of specific transcription initiation sites associated with higher levels of CB1 expression in the striatum compared to the cortex or between the striata of wild-type and HD transgenic mice. The progressive decline in CB1 mRNA levels in R6 compared to wild-type mice was due to decreased transcription, which is consistent with the hypothesis that mutant huntingtin exerts its effects by altering transcription factor activity.

The cell-specific conditions that allow for increased transcription of CB1 in the lateral striatum compared to other forebrain regions from all transcription start sites were affected by the expression of mutant huntingtin in a time-dependent manner.


Endocannabinoids form a novel class of retrograde messengers that modulate short- and long-term synaptic plasticity. Depolarization-induced suppression of excitation (DSE) and inhibition (DSI) are the best characterized transient forms of endocannabinoid-mediated synaptic modulation. Stimulation protocols consisting of long-lasting voltage steps to the postsynaptic cell are routinely used to evoke DSE-DSI. Little is known, however, about more physiological conditions under which these molecules are released in vitro. Moreover, the occurrence in vivo of such forms of endocannabinoid-mediated modulation is still controversial. Here we show that physiologically relevant patterns of synaptic activity induce a transient suppression of excitatory transmission onto dopamine neurons in vitro. Accordingly, in vivo endocannabinoids depress the increase in firing and bursting activity evoked in dopamine neurons by prefrontal cortex stimulation. This phenomenon is selectively mediated by the endocannabinoid 2-arachidonoyl-glycerol (2-AG), which activates presynaptic cannabinoid type 1 receptors. 2-AG synthesis involves activation of metabotropic glutamate receptors and Ca2+ mobilization from intracellular stores. These findings indicate that dopamine neurons release 2-AG to shape afferent activity and ultimately their own firing pattern. This novel endocannabinoid-mediated self-regulatory role of dopamine neurons may bear relevance in the pathogenesis of neuropsychiatric disorders such as schizophrenia and addiction.


Cannabinoids (CBs) are neuroprotective in vivo and in vitro, but the mechanisms of their actions are unknown. The aim of this study was to elucidate the signaling pathways that mediate the protective effect of CBs on primary cultured neurons. The neurotoxin S-AMPA induced significant death of rat primary cortical neurons, which was inhibited by the CB agonist HU-210.
Antagonists selective for CB(1) or CB(2) receptors (AM 281 or AM 630, respectively) reversed the neuroprotective effect of HU-210 on S-AMPA-induced cell death. HU-210 triggered activation of AKT, but not activation of the ERK1/2, JNK or p38 signaling pathways. The phosphatidylinositol 3-kinase (PI 3-K) inhibitors LY294002 and wortmannin prevented phosphorylation of AKT in response to HU-210, and reversed the neuroprotective effect of HU-210 on S-AMPA-induced excitotoxicity. Thus the PI 3-K/AKT signaling pathway mediates the neuroprotective effect of exogenous cannabinoids such as HU-210 in primary CNS neurons.


Although many studies have examined the acute behavioural effects of cannabinoids in rodents, few have examined the lasting effects of cannabinoids at different developmental ages. This study compared lasting effects of cannabinoid exposure occurring in adolescence to that occurring in early adulthood. Forty, 30-day old (adolescent) and 18, 56-day old (adult) female albino Wistar rats were injected with vehicle or incremental doses of the cannabinoid receptor agonist (-)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl) cyclohexanol (CP 55,940) once per day for 21 consecutive days (150, 200 and 300 mug/kg i.p. for 3, 8 and 10 days, respectively). Following a 21-day drug-free period, working memory was assessed using an object recognition task. Locomotor activity was also measured in the object recognition apparatus via a ceiling-mounted passive infrared sensor. Three days later, anxiety was assessed using a social interaction test. In the object recognition task, significantly poorer working memory was observed in the adolescent but not adult CP 55,940-treated rats. Adolescent, but not adult CP 55,940-treated rats, also exhibited a significant decrease in social interaction with a novel conspecific. These results suggest that chronic exposure to a cannabinoid receptor agonist well after the immediate postnatal period, but before reaching sexual maturity, can lead to increased anxiety and a lasting impairment of working memory.


A rapid and simple procedure using liquid-liquid extraction and subsequent gas chromatographic mass-spectrometric detection has been developed for determination of Delta(9)-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) in different hemp foods. After addition of Delta(8)-tetrahydrocannabinol as internal standard, both solid and liquid specimens were extracted with two volumes of 2ml of hexane/isopropanol (9:1): Chromatography was performed on a fused silica capillary column and analytes were determined in the selected-ion-monitoring (SIM) mode. The method was validated in the range 1-50ng/ml liquid samples or 1-50ng/g solid samples for THC and CBN, and 2-50ng/ml or ng/g for CBD. Mean recoveries ranged between 78.8 and 90.2% for the different analytes in solid and liquid samples. The quantification limits were 1ng/ml or ng/g for THC and CBN and 2ng/ml or ng/g CBD. The method was applied to analysis of various hemp foods. THC content in different products varied 50-fold, whereas CBN and CBD were absent in some samples and achieved hundreds of ng/ml or ng/g in others. The concentration ratio (THC + CBN)/CBD was used to differentiate between the phenotypes of cannabis plants in different specimens. Products possibly originating from drug-type cannabis plants were found in the majority of analyzed specimens.


Dopamine (DA) neurons in the ventral tegmental area have been implicated in psychiatric disorders and drug abuse. Understanding the mechanisms through which their activity is regulated via the modulation of afferent input is imperative to understanding their roles in these conditions. Here we demonstrate that endocannabinoids liberated from DA neurons activate cannabinoid CB1 receptors located on glutamatergic axons and on GABAergic terminals targeting GABA(B) receptors located on these cells. Endocannabinoid release was initiated by
inhibiting either presynaptic type-III metabotropic glutamate receptors or postsynaptic calcium-activated potassium channels, two conditions that also promote enhanced DA neuron excitability and bursting. Thus, activity-dependent release of endocannabinoids may act as a regulatory feedback mechanism to inhibit synaptic inputs in response to DA neuron bursting, thereby regulating firing patterns that may fine-tune DA release from afferent terminals.


Cannabinoids and endocannabinoids negatively influence sperm functions. These substances have been demonstrated in many mammalian tissues including male and female reproductive tract and previous studies have shown the presence of functional receptors for cannabinoids in human sperm. The present study, by means of RT-PCR and Western blot techniques, demonstrates that human sperm express the CB1 but not CB2 cannabinoid receptor subtype located in the head and middle piece of the sperm. The activation of this receptor by anandamide reduces sperm motility and inhibits capacitation-induced acrosome reaction. The activation of the CB1 receptor did not induce any variation of sperm intracellular calcium concentrations but produced a rapid plasma membrane hyperpolarization that was reduced by the K(+) channel blocker tetraethylammonium. The effects of anandamide on human sperm motility were dependent on the reduction of sperm mitochondrial activity as determined by rhodamine 123 fluorescence. The specificity of anandamide effects in human sperm were confirmed by the effects of the CB1 receptor antagonist SR141716. These findings provide additional evidence that human sperm express functional CB1 receptor which activation negatively influences important sperm functions and suggest a possible role of the cannabinoid system in the pathogenesis of some forms of male infertility.


Cannabinoid ligands are implicated in many physiological processes and to date two receptors have been identified. However, a growing body of evidence exists that suggests the presence of additional receptors. Whilst cloning the previously described hCB1a, we have identified a novel variant that we call hCB1b. Characterising these two splice variants demonstrates that they have a unique pharmacological profile and that their RNA's are expressed at low levels in a variety of tissues.


The aim of the present study was to investigate the effects of neonatal excitotoxic lesions of the medial prefrontal cortex (mPFC) on social play, social behavior unrelated to play, and self-grooming in juvenile and adult rats. We additionally examined the behavioral effects of chronic pubertal treatment with the cannabinoid agonist WIN 55,212-2 (WIN) in order to test the hypothesis that early lesions render the brain vulnerable to cannabinoid intake in later life. Neonatal mPFC lesions and pubertal WIN treatment disrupted social play, social behavior, and self-grooming in juvenile and adult rats. Additionally, we observed more social play behaviors during light cycle in WIN-treated than in vehicle-treated rats. Notably, the combination of surgery and WIN treatment disrupted social behavior in lesioned and sham-lesioned rats. The present data indicate that the mPFC is important for adequate juvenile response selection in the context of social play and might be involved in the development of adult social and nonsocial behavior. Moreover, our data add further evidence for an involvement of the cannabinoid system in anxiety and social behavior. Additive effects of neonatal surgery-induced stress or cortical lesions in combination with pubertal cannabinoid administration are also shown. The disturbances of social and nonsocial behavior in rats are comparable to symptoms of early frontal cortex damage, as well as neurodevelopmental disorders in humans, such as schizophrenia and autism. Therefore, we propose the combination of neonatal cortical lesions with chronic cannabinoid administration during puberty as an animal model for studying neuronal mechanisms of impaired social
functioning in neuropsychiatric disorders. Neuropsychopharmacology advance online publication, 8 December 2004; doi:10.1038/sj.npp.1300634.


A growing body of evidence suggests the existence of a functional interaction between opioid and cannabinoid systems. The present study further investigated this functional interaction by examining the combined effects of morphine and the cannabinoid receptor antagonist SR 141716 on Fos-immunoreactivity (Fos-IR), a marker for neural activation. Male albino Wistar rats were treated with SR 141716 (3 mg/kg, intraperitoneally), morphine HCl (10 mg/kg, subcutaneously), vehicle, or SR 141716 and morphine combined ([Formula: see text] per group). Rats were injected with morphine or its vehicle 30 min after administration of SR 141716 or its vehicle and perfused 3 h later. Locomotor activity and body temperature were both increased in the morphine-treated group and SR 141716 significantly inhibited these effects. Morphine increased Fos-IR in several brain regions including the caudate-putamen (CPu), cortex (cingulate, insular and piriform), nucleus accumbens (NAS) shell, lateral septum (LS), bed nucleus of the stria terminalis (BNST), median preoptic nucleus (MnPO), medial preoptic nucleus (MPO), hypothalamus (paraventricular, dorsomedial and ventromedial), paraventricular thalamic nucleus (PV), amygdala (central and basolateral nuclei), dorsolateral periaqueductal gray, ventral tegmental area (VTA), and Edinger-Westphal nucleus. SR 141716 alone increased Fos-IR in the cortex (cingulate, insular and piriform), NAS (shell), LS, BNST, hypothalamus (paraventricular, dorsomedial and ventromedial), PV, amygdala (central, basolateral and medial nuclei), VTA, and Edinger-Westphal nucleus. SR 141716 attenuated morphine-induced Fos-IR in several regions including the CPu, cortex, NAS (shell), LS, MnPO, MPO, paraventricular and dorsomedial hypothalamus, PV, basolateral amygdala, VTA, and Edinger-Westphal nucleus (EW). These results provide further support for functional interplay between the cannabinoid and opioid systems. Possible behavioural and physiological implications of the interactive effects of SR 141716 on morphine-induced Fos-IR are discussed.


We investigated the affinity of putative endocannabinoids (2-arachidonylglycerol, 2-AG; noladin ether, virodhamine) for the human neocortical CB(1) receptor. Functional activity of these compounds (including anandamide, AEA) was determined by examining basal and forskolin-stimulated cAMP formation. Assays were performed with synaptosomes, prepared from fresh human neocortical tissue. Receptor affinity was assessed from competition binding experiments with the CB(1/2) agonist [(3)H]-CP55,940 in absence or presence of a protease inhibitor to assess enzymatic stability. Noladin ether and virodhamine inhibited [(3)H]-CP55,940 binding (K(i): 98, 1740 nM, respectively). Protease inhibition decreased the K(i) value of virodhamine (K(i): 912nM), but left that of noladin ether unchanged. 2-AG almost lacked affinity (K(i): 10muM). Basal cAMP formation was unaffected by AEA and noladin ether, but strongly enhanced by 2-AG and virodhamine. Forskolin-stimulated cAMP formation was inhibited by AEA and noladin ether (IC(50): 69, 427nM, respectively) to the same extent as by CP55,940 (IC(max) each approximately 30%). Inhibitions by AEA or noladin ether were blocked by the CB(1) receptor antagonist AM251. Virodhamine increased forskolin-stimulated cAMP formation, also in presence of AM251, by approximately 20%. 2-AG had no effect; in presence of AM251, however, 10muM 2-AG stimulated cAMP formation by approximately 15%. Our results suggest, that AEA and noladin ether are full CB(1) receptor agonists in human neocortex, whereas virodhamine may act as a CB(1) receptor antagonist/inverse agonist. Particularly the (patho)physiological role of 2-AG should be further investigated, since its CB(1) receptor affinity and agonist activity especially in humans might be lower than generally assumed.

A method was developed and validated for the simultaneous determination of five cannabinoids, viz. cannabidiol (CBD), cannabidiol acid (CBD-COOH), cannabinol (CBN), delta9-tetrahydrocannabinol (THC), and 3’-carboxy-delta9-all-trans-tetrahydrocannabinol (THC-COOH) in cannabis products. The cannabinoids were extracted from the grinded cannabis samples with a mixture of methanol-chloroform and analysed using liquid chromatography with ion-trap-mass-spectrometry (LC-IT-MSn). For quantification the two most abundant diagnostic MS-MS ions of the analyte in the sample and external standard were monitored. For confirmation purposes the EU criteria as described in Commission Decision 2002/657/EC were followed. Fully satisfactory results were obtained, that is, unequivocal confirmation according to the most stringent EU criteria was possible. The limits of quantification were 0.1 g/kg for CBD, 0.04 g/kg for CBD-COOH, 0.03 g/kg for CBN, 0.28 g/kg for THC and 9.9 g/kg for THC-COOH. The repeatabilities, defined by R.S.D., were 2% for CBN, THC and THC-COOH at the concentration levels of respectively 0.023, 3.3 and 113 g/kg and 5% for CBD-COOH at the level of 0.34 g/kg (n = 6).


2-Arachidonoylglycerol is an endogenous ligand for the cannabinoid receptors. To date, two types of cannabinoid receptors (CB(1) and CB(2)) have been identified. The CB(1) receptor is assumed to be involved in the attenuation of synaptic transmission. On the other hand, the physiological roles of the CB(2) receptor, which is abundantly expressed in several types of inflammatory cells and immunocompetent cells, have not yet been fully elucidated. Recently, we investigated in detail possible physiological roles of the CB(2) receptor and 2-arachidonoylglycerol in inflammation. We found that 2-arachidonoylglycerol induces the activation of p42/44 and p38 mitogen-activated protein kinases and c-Jun N-terminal kinase; actin rearrangement and morphological changes; augmented production of chemokines in HL-60 cells; and the migration of HL-60 cells differentiated into macrophage-like cells, human monocytes, natural killer cells, and eosinophils. We also found that the level of 2-arachidonoylglycerol in mouse ear is markedly elevated following treatment with 12-O-tetradecanoylphorbol 13-acetate, which induces acute inflammation. Notably, the inflammation induced by 12-O-tetradecanoylphorbol 13-acetate was blocked by treatment with SR144528, a CB(2)-receptor antagonist. Similar results were obtained with an allergic inflammation model in mice. These results strongly suggest that 2-arachidonoylglycerol plays essential roles in the stimulation of various inflammatory reactions in vivo.

humans, then prudent selection of dose and receptor-specific agonists may allow an improved therapeutic separation from unwanted side effects.


RATIONALE: A growing body of in vitro and in vivo evidence indicates that a central endocannabinoid system, consisting of CB(1) receptors and endogenous cannabinoids, modulates specific aspects of mnemonic processes. Previous research has demonstrated that either permanent or drug-induced disruption of CB(1) receptor signaling interferes with the extinction of a conditioned fear response. OBJECTIVES: In the present study, we evaluated whether the endocannabinoid system also plays a role in extinguishing learned escape behavior in a Morris water maze task. METHODS: CB(1) (-/-) mice and mice repeatedly treated with 3 mg/kg of the CB(1) receptor antagonist SR 141716 (Rimonabant) were trained to locate a hidden platform in the Morris water maze. Following acquisition, the platform was removed and subjects were assigned to either a massed (i.e., five consecutive sessions consisting of four 2-min trials/session) or a spaced (a single, 1-min trial every 2-4 weeks) extinction protocol. RESULTS: Strikingly, both 3 mg/kg SR 141716-treated mice and CB(1) (-/-) mice continued to return to the target location across all five trials in the spaced extinction procedure, while the control mice underwent extinction by the third or fourth trial. In contrast, both the 3-mg/kg SR 141716-treated and CB(1) (-/-) mice exhibited extinction in the massed extinction trial procedure. CONCLUSIONS: These findings indicate that disruption of CB(1) receptor signaling impairs extinction processes in the Morris water maze, thus lending further support to the hypothesis that the endocannabinoid system plays an integral role in the suppression of non-reinforced learned behaviors.


BACKGROUND: Marijuana (Cannabis sativa) is the illicit drug most used by pregnant women, and behavioral and cognitive impairments have been documented in cannabis-exposed offspring. Despite the extensive use of marijuana, very limited information exists as to the consequences of prenatal cannabis exposure on the developing human brain. METHODS: We optimized an in situ hybridization histochemistry technique to visualize mRNA expression in midgestation (weeks 18-22) human fetal specimens from mothers with and without documented evidence of cannabis use during pregnancy. The cannabinoid receptor type 1 (CB(1)) and major dopamine receptor subtypes, D(1) and D(2), were examined in the striatum and mesocorticolimbic structures (amygdala and hippocampus). RESULTS: Adjusting for various covariates, we found a specific reduction, particularly in male fetuses, of the D(2) mRNA expression levels in the amygdala basal nucleus in association with maternal marijuana use. The reduction was positively correlated with the amount of maternal marijuana intake during pregnancy. No significant cannabis-related alterations were detected in the hippocampus or caudal striatum for the D(2), D(1), and CB(1) mRNA levels, although alcohol showed significant contribution to striatal D(1)/D(2) expression. CONCLUSIONS: These human fetal findings suggest that in utero cannabis exposure may impair distinct mesocorticolimbic neural systems that regulate emotional behavior.


The progesterone 17alpha-hydroxylase activity, which is one of the steroidogenic enzymes in rat testis microsomes, was significantly inhibited by crude marijuana extracts from Delta(9)-tetrahydrocannabinolic acid (THCA)- and cannabidiolic acid (CBD-A)-strains. Delta(9)-Tetrahydrocannabinol, cannabidiol and cannabino also inhibited the enzymatic activity with relatively higher concentration (100-1000muM). Testosterone 6beta- and 16alpha-hydroxylase activities together with androstenedione formation from testosterone in rat liver microsomes were
also significantly inhibited by the crude marijuana extracts and the cannabinoids. Crude marijuana extracts (1 and 10μg/ml) of THCA strain stimulated the proliferation of MCF-7 cells, although the purified cannabinoids (THC, CBD and CBN) did not show significant effects, such as the extract at the concentration of 0.01-1000nM. These results indicate that there are some metabolic interactions between cannabinoid and steroid metabolism and that the constituents showing estrogen-like activity exist in marijuana.


Growing evidence on the involvement of cannabinoids in the rewarding effects of various kinds of drugs of abuse has suggested that not only the classical dopaminergic and opioidergic, but also the most recently established endocannabinoid system is implicated in the brain reward system. Furthermore, the interplay between the three systems has been shown to be an essential neural substrate underlying many aspects of drug addiction including craving and relapse. Relapse, the resumption of drug taking following a period of drug abstinence, is considered the main hurdle in treating drug addiction. Yet, little is known about its underlying process mechanisms. The link between the endocannabinoid system and the arachidonic cascade is currently being clarified. While several findings have, indeed, shown the essential role of the endocannabinoid system in the reinstatement model, the endocannabinoid-arachidonic acid pathway may also be an important part in the neural machinery underlying relapse. This evidence may provide an alternative approach that will open a novel strategy in combating drug addiction.


Diarylpyrazoles are a group of 1,5-diphenylpyrazole analogues of which several have been found to exhibit antagonist properties towards the cannabinoid receptors. SR141716A, the first reported antagonist, is a highly potent and selective CB1 receptor ligand that prevents or reverses CB1-mediated effects. Other analogues such as AM251 and AM281 have also shown high binding affinities to the central cannabinoid receptor and behave as antagonists/inverse agonists. There has been no report on the metabolism of any of the diarylpyrazoles and it is unknown whether their metabolites retain any receptor binding properties. We report a study of the in vitro metabolisms of three diarylpyrazole analogues, SR141716A, AM251, and AM281 in rat liver microsomes. The metabolic profile was obtained using high performance liquid chromatography (HPLC) with UV and mass spectrometry detectors. All identified metabolites are characterized by structural modifications on the terminal group of the 3-substituent. Thus, three pairs of isomeric metabolites were identified from the microsomal incubation of SR141716A, which are products of hydroxylation, hydroxylation followed by dehydration, and a combination of the two. For AM251, only four metabolic products were detected, with two resulting from monohydroxylation of the piperidine ring and the other two being products of dehydration of the first pair of metabolites. For AM281 where the terminal group of the 3-substituent is a morpholine ring, dehydration of the first two metabolites yielded a single third metabolite due to only one possible position for the carbon-carbon double bond on the morpholinyl ring.

**CLINICAL SCIENCE**


The objective was to investigate the effectiveness of cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion. This condition is an excellent human model of central neuropathic pain as it represents an unusually homogenous group in terms of anatomical location of injury, pain descriptions and patient demographics. Forty-eight patients with at least one avulsed root and baseline pain score of four or more on an 11-
point ordinate scale participated in a randomised, double-blind, placebo-controlled, three period crossover study. All patients had intractable symptoms regardless of current analgesic therapy. Patients entered a baseline period of 2 weeks, followed by three, 2-week treatment periods during each of which they received one of three oromucosal spray preparations. These were placebo and two whole plant extracts of Cannabis sativa L.: GW-1000-02 (Sativex((R))), containing Delta(9)tetrahydrocannabinol (THC):cannabidiol (CBD) in an approximate 1:1 ratio and GW-2000-02, containing primarily THC. The primary outcome measure was the mean pain severity score during the last 7 days of treatment. Secondary outcome measures included pain related quality of life assessments. The primary outcome measure failed to fall by the two points defined in our hypothesis. However, both this measure and measures of sleep showed statistically significant improvements. The study medications were generally well tolerated with the majority of adverse events, including intoxication type reactions, being mild to moderate in severity and resolving spontaneously. Studies of longer duration in neuropathic pain are required to confirm a clinically relevant, improvement in the treatment of this condition.


BACKGROUND:: Adherence to antiretroviral therapy (ART) is essential to successful treatment of HIV infection. Two recent studies reported a negative correlation between marijuana use and adherence to ART. Some patients, however, report that smoking marijuana improves adherence to ART. This study therefore sought to identify which subgroups of patients may have differential adherence to ART in association with recent marijuana use. METHODS:: Cross-sectional survey design within a public health care system for HIV/AIDS. RESULTS:: With a 5% refusal rate, 252 patients completed the interview, 175 (69%) were on ART, and 168 (67%) provided ART adherence data. Forty-one subjects (24%), predominantly whites, used marijuana. In bivariate analysis, no association between ART adherence and marijuana use was found (odds ratio [OR] = 0.92, 95% CI = 0.4-1.9). Adherence was positively associated with undetectable plasma virus and negatively associated with alcohol and other illicit drug use. Examining subgroups of patients, among those with nausea, marijuana users were more likely to show an association with adherence than nonusers (OR = 3.3), while among those without nausea, marijuana use was lower associated with adherence (OR = 0.52, P for homogeneity 0.02). This relationship was confirmed in multivariate analyses controlling for the interactions between nausea and marijuana use, in which other illicit drug use remained a factor related to nonadherence. DISCUSSION:: These data suggest that medicinal use of marijuana may facilitate, rather than impede, ART adherence for patients with nausea, in contrast to the use of other illicit substances, which were associated with lower rates of ART adherence. To demonstrate any causal relationship between marijuana and adherence would require a longitudinal or controlled study.


Legalisation of cannabis use in Switzerland has recently been debated by the Swiss Parliament. Although legalisation has not yet been decided upon, it is still the subject of impassioned public discussion. If cannabis use is legalised, an increase in consumption is to be expected. One of the manifold negative consequences for mental health will probably be an increase in the prevalence of psychoses - not only acute, toxic psychosis but also chronic psychoses. Schizophrenic psychoses are expected to be triggered at an earlier age and to be negatively influenced in their course. This eventuality could have deleterious consequences not only for many currently healthy individuals predisposed to psychosis, but also for the disability pension.


OBJECTIVE: To investigate the relation between cannabis use and psychotic symptoms in individuals with above average predisposition for psychosis who first used cannabis during
adolescence. 

**DESIGN:** Analysis of prospective data from a population based sample. Assessment of substance use, predisposition for psychosis, and psychotic symptoms was based on standardised personal interviews at baseline and at follow up four years later.

**PARTICIPANTS:** 2437 young people (aged 14 to 24 years) with and without predisposition for psychosis.

**MAIN OUTCOME MEASURE:** Psychotic symptoms at follow up as a function of cannabis use and predisposition for psychosis at baseline.

**RESULTS:** After adjustment for age, sex, socioeconomic status, urbanicity, childhood trauma, predisposition for psychosis at baseline, and use of other drugs, tobacco, and alcohol, cannabis use at baseline increased the cumulative incidence of psychotic symptoms at follow up four years later (adjusted odds ratio 1.67, 95% confidence interval 1.13 to 2.46). The effect of cannabis use was much stronger in those with any predisposition for psychosis at baseline (23.8% adjusted difference in risk, 95% confidence interval 7.9 to 39.7, \( P=0.003 \)) than in those without (5.6%, 0.4 to 10.8, \( P=0.033 \)). The risk difference in the “predisposition” group was significantly greater than the risk difference in the “no predisposition” group (test for interaction 18.2%, 1.6 to 34.8, \( P=0.032 \)). There was a dose-response relation with increasing frequency of cannabis use. Predisposition for psychosis at baseline did not significantly predict cannabis use four years later (adjusted odds ratio 1.42, 95% confidence interval 0.88 to 2.31).

**CONCLUSION:** Cannabis use moderately increases the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis.


Introduction Since the end of the nineteen-nineties, cannabis is not only incriminated in the onset of thromboangiitis obliterans but also in inducing atheromatous lesions in young subjects. Observation A young, Caucasian, 18 year-old man was referred for cannabis withdrawal in the treatment of arteritis of the left leg. DISCUSSION: Cannabis is by far the illicit psychoactive substance most consumed by the 15-25 year-olds. Data in the literature, notably since the end of the nineteen-nineties, show that cannabis is accused of provoking arterial disease similar to that which is found in Buerger's disease (or thromboangiitis obliterans) in young subjects of whichever sex.


Trigeminal neuralgia is a disorder of paroxysmal and severely disabling facial pain and continues to be a real therapeutic challenge to the clinicians. While the exact cause and pathology of this disorder is uncertain, it is thought that trigeminal neuralgia caused by irritation of the trigeminal nerve. This irritation results from damage due to the change in the blood vessels, the presence of a tumor or other lesions that cause the compression of the trigeminal root. The pain of trigeminal neuralgia is characterized by unilateral pain attacks that start abruptly and last for varying periods of time from minutes to hours. The quality of pain is usually sharp, stabbing, lancinating, and burning. The attacks are initiated by mild stimuli such as light touch of the skin, eating, chewing, washing the face, brushing the teeth, and exposure to wind. Although antiepileptic drug therapy may be beneficial in the treatment of trigeminal neuralgia, up to one-half of the patients become refractory or intolerant to these medications. At present there are few other effective drugs. In cases of lacking effect after pharmacotherapy, surgical options may be considered. Currently there is growing amount of evidence to suggest that the psychoactive ingredient in cannabis and individual cannabinoids may be effective in alleviating neuropathic pain and hyperalgesia. Evidence suggests that cannabinoids may prove useful in pain modulation by inhibiting neuronal transmission in pain pathways. Considering the pronounced antinociceptive effects produced by cannabinoids, they may be a promising therapeutic approach for the clinical management of trigeminal neuralgia.


--In 1996, the Netherlands Health Council issued a negative recommendation regarding the use of medication on the basis of cannabis (marihuana). However, interest in medicinal
cannabis has certainly not waned since. --The neurological diseases for which cannabis could presently be used therapeutically are: multiple sclerosis, chronic (neuropathic) pain and the syndrome of Gilles de la Tourette. --Since September 2003, the Dutch Ministry of Health, Welfare and Sport delivers medicinal cannabis to Dutch pharmacies, so that now for the first time, medicinal cannabis can be given to patients on a prescription basis within the framework of the Opium Law. The result of this is that doctors and patients now assume that this is a medication for which the efficacy and safety have been established. --The question arises whether new scientific data have become available since 1996 that provide scientific support for the current Governmental policy. --In a recent clinical trial that has aroused much discussion, patients with multiple sclerosis and problematic spasticity were treated with oral cannabis or a placebo. There was no significant effect of treatment on the primary outcome measure, i.e. objectively determined spasticity. Nevertheless, it was concluded that the mobility was improved and that the pain was subjectively decreased. --Until now, convincing scientific evidence that cannabinoids are effective in neurological conditions is still lacking. --However, it is also not possible to conclude definitely that cannabinoids are ineffective; still, this is no basis for official stimulation of their use.


Marijuana is the most widely used illicit substance in the United States; however, previous imaging studies have not detected altered brain structure in marijuana users compared to non-users. Voxel-based morphometry was used to investigate possible differences in brain tissue composition in a group of 11 heavy marijuana users and a group of 8 non-users. All participants were male. Statistical comparisons were made at the voxel level on T1-weighted magnetic resonance images to determine differences in gray matter and white matter tissue density. Compared to non-users, marijuana users had lower gray matter density in a cluster of voxels in the right parahippocampal gyrus (P = 0.0001), and greater density bilaterally near the precentral gyrus and the right thalamus (P < 0.04). Marijuana users also had lower white matter density in the left parietal lobe (P = 0.03), and higher density around the parahippocampal and fusiform gyri on the left side compared to non-users (P < 0.002). Longer duration of marijuana use (in years) was significantly correlated with higher white matter tissue density in the left precentral gyrus (P = 0.045). Our preliminary results suggest evidence of possible structural differences in the brain of heavy marijuana users, and localize regions for further investigation of the effects of marijuana in the brain.


The Standardised Field Sobriety Tests (SFST) were developed to test for alcohol intoxication but are currently being used by the State Police of Victoria (Australia) to test for driving impairment associated with drugs other than alcohol. The aim of the present study was to assess whether the SFSTs provide a sensitive measure of impairment following the consumption of a drug other than alcohol: delta-9-tetrahydrocannabinol (THC or cannabis). In a repeated-measures design, 40 participants consumed cigarettes that contained either 0% THC (placebo), 1.74% THC (low dose) or 2.93% THC (high dose). For each condition, after smoking a cigarette, participants performed the SFSTs on three occasions: 5 min (Time 1), 55 min (Time 2) and 105 min (Time 3) after the smoking procedure had been completed. The results revealed that there was a positive relationship between the dose of THC administered and the number of participants classified as impaired based on the SFSTs. Results also revealed that the percentage of participants classified as impaired decreased from Time 1 to Time 3 and that the addition of a new sign, head movements or jerks (HMJ), increased the percentage of participants classified as impaired in both the low and high THC conditions. These findings suggest that impaired
performance on the SFSTs is positively related to the dose of THC administered and that the inclusion of HMJ as a scored sign in the SFSTs improves their predictive validity when testing for THC intoxication.


The objective of this study was to identify the differences in cerebral activation between chronic cannabis smokers and controls in response to finger sequencing. We hypothesized that attentional areas related to motor function as well as primary and supplementary motor cortices would show diminished activation in chronic cannabis smokers. Nine cannabis smokers and 16 controls were included in these analyses. Scanning was performed on a GE 1.5T scanner. Echo planar images and high-resolution MR images were acquired. The challenge paradigm included left and right finger sequencing. Group differences in cerebral activation were examined for Brodmann areas (BA) 4, 6, 24, and 32 using ROI analyses in SPM. Cannabis users, tested within 4-36h of discontinuation, exhibited significantly less activation than controls in BA 24 and 32 bilaterally during right- and left-sided sequencing and for BA 6 in all tasks except for left-sided sequencing in the left hemisphere. There were no statistically significant differences for BA 4. None of these regional activations correlated with urinary cannabis concentration and verbal IQ for smokers. These results suggest that recently abstinent chronic cannabis smokers produce reduced activation in motor cortical areas in response to finger sequencing compared to controls.


A 32-year-old woman presented with a painful leg and a gangrenous big toe. Her medical history included HIV-infection that had remained untreated for 8 years. In addition, she had smoked about 10 cannabis-cigarettes daily during the previous 15 years. Physical examination and angiography confirmed the presence of severe peripheral artery disease in the left lower leg. She received a femorodistal bypass graft but the gangrene was progressive, ultimately necessitating a lower leg amputation. Histopathological examination revealed intimal fibrosis and thrombosis with recanalisation in combination with fragmentation of the internal elastic membrane. Peripheral artery disease is often associated with lower extremity ischaemia, mostly affecting elderly patients and almost always caused by atherosclerosis. When ischaemic symptoms manifest themselves in young individuals (<40 years), rare causes of obliterative arterial disease, such as inflammation or post-traumatic vascular injury, must be excluded. Use of cannabis and untreated HIV infection are both relatively unknown risk factors for the onset of premature non-atherosclerotic arterial disease. Stopping the smoking of cannabis appears to have a favourable effect on the ischaemic symptoms. Whether treatment of HIV-infection can affect the course of premature peripheral vascular disease is unknown. When deciding whether or not to give antiviral therapy, care providers should also consider the increased cardiovascular mortality rates associated with these treatment regimens. In the case described, the HIV-infection was considered the most likely cause of the peripheral artery disease, based on all the histopathological findings.


Cannabis consumption may induce psychotic states in normal individuals, worsen psychotic symptoms of schizophrenic patients, and may facilitate precipitation of schizophrenia in vulnerable individuals. Recent studies provide additional biological and genetic evidence for the cannabinoid hypothesis of schizophrenia. Examinations using [(3)H]CP-55940 or [(3)H]SR141716A revealed that the density of CB(1) receptors, a central type of cannabinoid receptor, is increased in subregions of the prefrontal cortex in schizophrenia. Anandamide, an
endogenous cannabinoid, is also increased in the CSF in schizophrenia. A genetic study revealed that the CNR1 gene, which encodes CB(1) receptors, is associated with schizophrenia, especially the hebephrenic type. Individuals with a 9-repeat allele of an AAT-repeat polymorphism of the gene may have a 2.3-fold higher susceptibility to schizophrenia. Recent findings consistently indicate that hyperactivity of the central cannabinoid system is involved in the pathogenesis of schizophrenia or the neural mechanisms of negative symptoms.


Executive functioning impairments have been demonstrated following consumption of drugs of abuse. These executive impairments could play an important role on the development of the addictive process and rehabilitation of substance abusers. Recent neuropsychological models of executive functioning assume a multicomponent organization of these processes, suggesting different functions could contribute differentially to performance on executive tasks. The aim of this study was to analyze the relationship between severity of consumption of different drugs and neuropsychological performance on tasks sensitive to impairment in the executive subprocesses of working memory, response inhibition, cognitive flexibility, and abstract reasoning. Instruments sensitive to impairment in these four components were administered to 38 polysubstance abusers along with a severity of drug consumption interview. Multiple regression analyses were used. Results showed a differential impact of severity of MDMA abuse on working memory and abstract reasoning indices, of cocaine severity on an inhibitory control index and of cannabis on a cognitive flexibility index. Metabolic reorganization of monoamine frontal-subcortical pathways after drug exposure are proposed as possible explanations for these impairments.

BEHAVIOURAL SCIENCE


In this paper, university students' beliefs about different causes of drug addiction and cures for it were investigated. Principal component analysis (PCA) with Causes of Drug Abuse Scale (CADAS) revealed four components: problems and coping, sensation seeking, social environment, and disposition. PCA with Cures for Drug Abuse Scale (CUDAS) produced four components: help seeking and avoidance, self-change, social activity, and change. Separate MANOVAs were performed and significant gender differences were found between two of CADAS' and three of CUDAS' components. Analysis on attitude scale revealed gender and drug main effects and an interaction effect. Men had more positive attitudes toward "drug" vignette. The most negative attitudes were found toward "heroin" vignette and the most positive attitudes were found toward the "cannabis" vignette. Results indicated that those who has known a drug user had more positive attitudes.


Cannabis dependence is a prevalent comorbid substance use disorder among patients early in the course of a schizophrenia-spectrum disorder. Determining risk factors for substance abuse may be helpful in designing interventions to reduce the psychosocial morbidity associated with substance abuse among this population. This study aimed to determine whether or not African American, socially disadvantaged, first-episode schizophrenia-spectrum patients with cannabis dependence experienced greater levels of childhood abuse and neglect compared to similar patients without comorbid cannabis dependence. Among 29 eligible patients, 18 participated in this pilot study. First-episode patients with comorbid cannabis dependence (n = 8) reported significantly greater childhood physical and sexual abuse compared to those without comorbid cannabis dependence (n = 10). This represents preliminary evidence of an association between childhood maltreatment and cannabis dependence among this especially vulnerable
population. Childhood physical and sexual abuse may be a risk factor for the initiation of cannabis dependence and other substance use disorders in the early course of schizophrenia.


Timeline followback (TLFB) methodology was used to assess the daily use of cigarettes, alcohol, and marijuana in adolescent cigarette smokers and nonsmokers over the prior 30 days. Adolescent smokers reported more frequent daily use of both alcohol and marijuana than nonsmokers did. Of those smokers and nonsmokers who drank alcohol and used marijuana, smokers reported more frequent daily use of alcohol, but not marijuana. In examining daily use patterns, there were very few instances when adolescent smokers used alcohol but did not smoke cigarettes, and smokers used marijuana alone on more days than alcohol alone. One-fifth of the adolescent smokers used all three substances on the same day in the past month. There were no significant differences in the patterns of alcohol and marijuana use between female and male smokers, regardless of age. Implications for clinical interventions and future research are discussed.


Few studies have attempted to investigate the nature of adolescents' and adults' conceptions and perceptions of cannabis use. Our objectives were to explore adolescent and adult perception of use and misuse of cannabis, and their opinions and beliefs about the current legal context and preventive strategies. We used focus group discussions with four categories of stakeholders: younger (12-15 year old) adolescents, older (16-19 year old) adolescents, parents of teenagers and professionals working with young people. In some areas (legal framework, role of the media, importance of early preventive interventions), we found consensual attitudes and beliefs across the four groups of participants. In all four groups, participants did not have any consensual vision of the risks of cannabis use or the definition of misuse. In the area of the prevention of cannabis use/misuse, while parents focused on the potential role of professionals and the media, thus minimizing their own educational and preventive role, professionals stressed the importance of parental control and education. Within the Swiss context, we conclude there exists an urgent need for information and clarification of the issues linked with cannabis use and misuse directed at parents and professionals.


In this study, I examined direct and indirect influences of sensation seeking, a personality trait, on adolescent drug use. I hypothesized that some or even most of the contribution of sensation seeking to drug use by adolescents is mediated through association with deviant peers and communication with peers that is favorable toward drug use. I examined the role of additional risk or protective factors in facilitating or impeding association with deviant peers, pro-drug communication, and marijuana use as well. The results of analyzing nationally representative cross-sectional data from the evaluation of the National Youth Anti-Drug Media Campaign support the study's hypotheses and suggest that different factors may protect high sensation-seeking adolescents from using drugs or engaging in activities (e.g., association with deviant peers) that may increase their risk for drug use.

This newsletter is supported in part by an unrestricted educational grant from Valeant Pharmaceuticals (Canada)