INTRODUCTION

Here is the latest summary of research abstracts. The abstracts from the recent ICRS meeting in Cornwall, Ontario are available from the ICRS office (www.cannabinoidsociety.org). Regarding upcoming events, the International Association of Cannabis as Medicine meets in Cologne, Germany on Sept 12-13th, 2003 (details at http://www.cannabismed.org/Meeting/Cologne2003/home.htm), and there will be a day dedicated to advances in cannabinoids and pain at the American Academy of Pain Management in Denver, Colorado on Sept 3-7th, 2003 (details at http://www.aapainmanage.org/conference/Conference.php).

BASIC SCIENCE


The effect of anandamide, which activates both the cannabinoid 1 (CB1) receptor and the vanilloid receptor 1 (VR1), was studied on calcitonin gene-related peptide (CGRP) release from cultured primary sensory neurons, the majority of which coexpress the CB1 receptor and VR1. Concentrations of anandamide < 1 micro m produced a small but significant CB1 receptor-mediated inhibition of basal CGRP release while higher concentrations induced VR1-mediated CGRP release. The excitatory effect of anandamide was potentiated by the CB1 receptor antagonist SR141716A. In the presence of SR141716A at concentrations < 100 nm, anandamide was equipotent with capsaicin in stimulating CGRP release. However, at higher concentrations anandamide produced more CGRP release than equimolar concentrations of capsaicin. Three and ten nanomolar anandamide inhibited the capsaicin-evoked CGRP release. In the presence of SR141716A, treatments which activated protein kinase A, protein kinase C and phospholipase C significantly potentiated the anandamide-evoked CGRP release at all anandamide concentrations. Although this potentiation was reduced when the CB1 receptor antagonist was omitted from the buffer, the CGRP release evoked by 300 nm and 1 micro m anandamide was still significantly larger than that seen with nonpotentiated cells. These data indicate that anandamide may regulate CGRP release from capsaicin-sensitive primary sensory neurons in vivo, and that the net effect of anandamide on transmitter release from capsaicin-sensitive primary sensory neurons depends on the concentration of anandamide and the state of the CB1 receptor and VR1. These findings also suggest that anandamide could be one of the molecules responsible for the development of inflammatory heat hyperalgesia.


Microsatellite markers were developed for Cannabis sativa L. (marijuana) to be used for DNA typing (genotype identification) and to measure the genetic relationships between the different plants. Twelve different oligonucleotide probes were used to screen an enriched microsatellite library of Cannabis sativa in which 49% of the clones contained microsatellite sequences. Characterization of microsatellite loci in Cannabis revealed that GA/CT was the most abundant class of the isolated microsatellites representing 50% overall followed by GTT/CAA, AAG/TTC, and GAT/CTA representing 16%, 15%, and 10%, respectively. Eleven polymorphic
STR markers were developed, three derived from dinucleotide motifs and eight from trinucleotide motifs. A total of 52 alleles were detected, averaging 4.7 alleles/locus. The expected heterozygosity of the eleven loci ranged between 0.368 and 0.710 and the common probability of identical genotypes was $1.8 \times 10^{-7}$. The loci identified 27 unique profiles of the 41 Cannabis samples. The 11 microsatellite markers developed in this study were found to be useful for DNA typing and for assessing genetic relatedness in Cannabis.


In this study we used in situ hybridisation and double-labelling immunohistochemistry to characterise cannabinoid receptor 1 (CB1) expression in rat lumbar dorsal root ganglion (DRG) neurons. Approximately 25% of DRG neurons expressed CB1 mRNA and displayed immunoreactivity for CB1. Sixty-nine percent to 82% of CB1-expressing cells were also immunoreactive for neurofilament 200, indicative of myelinated A-fibre neurons, which tend to be large- and medium-sized DRG neurons (>600 μm²). Approximately 10% of CB1-expressing cells also expressed transient receptor potential vanilloid family ion channel 2 (TRPV2), the noxious heat-transducing channel found in medium to large lightly myelinated Adelta-fibre DRG neurons. Seventeen percent to 26% of CB1-expressing cells co-stained using Isolectin B4, 9-10% for calcitonin gene-related peptide and 11-20% for transient receptor potential vanilloid family ion channel 1 (TRPV1), predominantly markers of small non-myelinated C-fibre DRG neurons (<600 μm²). These findings suggest that whilst a wide range of DRG neuron phenotypes express CB1, it is predominantly associated with myelinated fibres.


Cannabinoids exhibit immunosuppressive actions that include inhibition of interleukin-2 production in response to a variety of T cell activation stimuli. Traditionally, the effects of these compounds have been attributed to cannabinoid receptors, CB1 and CB2, both of which are expressed in mouse splenocytes. Therefore, SR141716A, a CB1 antagonist, and SR144528, a CB2 antagonist, were utilized to investigate the role of cannabinoid receptors in the cannabinoid-induced inhibition of phorbol ester plus calcium ionophore (PMA/Io)-stimulated interleukin-2 production by mouse splenocytes. PMA/Io-stimulated interleukin-2 production was inhibited by cannabiol, cannabidiol and both WIN 55212-2 stereoisomers with a rank order potency of WIN 55212-2 approximately cannabidiol > WIN 55212-3 approximately cannabiol. Cannabinoid-induced inhibition of PMA/Io-stimulated interleukin-2 was not attenuated by the presence of both SR144528 and SR141716A. Using pertussis toxin to address the role of G protein-coupled receptors in this response, it was determined that pertussis toxin treatment did not attenuate cannabinoid-induced inhibition of PMA/Io-stimulated interleukin-2. With the demonstration that cannabinoid-induced inhibition of PMA/Io-stimulated interleukin-2 was not mediated via CB1 or CB2, alternative targets of cannabinoids in T cells were examined. Specifically, it was demonstrated that cannabinoids elevated intracellular calcium concentration in resting splenocytes and that the cannabinoid-induced elevation in intracellular calcium concentration was attenuated by treatment with both SR144528 and SR141716A. Interestingly, pretreatment of splenocytes with agents that elevate intracellular calcium concentration inhibited PMA/Io-stimulated interleukin-2 production, suggesting that an elevation in intracellular calcium concentration might be involved in the mechanism of interleukin-2 inhibition. These studies suggest that immune modulation produced by cannabinoids involves multiple mechanisms, which might be both cannabinoid receptor-dependent and -independent.


Cannabis has a long history of consumption both for recreational and medicinal uses. Recently there have been significant advances in our understanding of how cannabis and related compounds (cannabinoids) affect the brain and this review addresses the current state of knowledge of these effects. Cannabinoids act primarily via two types of receptor, CB1 and CB2, with CB1 receptors mediating most of the central actions of cannabinoids. The presence of a new
type of brain cannabinoid receptor is also indicated. Important advances have been made in our understanding of cannabinoid receptor signaling pathways, their modulation of synaptic transmission and plasticity, the cellular targets of cannabinoids in different central nervous system (CNS) regions and, in particular, the role of the endogenous brain cannabinoid (endocannabinoid) system. Cannabinoids have widespread actions in the brain: in the hippocampus they influence learning and memory; in the basal ganglia they modulate locomotor activity and reward pathways; in the hypothalamus they have a role in the control of appetite. Cannabinoids may also be protective against neurodegeneration and brain damage and exhibit anticonvulsant activity. Some of the analgesic effects of cannabinoids also appear to involve sites within the brain. These advances in our understanding of the actions of cannabinoids and the brain endocannabinoid system have led to important new insights into neuronal function which are likely to result in the development of new therapeutic strategies for the treatment of a number of key CNS disorders.


Two cannabinoid receptors, CB1 and CB2, have been identified. The CB1 receptor is preferentially expressed in brain, and the CB2 receptor in cells of leukocyte lineage. We identified the mRNA for the CB1 receptor in human neuroblastoma SH-SY5Y cells, and the mRNA and protein for the CB2 receptor in human microglia and THP-1 cells. 2 Delta(9)- and Delta(8)-tetrahydrocannabinol (THC) were toxic when added directly to SH-SY5Y neuroblastoma cells. The toxicity of Delta(9)-THC was inhibited by the CB1 receptor antagonist SR141716A but not by the CB2 receptor antagonist SR144528. The endogenous ligand anandamide was also toxic, and this toxicity was enhanced by inhibitors of its enzymatic hydrolysis. 3 The selective CB2 receptor ligands JWH-015 and indomethacin morpholinylamide (BML-190), when added to THP-1 cells before stimulation with lipopolysaccharide (LPS) and IFN-gamma, reduced the toxicity of their culture supernatants to SH-SY5Y cells. JWH-015 was more effective against neurotoxicity of human microglia than THP-1 cells. The antineurotoxic activity of JWH-015 was blocked by the selective CB2 receptor antagonist SR144528, but not by the CB1 receptor antagonist SR141716A. This activity of JWH-015 was synergistic with that of the 5-lipoxigenase (5-LOX) inhibitor REV 5901. 4 Cannabinoids inhibited secretion of IL-1beta and tumor necrosis factor-alpha (TNF-alpha) by stimulated THP-1 cells, but these effects could not be directly correlated with their antineurotoxic activity. 5 Specific CB2 receptor ligands could be useful anti-inflammatory agents, while avoiding the neurotoxic and psychoactive effects of CB1 receptor ligands such as Delta(9)-THC. {doi:10.1038/sj.bjp.0705304}


The study was undertaken to explore the effect of CP55,940 ([(-)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol], a drug commonly used as a CB1/CB2 cannabinoid receptor agonist, on intracellular free Ca2+ levels ([Ca2+]i) in MG63 human osteoblast-like epithelial cells. [Ca2+]i was measured in suspended cells by using the fluorescent dye fura-2 as an indicator. At concentrations between 2-20 microM, CP55,940 increased [Ca2+]i in a concentration-dependent manner with an EC50 of 8 microM. The [Ca2+]i signal comprised an initial rise, a slow decay, and a sustained phase. CP55940 (10 microM)-induced [Ca2+]i signal was not altered by 5 microM of two cannabinoid receptor antagonists (AM-251, N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyr azole-3-carboxamide; AM-281, 1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-4-morpholinyl-1H-pyrazole le-3-carboxamide). Extracellular Ca2+ removal decreased the maximum value of the Ca2+ signals by 50%. CP55,940 induced quench of fura-2 fluorescence by Mn2+ (50 microM), suggesting the presence of Ca2+ influx across the plasma membrane. CP55,940 (10 microM)-induced [Ca2+]i increase in Ca(2+)-free medium was inhibited by 84% by pretreatment with 1 microM thapsigargin, an endoplasmic reticulum Ca2+ pump inhibitor. Conversely, pretreatment with 10 microM CP55,940 in Ca(2+)-free medium abolished thapsigargin-induced [Ca2+]i...
increase. At 1 microM, nifedipine, verapamil, and diltiazem did not alter CP55,940 (10 microM)-induced [Ca2+]i increase. CP55,940 (20 microM)-induced Ca2+ release was not affected when phospholipase C was inhibited by 2 microM U73122 (1-((6-((17beta-3-methoxyestra-1,3,5(10)-trien-17-yl)amino) hexyl)-1H-pyrrole-2,5-dione). CP55,940 (20 microM) did not induce acute cell death after incubation for 30 min as assayed by trypan blue exclusion. Collectively, CP55,940 induced significant [Ca2+]i increases in osteoblasts by releasing store Ca2+ from thapsigargin-sensitive stores and by causing Ca2+ entry. The CP55,940's action appears to be independent of stimulation of CB1 cannabinoid receptors.


Anandamide (AEA), a prominent member of the endogenous ligands of cannabinoid receptors (endocannabinoids), is known to affect several functions of brain and peripheral tissues. A potential role for AEA in skin pathophysiology has been proposed, yet its molecular basis remains unknown. Here we report unprecedented evidence that spontaneously immortalized human keratinocytes (HaCaT) and normal human epidermal keratinocytes (NHEK) have the biochemical machinery to bind and metabolize AEA, i.e. a functional type-1 cannabinoid receptor (CB1R), a selective AEA membrane transporter (AMT), an AEA-degrading fatty acid amide hydrolase (FAAH), and an AEA-synthesizing phospholipase D (PLD). We show that, unlike CB1R and PLD, the activity of AMT and the activity and expression of FAAH increase while the endogenous levels of AEA decrease in HaCaT and NHEK cells induced to differentiate in vitro by 12-O-tetradecanoylphorbol 13-acetate (TPA) + calcium. We also show that exogenous AEA inhibits the formation of cornified envelopes, a hallmark of keratinocyte differentiation, in HaCaT and NHEK cells treated with TPA + calcium, through a CB1R-dependent reduction of transglutaminase and protein kinase C activity. Moreover, transient expression in HaCaT cells of the chloramphenicol acetyltransferase reporter gene under control of the loricrin promoter, which contained a wild-type or mutated activating protein-1 (AP-1) site, showed that AEA inhibited AP-1 in a CB1R-dependent manner. Taken together, these data demonstrate that human keratinocytes partake in the peripheral endocannabinoid system, and show a novel signaling mechanism of CB1 receptors, that may have important implications in epidermal differentiation and skin development.


Cannabinoids and alcohol activate the same reward pathways, and the cannabinoid CB(1) receptor system plays an important role in regulating the positive reinforcing properties of alcohol. Indeed, both cannabinoids and alcohol cause the release of dopamine in the nucleus accumbens. Recent research suggests that ethanol preference, which is dependent on CB(1) receptors, is higher in young mice than in old mice, and higher in female mice than in male mice.


The purpose of this review is to summarize the status of DNA-based methods for the identification and individualization of marijuana. In forensics, both identification of a substance as marijuana and the subsequent individualization of a sample may be desired for casework. Marijuana identification methods in the United States primarily include biochemical tests and, less frequently, DNA-based tests. Under special circumstances, DNA-based tests can be useful. For example, if the quantity of seized marijuana is extremely small and/or biochemical tests do not detect any D9-tetrahydrocannabinol (THC), DNA identification of plant material as Cannabis is still possible. This circumstance can arise when seeds, trace residue, tiny leaf fragments, or fine roots need to be analyzed. Methods for the individualization of marijuana include amplified fragment length polymorphism (AFLP), random amplified polymorphic DNA (RAPD), and short tandem repeat (STR) techniques that link an evidentiary sample to a source. Marijuana growers propagate their plants either by seed or by cloning. Seed-generated marijuana plants are expected to have unique DNA profiles analogous to a human population. Cloned marijuana...
plants, however, exhibit identical DNA profiles that allow for tracking of plant material derived from a common genetic lineage. The authors have validated the AFLP method for marijuana samples and are constructing a comparative database of marijuana seizure samples to estimate the expected frequency of a DNA profile match between unrelated plants. Continued development of DNA-based methods for plants can be useful for marijuana and other types of plant evidence in forensics.


Activation of cannabinoid CB(2) receptors attenuates thermal nociception in untreated animals while failing to produce centrally mediated effects such as hypothermia and catalepsy [Pain 93 (2001) 239]. The present study was conducted to test the hypothesis that activation of CB(2) in the periphery suppresses the development of inflammatory pain as well as inflammation-evoked neuronal activity at the level of the CNS. The CB(2)-selective cannabinoid agonist AM1241 (100, 330 &mgr;g/kg i.p.) suppressed the development of carrageenan-evoked thermal and mechanical hyperalgesia and allodynia. The AM1241-induced suppression of carrageenan-evoked behavioral sensitization was blocked by the CB(2) antagonist SR144528 but not by the CB(1) antagonist SR141716A. Intraplantar (ipl) administration of AM1241 (33 &mgr;g/kg ipl) suppressed hyperalgesia and allodynia following administration to the carrageenan-injected paw but was inactive following administration in the contralateral (noninflamed) paw, consistent with a local site of action. In immunocytochemical studies, AM1241 suppressed spinal Fos protein expression, a marker of neuronal activity, in the carrageenan model of inflammation. AM1241 suppressed carrageenan-evoked Fos protein expression in the superficial and neck region of the dorsal horn but not in the nucleus proprius or the ventral horn. The suppression of carrageenan-evoked Fos protein expression induced by AM1241 was blocked by coadministration of SR144528 in all spinal laminae. These data provide evidence that actions at cannabinoid CB(2) receptors are sufficient to suppress inflammation-evoked neuronal activity at rostral levels of processing in the spinal dorsal horn, consistent with the ability of AM1241 to normalize nociceptive thresholds and produce antinociception in inflammatory pain states.


A series of C3 cyclic side-chain analogues of classical cannabinoids were synthesized to probe the ligand binding pocket of the CB1 and CB2 receptors. The analogues were evaluated for CB1 and CB2 receptor binding affinities relative to Delta(8)-THC. The C3 side-chain geometries of the analogues were studied using high field NMR spectroscopy and quantum mechanical calculations. The results of these studies provide insights into the geometry of the ligand binding pocket of the CB1 and CB2 receptors.


In spite of their popular uses as recreational drugs and their potential therapeutic uses, little direct information has been obtained about the synaptic effects of cannabinoids in the human brain. In the present study, patch-clamp recordings were performed on granule cells of the human dentate gyrus and the effects of cannabinoid receptor-1 (CB1) activation on inhibitory synaptic activity were examined. Activation of CB1 receptors by WIN55212-2 significantly suppressed both frequency and amplitude of spontaneous inhibitory synaptic currents (IPSCs) to about 50% of control. The suppressive effects were completely abolished in the presence of the CB1 receptor antagonist, AM251. WIN55212-2 also suppressed evoked IPSCs. However, neither frequency nor amplitude of miniature IPSCs were affected by WIN55212-2. These results provide electrophysiological evidence for the role of CB1 receptors in modulating inhibitory activity in human dentate gyrus.

Fatty acid amide hydrolase (FAAH), an intracellular serine hydrolase enzyme, participates in the deactivation of fatty acid ethanolamides such as the endogenous cannabinoid anandamide, the intestinal satiety factor oleylethanolamide, and the peripheral analgesic and anti-inflammatory factor palmitoylethanolamide. In the present study, we report on the design, synthesis, and structure-activity relationships (SAR) of a novel class of potent, selective, and systemically active inhibitors of FAAH activity, which we have recently shown to exert potent anxiolytic-like effects in rats. These compounds are characterized by a carbamic template substituted with alkyl or aryl groups at their O- and N-termini. Most compounds inhibit FAAH, but not several other serine hydrolases, with potencies that depend on the size and shape of the substituents. Initial SAR investigations suggested that the requirements for optimal potency are a lipophilic N-alkyl substituent (such as n-butyl or cyclohexyl) and a bent O-aryl substituent. Furthermore, the carbamic group is essential for activity. A 3D-QSAR analysis on the alkylcarbamic acid aryl esters showed that the size and shape of the O-aryl moiety are correlated with FAAH inhibitory potency. A CoMFA model was constructed, indicating that whereas the steric occupation of an area corresponding to the meta position of an O-phenyl ring improves potency, a region of low steric tolerance on the enzyme active site exists corresponding to the para position of the same ring. The bent shape of the O-aryl moieties that best fit the enzyme surface closely resembles the folded conformations observed in the complexes of unsaturated fatty acids with different proteins. URB524 (N-cyclohexylcarbamic acid biphenyl-3-yl ester, 9g) is the most potent compound of the series (IC(50) = 63 nM) and was therefore selected for further optimization.


Effects of cannabinoids on endogenous potassium and calcium currents in HEK293 cells were studied using the whole-cell variant of the patch-clamp technique. The cannabinoid agonists WIN 55,212-2, methanandamide, and anandamide (1 microM) decreased the calcium current by 53.1 +/- 2.6, 47.5 +/- 1.2, and 38.8 +/- 3.1%, respectively, after transfection of human CB1 cannabinoid receptor (hCB1) cDNA into HEK293 cells. The delayed rectifier-like current was not changed after application of these agonists, but the inward rectifier was increased by 94.0 +/- 3.6, 83.7 +/- 5.1, and 63.0 +/- 2.5% after application of WIN 55,212-2, methanandamide, and anandamide, respectively. The effects of the cannabinoid antagonists (AM251, AM281, and AM630) on the inward rectifier and calcium currents were the opposite of those seen with cannabinoid agonists; thus, these compounds act as inverse agonists in this preparation. These results suggest that endogenous inward rectifier and calcium currents are modulated by cannabinoids in HEK293 cells, and that some expressed receptors may be constitutively active.


Cannabinoids have been considered for some time as potent therapeutic agents in chronic pain management. Central and systemic administration of natural, synthetic and endogenous cannabinoids produce antinoceptive and antihyperalgesic effects in both acute and chronic animal pain models. Although much of the existing data suggest that the analgesic effects of cannabinoids are mediated via neuronal CB1 receptors, there is increasing evidence to support a role for peripheral CB2 receptors, which are expressed preferentially on immune cells. As yet, little is known about the central contribution of CB2 in neuropathic pain states. We report here that chronic pain models associated with peripheral nerve injury, but not peripheral inflammation, induce CB2 receptor expression in a highly restricted and specific manner within the lumbar spinal cord. Moreover, the appearance of CB2 expression coincides with the appearance of activated microglia.
**CLINICAL SCIENCE**


BACKGROUND: Urinary cannabinoid excretion and immunoassay performance were evaluated by semiquantitative immunoassay and gas chromatography-mass spectrometry (GC/MS) analysis of metabolite concentrations in 4381 urine specimens collected before, during, and after controlled oral administration of tetrahydrocannabinol (THC). METHODS: Seven individuals received 0, 0.39, 0.47, 7.5, and 14.8 mg THC/day in this double-blind, placebo-controlled, randomized, clinical study conducted on a closed research ward. THC doses (hemp oils with various THC concentrations and the therapeutic drug Marinol((R))) were administered three times daily for 5 days. All urine voids were collected over the 10-week study and later tested by Emit II((R)), DRI ((R)), and CEDIA((R)) immunoassays and by GC/MS. Detection rates, detection times, and sensitivities, specificities, and efficiencies of the immunoassays were determined. RESULTS: At the federally mandated immunoassay cutoff (50 micro g/L), mean detection rates were <0.2% during ingestion of the two low doses typical of current hemp oil THC concentrations. The two high doses produced mean detection rates of 23-46% with intermittent positive tests up to 118 h. Maximum metabolite concentrations were 5.4-38.2 micro g/L for the low doses and 19.0-436 micro g/L for the high doses. Emit II, DRI, and CEDIA immunoassays had similar performance efficiencies of 92.8%, 95.2%, and 93.9%, respectively, but differed in sensitivity and specificity. CONCLUSIONS: The use of cannabinoid-containing foodstuffs and cannabinoid-based therapeutics, and continued abuse of oral cannabis require scientific data for accurate interpretation of cannabinoid tests and for making reliable administrative drug-testing policy. At the federally mandated cannabinoid cutoffs, it is possible but unlikely for a urine specimen to test positive after ingestion of manufacturer-recommended doses of low-THC hemp oils. Urine tests have a high likelihood of being positive after Marinol therapy. The Emit II and DRI assays had adequate sensitivity and specificity, but the CEDIA assay failed to detect many true-positive specimens.


Purpose: There is no published data looking at tolerance of efavirenz (EFV) in patients who abuse cocaine or alcohol (EtOH). The objective of this study was to determine whether individuals with a current or past history of cocaine or EtOH abuse are more likely to experience EFV-induced central nervous system (CNS) side effects that warrant discontinuation of EFV compared with those who do not abuse substances. Method: Retrospective chart review of all patients who received a nonnucleoside reverse transcriptase inhibitor (NNRTI) at an inner city Ryan White Title III-supported health clinic during 1992-2001. Results: During the study period, 99/279 (78% African American, 88% male) patients were prescribed an NNRTI. Patients on an NNRTI with either a history of or current substance abuse (SA) abused cocaine (30%), EtOH (70%), or marijuana (33%). Of these, 38% abused more than one substance. There were 39/63 EFV patients who were substance abusers compared with 16/36 patients not on EFV who were substance abusers (p =.09). Examining patients on EFV, 6/24 with SA and 7/39 without SA reported a CNS side effect (p =.54). Among patients on EFV, 4/24 with SA versus 13/39 without SA reported stopping EFV (p =.24). Conclusion: SA did not have a significant effect on patients' ability to remain on EFV. Patients who abused cocaine or EtOH or smoked marijuana were at no more risk of exhibiting CNS side effects than those who denied a history of substance abuse.


The effects of marijuana on brain perfusion and internal timing were assessed using [15O] water PET in occasional and chronic users. Twelve volunteers who smoked marijuana
recreationally about once weekly, and 12 volunteers who smoked daily for a number of years performed a self-paced counting task during PET imaging, before and after smoking marijuana and placebo cigarettes. Smoking marijuana increased rCBF in the ventral forebrain and cerebellar cortex in both groups, but resulted in significantly less frontal lobe activation in chronic users. Counting rate increased after smoking marijuana in both groups, as did a behavioral measure of self-paced tapping, and both increases correlated with rCBF in the cerebellum. Smoking marijuana appears to accelerate a cerebellar clock altering self-paced behaviors.


Abstract Both the gaseous and the particulate phases of tobacco and cannabis smoke contain a similar range of harmful chemicals. However, differing patterns of inhalation mean that smoking a ‘joint’ of cannabis results in exposure to significantly greater amounts of combusted material than with a tobacco cigarette. The histopathological effects of cannabis smoke exposure include changes consistent with acute and chronic bronchitis. Cellular dysplasia has also been observed, suggesting that, like tobacco smoke, cannabis exposure has the potential to cause malignancy. These features are consistent with the clinical presentation. Symptoms of cough and early morning sputum production are common (20-25%) even in young individuals who smoke cannabis alone. Almost all studies indicate that the effects of cannabis and tobacco smoking are additive and independent. Public health education should dispel the myth that cannabis smoking is relatively safe by highlighting that the adverse respiratory effects of smoking cannabis are similar to those of smoking tobacco, even although it remains to be confirmed that smoking cannabis alone leads to the development of chronic lung disease. (Intern Med J 2003; 33: 310-313)

BEHAVIOURAL SCIENCE


AIMS: To model consumption patterns and problems associated with alcohol, cannabis, ecstasy, amphetamine and cocaine hydrochloride use in a non-treatment sample of young polysubstance users. DESIGN: A cross-sectional survey of 364 16-22-year-old (56.3% male) polysubstance users recruited and interviewed by peer interviewers. MEASUREMENTS: Structured questionnaires were used to gather identical datasets on the five target psychoactive substances, recording patterns of substance use; adverse consequences from use; negative effects; functions for substance use; and perceived peer use. FINDINGS: Functions for substance use strongly predicted intensity of use in all five substances when peer use, age of first use and demographics were controlled, explaining an additional 11-19% of the variance in scores. Functions also explained an average of 22% of the variance in problem scores over and above the effects of background variables and current intensity of use. In particular, functions concerned with relief from negative mood states were strong predictors of problem scores in alcohol, cannabis and cocaine. CONCLUSIONS: The potential implications of using a functional approach to explaining and responding to substance use are considerable. This could help to enhance our understanding of how experimental substance use becomes regular and how regular use becomes problematic, and could thus inform prevention, education and intervention efforts.


After reviewing the pertinent scientific data, it is clear that there is more than sufficient medical and ethical evidence to warrant the Bush Administration to authorize the Drug
Enforcement Agency to reclassify marijuana as a Schedule II drug so that it can be used for medical purposes. Failure to give an effective therapy to seriously ill patients, either adults or children, violates the core principles of both medicine and ethics. Medically, to deny physicians the right to prescribe to their patients a therapy that relieves pain and suffering violates the physician-patient relationship. Ethically, failure to offer an available therapy that has proven to be effective violates the basic ethical principle of nonmaleficence, which prohibits the infliction of harm, injury, or death and is related to the maxim primum non nocere ('above all, or first, do no harm'), which is widely used to describe the duties of a physician. Therefore, in the patient's best interest, patients and parents/surrogates, have the right to request medical marijuana under certain circumstances and physicians have the duty to disclose medical marijuana as an option and prescribe it when appropriate. The right to an effective medical therapy, whose benefits clearly outweigh the burdens, must be available to all patients including children. To deny children the use of medical marijuana when appropriate is a grave injustice which violates the basic foundational beliefs of both medicine and… (abstract truncated).


AIM: To model the impact of rising rates of cannabis use on the incidence and prevalence of psychosis under four hypotheses about the relationship between cannabis use and psychosis. METHODS: The study modelled the effects on the prevalence of schizophrenia over the lifespan of cannabis in eight birth cohorts: 1940-1944, 1945-1949, 1950-1954, 1955-1959, 1960-1964, 1965-1969, 1970-1974, 1975-1979. It derived predictions as to the number of cases of schizophrenia that would be observed in these birth cohorts, given the following four hypotheses: (1) that there is a causal relationship between cannabis use and schizophrenia; (2) that cannabis use precipitates schizophrenia in vulnerable persons; (3) that cannabis use exacerbates schizophrenia; and (4) that persons with schizophrenia are more liable to become regular cannabis users. RESULTS: There was a steep rise in the prevalence of cannabis use in Australia over the past 30 years and a corresponding decrease in the age of initiation of cannabis use. There was no evidence of a significant increase in the incidence of schizophrenia over the past 30 years. Data on trends the age of onset of schizophrenia did not show a clear pattern. Cannabis use among persons with schizophrenia has consistently been found to be more common than in the general population. CONCLUSIONS: Cannabis use does not appear to be causally related to the incidence of schizophrenia, but its use may precipitate disorders in persons who are vulnerable to developing psychosis and worsen the course of the disorder among those who have already developed it.


Most prior literature examining the relations among attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and substance use and abuse suggests that CD fully account for the ADHD-substance abuse relation. This study sought to test an alternate theory that individuals with symptoms of both ADHD and CD are at a special risk for substance abuse. Relations between childhood ADHD and CD symptoms, and young adult tobacco, alcohol, marijuana, and hard drug use and dependence symptoms, were examined in a sample of 481 young adults. ADHD and CD symptoms interacted to predict marijuana dependence symptoms and hard drug use and dependence symptoms, such that individuals with high levels of both ADHD and CD had the highest levels of these outcomes.


AIMS: To use event-related potentials (ERPs) to investigate the response to alcohol-related stimuli in African-American young adults. METHODS: ERPs to an object recognition task, that included pictures of objects, food and alcohol-related and non-alcohol-related drinks as
stimuli, were obtained in 81 African-American young adult men and women (18-25 years old) without a personal history of alcohol dependence. Information on: psychiatric diagnoses, personal drinking and drug use history, and familial history of alcoholism was also obtained. RESULTS: Family history was found to be associated with lowered P3 components and higher N1 components in response to the non-alcohol-related drinks. Additionally, an exploratory analyses revealed that lower amplitude N1 components were generated in response to alcohol-related stimuli in regular marijuana users compared with non-regular users. No associations of N1 or P3 amplitudes with conduct disorder symptoms or current drinking status were found in this population. CONCLUSIONS: These studies demonstrated that family history is significantly and selectively associated with lower P3 amplitudes in this group of young adult men and women of African-American heritage. Additionally, current usage of marijuana and alcohol do not modify P3 amplitudes. However, regular marijuana use may diminish N1 response to alcohol-related stimuli, whereas, family history of alcoholism may augment N1 responses. Taken together these studies further suggest that ERPs can provide specific information on alcoholism risk as well as use of other misused drugs.


OBJECTIVE: To examine the familial aggregation of marijuana use, abuse, and dependence. METHOD: Adolescents recruited from residential and day treatment programs for youths with conduct and substance problems, matched controls, and all available family members were interviewed with structured research instruments. A total of 2,546 individuals from 781 families were interviewed. Risk ratios of relatives of clinical cases were calculated, compared with controls, for marijuana use, abuse, or dependence. Spousal, parent-offspring, and sibling correlations and the proportion of variance attributable to parent-offspring transmission were estimated using structural equation modeling. RESULTS: For all three measures, the risk ratios were elevated in the family members of clinical probands, with estimates ranging from 1.5 to 3.3. Spousal correlations ranged from 0.33 to 0.70. Parent-offspring correlations ranged from 0.17 to 0.30. Sibling correlations ranged from 0.34 to 0.44. The proportion of variance attributable to factors transmitted from parents to children ranged between 25% and 44%. CONCLUSIONS: Familial aggregation of marijuana use, abuse, and dependence is present for all three measures. The results suggest significant parent-offspring transmission of risk, sibling environmental influences, and assortative mating for all three levels of marijuana use.


Drug testing is widely used and employed in diverse contexts, including drug treatment clinics. Building on previous research, this paper aims to (i) compare self-report data and oral fluid (OMT) testing in detecting drug use amongst individuals beginning a new episode of drug treatment and (ii) identify factors that may predict drug users who have discordant self-report and OMT test results. Two hundred and seventy-one new drug treatment clients completed a structured questionnaire that included questions relating to drug use during the preceding 3 days and provided an oral fluid sample that was independently tested for opiates, benzodiazepines, methadone and cannabis. Data were analysed using kappa statistics (Cohen, 1960) and univariate and multivariate logistic regression. Findings indicated a high level of consistency between self-reported drug use and OMT testing. However, agreement varied by drug type and respondents commonly reported consumption that screening failed to identify. Inconsistencies appeared to relate to a number of factors and were not necessarily a function of deliberate distortion by the drug user. Overall, it is concluded that OMT testing is a good indicator of the validity and reliability of drug users' self-report data. Nonetheless, its accuracy might be greater for some drug categories than for others. Equally, further study comparing test results and self-reported drug use amongst different populations and in different contexts is required.

OBJECTIVE: This study reports trends from 1976 to 2001 in the number of tickets or warnings that high school seniors receive, the number of vehicle accidents in which they are drivers and the number of these events that occur after use of alcohol, marijuana or other illegal drugs. METHOD: The data come from the Monitoring the Future study, in which nationally representative samples of high school seniors have been surveyed annually since 1976. RESULTS: Results demonstrate that the problem of unsafe or inappropriate driving among American youth is of considerable magnitude, although there has been a downward trend when adjusted for number of miles driven. The frequency of tickets received and vehicle accidents that occurred after use of alcohol has diminished markedly compared to the incidence of tickets and accidents after use of marijuana over the interval from 1976 to 2001. CONCLUSIONS: Despite the decline in the number of vehicle accidents occurring and tickets received after drinking or using illicit drugs, aggressive policies are still needed to deter youths from engaging in such risky behaviors.


OBJECTIVE: Illicit substance use is a potent risk factor for poor outcomes in schizophrenia, yet methods for detecting substance use consistently underestimate the problem. The purpose of this study was to assess whether use of a relatively new method of detection, radioimmunoassay of hair, improved detection and was acceptable to patients with serious mental illness. METHODS: Persons already participating in a longitudinal naturalistic study of schizophrenia treatment were approached for participation in this study. The 203 persons who consented were interviewed and submitted urine and hair samples for laboratory measures of potential substances of abuse. Radioimmunoassay of hair was used to detect the use of amphetamines, cocaine, marijuana, opiates, and phencyclidine (PCP) in the preceding three months. RESULTS: Of the 203 participants, only 33 (16.3 percent) self-reported illicit substance use, and only 25 (12.4 percent) had a positive urine test, but 63 (31.0 percent) had a positive hair assay. When all detection methods were combined-self-report, urine test, and hair assay-78 participants (38.4 percent) were classified as users in the preceding three months. Few of those asked to participate (20, or 9.9 percent) refused hair analysis. CONCLUSIONS: Radioimmunoassay of hair appears to be a promising method for improving assessment of illicit substance use among persons with schizophrenia. Most participants appeared to find hair analysis an acceptable procedure, although this conclusion warrants further study. The test's three-month window of detection may make it a valuable method for assessing and monitoring use over time.

This newsletter is supported in part by unrestricted educational grants from GW Pharmaceuticals and ICN Pharmaceuticals (Canada)