INTRODUCTION
Here is the latest summary of research abstracts. The appearance of increasing numbers of clinical trial reports is noteworthy.

BASIC SCIENCE


CB1 receptor expression has been reported to be low in the brainstem compared with the forebrain, and low in the vestibular nucleus complex (VNC) compared with other regions in the brainstem. However, a frequent effect of cannabis is dizziness and loss of balance. This may be due to the activation of cannabinoid receptors in the central vestibular pathways. We used immunohistochemistry to study the distribution of CB1 receptor protein in the VNC, and Western blotting to measure CB1 receptor expression in the VNC following unilateral vestibular deafferentation (UVD); the hippocampal CA1, CA2/3 and dentate gyrus (DG) regions were also analysed for comparison. This study confirms a previous electrophysiological demonstration that CB1 receptors exist in significant densities in the VNC and are likely to contribute to the neurochemical control of the vestibular reflexes. Nonetheless, CB1 receptor expression did not change significantly in the VNC during vestibular compensation. In addition, despite some small but significant changes in CB1 receptor expression in the CA2/3 and the DG following UVD, in no case were these differences statistically significant in comparison to both control groups.


Neocortical GABA-containing interneurons form complex functional networks responsible for feedforward and feedback inhibition and for the generation of cortical oscillations associated with several behavioural functions. We previously reported that fast-spiking (FS), but not low-threshold-spiking (LTS), neocortical interneurons from rats generate a fast and precise self-inhibition mediated by inhibitory autaptic transmission. Here we show that LTS cells possess a different form of self-inhibition. LTS, but not FS, interneurons undergo a prominent hyperpolarization mediated by an increased K+ channel conductance. This self-induced inhibition lasts for many minutes, is dependent on an increase in intracellular [Ca2+] and is blocked by the cannabinoid receptor antagonist AM251, indicating that it is mediated by the autocrine release of endogenous cannabinoids. Endocannabinoid-mediated slow self-inhibition represents a powerful and long-lasting mechanism that alters the intrinsic excitability of LTS neurons, which selectively target the major site of excitatory connections onto pyramidal neurons; that is, their dendrites. Thus, modulation of LTS networks after their sustained firing will lead to long-lasting changes of glutamate-mediated synaptic strength in pyramidal neurons, with consequences during normal and pathophysiological cortical network activities.

Exogenous cannabinoids affect multiple hormonal systems including the hypothalamo-pituitary-adrenocortical (HPA) axis. These data suggest that endogenous cannabinoids are also involved in the HPA control; however, the mechanisms underlying this control are poorly understood. We assessed the role of endogenous cannabinoids in the regulation of the HPA-axis by studying CB1 receptor knockout (KO) and wild type (WT) mice. Basal and novelty-stress-induced plasma levels of adrenocorticotropic (ACTH) and corticosterone were higher in CB1-KO than in WT mice. We investigated the involvement of the pituitary in the hormonal effects of CB1 gene disruption by studying the in vitro release of ACTH from anterior pituitary fragments using a perfusion system. Both the basal and corticotropin releasing hormone (CRH)-induced ACTH secretion were similar in CB1-KO and WT mice. The synthetic glucocorticoid, dexamethasone suppressed the CRH-induced ACTH secretion in both genotypes; thus, the negative feedback of ACTH secretion was not affected by CB1 gene disruption. The cannabinoid agonist, WIN 55,212-2 had no effects on basal and CRH-stimulated ACTH secretion by anterior pituitary slices. In our hands, the disruption of the CB1 gene lead to HPA axis hyperactivity, but the pituitary seems not to be involved in this effect. Our data are consistent with the assumption that endogenous cannabinoids inhibit the HPA-axis via centrally located CB1 receptors, however the understanding of the exact underlying mechanism needs further investigation.


BACKGROUND: Endocannabinoids are novel lipid mediators with hypotensive and cardiodepressor activity. Here, we examined the possible role of the endocannabinergic system in cardiovascular regulation in hypertension. METHODS AND RESULTS: In spontaneously hypertensive rats (SHR), cannabinoid-1 receptor (CB1) antagonists increase blood pressure and left ventricular contractile performance. Conversely, preventing the degradation of the endocannabinoid anandamide by an inhibitor of fatty acid amidohydrolase reduces blood pressure, cardiac contractility, and vascular resistance to levels in normotensive rats, and these effects are prevented by CB1 antagonists. Similar changes are observed in 2 additional models of hypertension, whereas in normotensive control rats, the same parameters remain unaffected by any of these treatments. CB1 agonists lower blood pressure much more in SHR than in normotensive Wistar-Kyoto rats, and the expression of CB1 is increased in heart and aortic endothelium of SHR compared with Wistar-Kyoto rats. CONCLUSIONS: We conclude that endocannabinoids tonically suppress cardiac contractility in hypertension and that enhancing the CB1-mediated cardiodepressor and vasodilator effects of endogenous anandamide by blocking its hydrolysis can normalize blood pressure. Targeting the endocannabinoid system offers novel therapeutic strategies in the treatment of hypertension.


Cannabinoid (CB)(1) receptors are present throughout the nervous system, including several areas implicated in the control of food intake. Central and peripheral administration of CB(1) agonists increase food intake while CB(1) receptor antagonists reduce food intake. However, in some previous studies, tolerance to the anorectic effects of CB(1) antagonists develops within days. To further delineate the role of endogenous cannabinoid signaling in energy intake, we studied the effects of the CB(1) antagonist AM 251 (1.25, 2.5 and 5 mg/kg ip), the anandamide membrane transporter inhibitor VDM 11 (10 mg/kg ip), and the CB1 agonists anandamide (1 mg/kg ip), and methanandamide (1 mg/kg ip), on food intake. A single administration of the CB(1) antagonist AM 251 significantly reduced food intake for a total of 6 days (P<.05). Reductions in food intake brought about by AM 251 were accompanied by reductions in weight gain for 6 days (P<.05). Contrary to expectations, VDM 11 did not increase food intake in this study. Anandamide was also unable to increase food intake; however, the more stable agonist methanandamide significantly increased food intake 3 h after administration.
These results support the role of CB(1) receptor antagonists in the treatment of obesity and suggest that the anorectic effect of AM 251 may last longer than previously reported.


Experiments were designed to determine whether cannabinoids affect salivary gland function. For this purpose, the effect of anandamide on cAMP accumulation, amylase release and Na(+)-K(+)-ATPase activity was studied in rat parotid glands. Anandamide induced a concentration-dependent increase in cAMP and led to amylase release but inhibited Na(+)-K(+)-ATPase activity. These effects were blocked by the CB(1) cannabinoid receptor antagonist, AM281. The inhibition of adenylyl cyclase activity by SQ 22536 impaired amylase release and Na(+)-K(+)-ATPase inhibition. The effect of anandamide on cAMP accumulation significantly correlated with its action either on amylase release or on Na(+)-K(+)-ATPase activity. Such correlation strongly supports the view that the effect of anandamide on amylase release and Na(+)-K(+)-ATPase activity is the result of cAMP accumulation. The relative potencies of the CB(1) cannabinoid receptor antagonist, AM281, to block these three functional responses were similar, supporting the view that anandamide actions in parotid glands were achieved through a single receptor subtype, the CB(1). Binding studies using the selective cannabinoid CB(1) receptor antagonist, [3H]SR141716A, indicated the presence of the specific binding site. It may be concluded that in parotid glands the endogenous cannabinoid anandamide, bound to the CB(1) cannabinoid receptor subtype, induces cAMP accumulation which in turn leads to amylase release and Na(+)-K(+)-ATPase inhibition.


Repetitive activation of glutamatergic fibers that normally induces long-term potentiation (LTP) at excitatory synapses in the hippocampus also triggers long-term depression at inhibitory synapses (I-LTD) via retrograde endocannabinoid signaling. Little is known, however, about the physiological significance of I-LTD. Here, we show that synaptic-driven release of endocannabinoids is a highly localized and efficient process that strongly depresses cannabinoid-sensitive inhibitory inputs within the dendritic compartment of CA1 pyramidal cells. By removing synaptic inhibition in a restricted area of the dendritic tree, endocannabinoids selectively "primed" nearby excitatory synapses, thereby facilitating subsequent induction of LTP. This induction of local metaplasticity is a novel mechanism by which endocannabinoids can contribute to the storage of information in the brain.


Administration of the cannabinoid CB(1) receptor antagonist, SR 141716 [N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide], has been reported to reduce alcohol intake and alcohol self-administration in different models of excessive alcohol consumption, including the selectively bred Sardinian alcohol-preferring (sP) rats. The present study investigated whether SR 141716 was also capable of decreasing, in this rat line, alcohol's motivational properties. Extinction responding for alcohol, defined as the maximal number of lever responses reached in the absence of alcohol in rats trained to lever-press for alcohol, was used as index of alcohol's motivational properties. Rats were initially trained to lever-press for oral alcohol (15%, v/v) under a fixed ratio (FR) schedule of FR4. Once self-administration behavior was established, extinction sessions were conducted. SR 141716 (0, 0.3, 1 and 3 mg/kg; i.p.) was acutely administered before extinction sessions. In order to assess the specificity of SR 141716 action on extinction responding for alcohol, a separate group of sP rats was trained to lever-press for a 3% (w/v) sucrose solution under an FR4 schedule. SR 141716 administration produced a dose-dependent, virtually complete suppression of extinction responding for alcohol. In contrast, extinction responding for sucrose was not significantly altered by treatment with SR 141716. Further to the consummatory aspects, these results also extend the suppressing effect of SR 141716 to the appetitive aspects of alcohol drinking behavior in sP rats. The results also
Implicate the cannabinoid CB(1) receptor in the neural substrate mediating alcohol's motivational properties in this rat line.


The anti-tumor properties of cannabinoids have recently been evidenced, mainly with delta9-tetrahydrocannabinol (THC). However, the clinical application of this drug is limited by possible undesirable side effects due to a broad expression of cannabinoid receptors (CB1 and CB2). An attractive field of research therefore is to identify molecules with more selective tumor targeting. This is particularly important for malignant gliomas, considering their poor prognosis and their location in the brain. Here we investigated whether the most potent endogenous cannabinoid, arachidonylethanolamide (AEA), could be a candidate. We observed that AEA induced apoptosis in long-term and recently established glioma cell lines via aberrantly expressed vanilloid receptor-1 (VR1). In contrast with their role in THC-mediated death, both CB1 and CB2 partially protected glioma against AEA-induced apoptosis. These data show that the selective targeting of VR1 by AEA or more stable analogues is an attractive research area for the treatment of glioma.


The analgesic properties of exogenous cannabinoids have been recognized for many years and suggest a regulatory role for the endogenous cannabinoid ("endocannabinoid") system in mammalian nociceptive pathways. The endocannabinoid system includes: (1) at least two families of lipid signaling molecules, the N-acyl ethanolamines (e.g., anandamide) and the monoacylglycerols (e.g., 2-arachidonoyl glycerol); (2) multiple enzymes involved in the biosynthesis and degradation of these lipids, including the integral membrane enzyme fatty acid amide hydrolase; and (3) two G-protein coupled receptors, CB1 and CB2, which are primarily localized to the nervous system and immune system, respectively. Here, we review recent genetic, behavioral, and pharmacological studies that have tested the function of the endocannabinoid system in pain sensation. Collectively, these investigations support a role for endocannabinoids in modulating behavioral responses to acute, inflammatory, and neuropathic pain stimuli. Copyright 2004 Wiley Periodicals, Inc. J Neurobiol 61: 149-160, 2004


Diabetic neuropathic pain is one of the most commonly encountered neuropathic pain syndromes. However, the treatment of diabetic neuropathic pain is challenging because of partial effectiveness of currently available pain relievers. It is well known that diabetic animals are less sensitive to the analgesic effect of morphine, and opioids are found to be ineffective in the treatment of diabetic neuropathic pain. Cannabinoids are promising drugs and they share a similar pharmacological properties with opioids. It has been reported that cannabinoid analgesia remained intact and to be effective in some models of nerve injury. Thus, we investigated antinociceptive efficacy and the effects of cannabinoids on behavioral sign of diabetic neuropathic pain in diabetic mice by using WIN 55, 212-2, a cannabinoid receptor agonist. Diabetes was induced by streptozotocin (STZ) (200mg/kg) and animals were tested between 45 and 60 days after onset of diabetes. Antinociception was assessed using the radiant tail-flick test. Mechanical and thermal sensitivities were measured by Von Frey filaments and hot-plate test, respectively. Tactile allodynia, but not thermal hyperalgesia developed in diabetic mice. Systemic WIN 55, 212-2 (1, 5 and 10mg/kg) produced a dose-dependent antinociception both in diabetic and control mice. WIN 55, 212-2-induced antinociception were found to be similar in diabetic mice when compared to controls suggesting efficacy of cannabinoid antinociception was not diminished in diabetic mice. WIN 55, 212-2 also produced a dose-dependent antiallodynic effect in diabetic mice. This study suggests that cannabinoids have a potential beneficial effect on experimental diabetic neuropathic pain.

Cannabinoids were shown to induce apoptosis of glioma cells in vitro and tumor regression in vivo, but mechanisms of their antiproliferative action remain elusive. In the present studies, C6 cells were exposed to a synthetic cannabinoid, WIN 55,212-2, which produced down-regulation of the Akt and Erk signalling pathways prior to appearance of any sign of apoptosis. We hypothesized that cannabinoid-induced cell death may be mediated by a Bcl-2 family member-Bad, whose function is hampered by these kinases due to control of its phosphorylation state. Using Western blot analysis, we found that levels of phosphorylated Bad, but not total Bad protein, decreased under exposure to WIN 55,212-2. WIN 55,212-2 treatment further resulted in mitochondrial depolarization and activation of caspase cascade. Thus, we suggest that the increase of proapoptotic Bad activity is an important link between the inhibition of survival pathways and an onset of execution phase of cannabinoid-induced glioma cell death.


The endocannabinoids are a family of bioactive lipids that activate CB(1) cannabinoid receptors in the brain and exert intense emotional and cognitive effects. Here, we have examined the role of endocannabinoid signaling in psychotic states by measuring levels of the endocannabinoid anandamide in cerebrospinal fluid (CSF) of acute paranoid-type schizophrenic patients. We found that CSF anandamide levels are eight-fold higher in antipsychotic-naive first-episode paranoid schizophrenics (n=47) than healthy controls (n=84), dementia patients (n=13) or affective disorder patients (n=22). Such an alteration is absent in schizophrenics treated with ‘typical’ antipsychotics (n=37), which antagonize dopamine D(2)-like receptors, but not in those treated with ‘atypical’ antipsychotics (n=34), which preferentially antagonize SHT(2A) receptors. Furthermore, we found that, in nonmedicated acute schizophrenics, CSF anandamide is negatively correlated with psychotic symptoms (r(S)=-0.452, P=0.001). The results suggest that anandamide elevation in acute paranoid schizophrenia may reflect a compensatory adaptation to the disease state.Neuropsychopharmacology advance online publication, 8 September 2004; doi:10.1038/sj.npp.1300558


Chronic alcohol exposure modifies endocannabinoid levels in different brain regions, while pharmacological targeting of the endocannabinoid system has been reported to influence ethanol intake in laboratory animals. The present study was aimed at evaluating the pattern of changes of endocannabinoids and their receptors, with emphasis on reward-related brain areas, in Wistar rats subjected to consecutive phases of alcoholization, alcohol deprivation (abstinence), and voluntary consumption of alcohol (relapse). We observed that, in the limbic forebrain, anandamide (AEA) and 2-arachidonoylglycerol (2-AG) contents increased after 7 days of alcoholization, then to dramatically decrease after 48 h of alcohol deprivation and, in the case of 2-AG, to further decrease when rats were allowed to relapse to alcohol consumption. By contrast, in the midbrain, there was a marked reduction in AEA, but not 2-AG, content, after alcoholization. This decrease was not affected during alcohol abstinence, but both AEA and 2-AG contents were then significantly reduced when rats were allowed to relapse to alcohol consumption. Based on these data, we examined whether pharmacological activation/blockade of endocannabinoid transmission might influence ethanol intake in rats allowed to relapse to alcohol consumption after subsequent periods of alcoholization and alcohol deprivation. Treatment with either Delta(9)-tetrahydrocannabinol or CP55,940, two cannabinoid agonists, reduced both total liquid and ethanol intake but did not affect ethanol preference. Treatment with SR141716, a selective cannabinoid CB1 receptor antagonist, also produced a significant reduction in both total liquid and ethanol intake without affecting ethanol preference. Accordingly, none of these effects on ethanol intake were accompanied by changes in dopamine and GABA in limbic structures. In
summary, the levels of endocannabinoids underwent significant changes in reward-related areas during alcoholization, alcohol deprivation, and relapse, showing the lowest values in this latter phase. Treatment with cannabinoid agonists or a selective CB1 receptor antagonist resulted in a reduction of ethanol intake by rats allowed to relapse to alcohol consumption after periods of alcoholization and alcohol deprivation, but these effects did not appear to be due to changes in neurobiological substrates currently involved in alcohol reinforcement/relapse.


Cannabinoids have been implicated in the reduction of glioma growth. The present study investigated a possible relationship between the recently shown induction of COX-2 expression by the endocannabinoid analogue, R(+)-methanandamide (R(+)-MA), and its effect on the viability of H4 human neuroglioma cells. Incubation with R(+)-MA for up to 72 h decreased the cellular viability and enhanced accumulation of cytoplasmic DNA fragments in a time-dependent manner. Suppression of R(+)-MA-induced prostaglandin (PG) E2 synthesis with the selective COX-2 inhibitor celecoxib (0.01-1 micro M) or inhibition of COX-2 expression by COX-2-silencing small-interfering RNA (siRNA) was accompanied by inhibition of R(+)-MA-mediated DNA fragmentation and cell death. In contrast, the selective COX-1 inhibitor SC-560 was inactive in this respect. Cells were also protected from apoptotic cell death by other COX-2 inhibitors (NS-398, diclofenac) and by the ceramide synthase inhibitor fumonisin B1 which interferes with COX-2 expression by R(+)-MA. Moreover, the proapoptotic action of R(+)-MA was mimicked by the major COX-2 product PGE2. Apoptosis and cell death by R(+)-MA were not affected by antagonists of CB1-, CB2- and VR1 receptors. In further experiments, celecoxib was demonstrated to suppress apoptotic cell death elicited by anandamide which is structurally similar to R(+)-MA. Collectively, this study defines COX-2 as a hitherto unknown target by which a cannabinoid induces apoptotic death of glioma cells. Furthermore, our data show that pharmacological concentrations of celecoxib may interfere with the proapoptotic action of R(+)-MA and anandamide suggesting that co-treatment with COX-2 inhibitors could diminish glioma regression induced by these compounds.

Lange, J. H. and C. G. Kruse (2004). "Recent advances in CB1 cannabinoid receptor antagonists." 

Cannabinoid CB1 receptor antagonists are currently the subject of intensive research due to their highly promising therapeutic prospects. Novel chemical entities having CB1 antagonistic properties have recently been disclosed by several pharmaceutical companies and some academic research groups, some of which are close structural analogs of the leading compound rimonabant (SR-141716A; Sanofi-Synthelabo). A considerable number of these CB1 antagonists are bioisosteres that are derived from rimonabant by the replacement of the pyrazole moiety with an alternative heterocycle. As well as these achiral compounds, Solvay Pharmaceuticals have disclosed a novel class of chiral pyrazolines that are potent and CB1/CB2 subtype-selective cannabinoid receptor antagonists, in which the interactions with the CB1 receptor are highly stereoselective.


Alcoholism is characterized by successive relapses. Recent data have shown a cross-talk between the cannabinoid system and ethanol. In this study, male Wistar rats with a limited (30 min sessions), intermittent, and extended background of alcohol operant self-administration were used. The relapse to alcohol after 1 week of alcohol deprivation was evaluated. Two weeks later, the animals were treated with the cannabinoid agonist WIN 55,212-2 (R(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethylone mesylate) (0, 0.4, 2.0, and 10.0 mg/kg, s.c.) during a similar alcohol deprivation period, and alcohol relapse during 2 weeks was assessed. A conditioned place preference (CPP) paradigm was used to study the rewarding properties of the cannabinoid agonist. Locomotor activity was also recorded. All doses of WIN 55,212-2 produced aversion in the CPP paradigm. The doses of
2.0 and 10.0 mg/kg resulted in an important suppression of spontaneous locomotor activity and a progressive weight loss during the next 2 weeks. The single alcohol deprivation was followed by a transient increase in their responding for alcohol from a range of 20-24 lever presses at baseline to a range of 38-48 responses in the first and second days (alcohol deprivation effect). However, the administration of WIN 55,212-2 during ethanol deprivation produced similar increased responses for alcohol but in a long-term way (at least over 2 weeks). These findings suggest that noncontingent chronic exposure to cannabinoids during alcohol deprivation can potentiate the relapse into alcohol use, indicating that functional changes in the cannabinoid brain receptor may play a key role in ethanol relapse.


Neurons intensively exchange information among each other using both inhibitory and excitatory neurotransmitters. However, if the balance of excitation and inhibition is perturbed, the intensity of excitatory transmission may exceed a certain threshold and epileptic seizures can occur. As the occurrence of epilepsy in the human population is about 1%, the search for therapeutic targets to alleviate seizures is warranted. Extracts of Cannabis sativa have a long history in the treatment of various neurological diseases, including epilepsy. However, cannabinoids have been reported to exert both pro- and anti-convulsive activities. The recent progress in understanding the endogenous cannabinoid system has allowed new insights into these opposing effects of cannabinoids. When excessive neuronal activity occurs, endocannabinoids are generated on demand and activate cannabinoid type 1 (CB(1)) receptors. Using mice lacking CB(1) receptors in principal forebrain neurons in a model of epileptiform seizures, it was shown that CB(1) receptors expressed on excitatory glutamatergic neurons mediate the anti-convulsive activity of endocannabinoids. Systemic activation of CB(1) receptors by exogenous cannabinoids, however, are anti- or pro-convulsive, depending on the seizure model used. The pro-convulsive activity of exogenous cannabinoids might be explained by the notion that CB(1) receptors expressed on inhibitory GABAergic neurons are also activated, leading to a decreased release of GABA, and to a concomitant increase in seizure susceptibility. The concept that the endogenous cannabinoid system is activated on demand suggests that a promising strategy to alleviate seizure frequency is the enhancement of endocannabinoid levels by inhibiting the cellular uptake and the degradation of these endogenous compounds.


The term 'endocannabinoid' - originally coined in the mid-1990s after the discovery of membrane receptors for the psychoactive principle in Cannabis, Delta9-tetrahydrocannabinol and their endogenous ligands - now indicates a whole signalling system that comprises cannabinoid receptors, endogenous ligands and enzymes for ligand biosynthesis and inactivation. This system seems to be involved in an ever-increasing number of pathological conditions. With novel products already being aimed at the pharmaceutical market little more than a decade since the discovery of cannabinoid receptors, the endocannabinoid system seems to hold even more promise for the future development of therapeutic drugs. We explore the conditions under which the potential of targeting the endocannabinoid system might be realized in the years to come.


Prenatal exposure to tobacco smoke increases risk of sudden infant death syndrome (SIDS). Marijuana is frequently smoked in conjunction with tobacco, and perinatal exposure to marijuana is associated with increased incidence of SIDS. Abnormalities in peripheral arterial chemoreceptor responses during sleep may be operative in infants at risk for SIDS, and nicotine exposure adversely affects peripheral arterial chemoreceptor responses. To determine whether marijuana could potentially affect the activity of peripheral arterial chemoreceptors during early postnatal development, we used in situ hybridization histochemistry to characterize the pattern and level of mRNA expression for cannabinoid type 1 receptor (CB1R) in the carotid body, superior cervical ganglia (SCG), and nodose-petrosal-jugular ganglia (NG-PG-JG) complex in
newborn rats. We used immunohistochemistry and light, confocal, and electron microscopy to characterize the pattern of CB1R and tyrosine hydroxylase protein expression. CB1R mRNA expression was intense in the NG-PG-JG complex, low to moderate in the SCG, and sparse in the carotid body. With maturation, CB1R gene expression significantly increased (P < 0.01) in the NG-PG-JG complex. CB1R immunoreactivity was localized to nuclei of ganglion cells in the SCG and NG-PG-JG complex, whereas tyrosine hydroxylase immunoreactivity was localized to the cytoplasm. Exposure to marijuana during early development could potentially modify cardiorespiratory responses via peripheral arterial chemoreceptors. The novel finding of nuclear localization of CB1Rs in peripheral ganglion cells suggests that these receptors may have an, as yet, undetermined role in nuclear signaling in sensory and autonomic neurons.


BACKGROUND: The major psychoactive cannabinoid compound of marijuana delta-9 tetrahydrocannabinol (THC) has been shown to modulate immune responses and lymphocyte function. After primary infection the viral DNA genome of gamma herpesviruses persists in nuclei of lymphoid cells in a latent episomal circular form. In response to extracellular signals, the latent virus can be activated, which leads to production of infectious virus progeny. Therefore, we evaluated potential effects of THC on gamma herpesvirus replication. METHODS: Tissue cultures infected with various gamma herpesviruses were cultured in the presence of increasing concentrations of THC and the amount of viral DNA or infectious virus yield was compared to those of control cultures. The effect of THC on Kaposi's Sarcoma Associated Herpesvirus (KSHV) and Epstein-Barr virus (EBV) replication was measured by the Gardella method and replication of herpesvirus saimiri (HVS) of monkeys, murine gamma herpesvirus 68 (MHV 68), and herpes simplex type 1 (HSV-1) was measured by yield reduction assays. Inhibition of the immediate early ORF 50 gene promoter activity was measured by the dual luciferase method. RESULTS: Data presented in this work show that micro molar concentrations of THC inhibit KSHV and EBV reactivation in virus infected/immortalized B cells. THC also strongly inhibits lytic replication of MHV 68 and HVS in vitro. Importantly, concentrations of THC that inhibit virus replication of gamma herpesviruses had no effect on cell growth or HSV-1 replication indicating selectivity. THC was shown to selectively inhibit the immediate early ORF 50 gene promoter of KSHV and MHV 68. CONCLUSIONS: THC specifically targets viral and/or cellular mechanisms required for replication and possibly shared by these gamma herpesviruses, and the endocannabinoid system is possibly involved in regulating gamma herpesvirus latency and lytic replication. The immediate early gene ORF 50 promoter activity was specifically inhibited by THC. These studies may also provide the foundation for the development of antiviral strategies utilizing non-psychoactive derivatives of THC.


Anandamide (arachidonylethanolamide or AEA) is an endocannabinoid that acts at vanilloid (VR1) as well as at cannabinoid (CB1/CB2) and NMDA receptors. Here, we show that AEA, in a dose-dependent manner, causes cell death in cultured rat cortical neurons and cerebellar granule cells. Inhibition of CB1, CB2, VR1 or NMDA receptors by selective antagonists did not reduce AEA neurotoxicity. Anandamide-induced neuronal cell loss was associated with increased intracellular Ca(2+), nuclear condensation and fragmentation, decreases in mitochondrial membrane potential, translocation of cytochrome c, and upregulation of caspase-3-like activity. However, caspase-3, caspase-8 or caspase-9 inhibitors, or blockade of protein synthesis by cycloheximide did not alter anandamide-related cell death. Moreover, AEA caused cell death in caspase-3-deficient MCF-7 cell line and showed similar cytotoxic effects in caspase-9 dominant-negative, caspase-8 dominant-negative or mock-transfected SH-SY5Y neuroblastoma cells. Anandamide upregulated calpain activity in cortical neurons, as revealed by alpha-spectrin cleavage, which was attenuated by the calpain inhibitor calpstatin. Calpain inhibition significantly limited anandamide-induced neuronal loss and associated cytochrome c release. These data indicate that AEA neurotoxicity appears not to be mediated by CB1, CB2, VR1 or NMDA receptors and suggest that calpain activation, rather than intrinsic or extrinsic


Delta9-tetrahydrocannabinol (THC) is the active metabolite of cannabis. THC causes cell death in vitro through the activation of complex signal transduction pathways. However, the role that the cannabinoid 1 and 2 receptors (CB1-R and CB2-R) play in this process is less clear. We therefore investigated the role of the CB-Rs in mediating apoptosis in 3 leukaemic cell lines, and performed microarray and immunoblot analyses to establish further the mechanism of cell death. We developed a novel flow cytometric technique of measuring the expression of functional receptors, and utilised combinations of selective CB1-R and CB2-R antagonists and agonists to determine their individual roles in this process. We have shown that THC is a potent inducer of apoptosis, even at 1X IC50 concentrations, and as early as six hours after exposure to the drug. These effects were seen in leukaemic cell lines (CEM, HEL-92 and HL60) as well as in peripheral blood mononuclear cells. Additionally, THC did not appear to act synergistically with cytotoxic agents such as cisplatin. One of the most intriguing findings was that THC-induced cell death was preceded by significant changes in the expression of genes involved in the MAPK signal transduction pathways. Both apoptosis and gene expression changes were altered independent of p53 and the CB-Rs.


Leaf extract of C. sativa causes paralysis leading to death in larvae of C. samoensis. The extract brought a drastic change in the morphology of sensilla trichoidea and the general body cuticle. The larvae exposed to the leaf extract also showed a significant reduction in the concentration of Mg and Fe, while Mn showed only slight average increase. Since the sensilla trichoidea has nerve connection, it is expected that the toxic principle of the leaf extract has affected the central nervous system. The significant reduction of the level of Fe indicates that the extract could cause the reduction in oxygen binding capacity of the haemolymph, thereby acting as a respiratory poison in addition to its known role as a neurotoxic substance.


Activated glial cells have been implicated in the neuropathogenesis of many infectious and inflammatory diseases of the brain. A number of inflammatory mediators have been proposed to play a role in glial cell-related brain damage; e.g., free radicals such as nitric oxide (NO), cytokines, and chemokines. Our laboratory has been interested in the effect of psychoactive drugs and their derivatives on the production of these mediators. Cannabinoids have been shown to possess immunomodulatory as well as psychoactive properties. We previously have shown that interleukin (IL)-1beta-stimulated human astrocytes, but not microglia, produce NO. In this study, we investigated the effects of the synthetic cannabinoid WIN55,212-2 on the production of several key inflammatory mediators by human fetal astrocytes activated by IL-1beta. Expression of the cannabinoid receptors CB(1) and CB(2) was detected on human astrocytes. WIN55,212-2 (10(-5) M) potently inhibited inducible NO synthase (iNOS) and corresponding NO production by IL-1beta-stimulated astrocytes. The CB(1) and CB(2) receptor-specific antagonists SR141716A and SR144528, respectively, partially blocked this suppressive effect. In addition, treatment of astrocytes with WIN55,212-2 downregulated in a concentration-dependent manner IL-1beta-induced tumor necrosis factor (TNF)-alpha release. Treatment with WIN55,212-2 also inhibited production of the chemokines CXCL10, CCL2 and CCL5 by IL-1beta-activated astrocytes. These findings indicate that WIN55,212-2 inhibits the production of inflammatory mediators by IL-1beta-stimulated human astrocytes and suggest that comparable agents may have therapeutic potential for the management of brain inflammation. Copyright 2004 Wiley-Liss, Inc.

Food-storing birds demonstrate remarkable memory ability in recalling the locations of thousands of hidden food caches. Although this behaviour requires the hippocampus, its synaptic mechanisms are not understood. Here we show the effects of cannabinoid receptor (CB1-R) blockade on spatial memory in food-storing black-capped chickadees (Poecile atricapilla). Intra-hippocampal infusions of the CB1-R antagonist SR141716A enhanced long-term memory for the location of a hidden food reward, measured 72 h after encoding. However, when the reward location changed during the retention interval, birds that had received SR141716A during initial learning showed impairments in recalling the most recent reward location. Thus, blocking CB1-R activity may lead to more robust, long-lasting memories, but these memories may be a source of proactive interference. The relationship between trace strength and interference may be important in understanding neural mechanisms of hippocampal function in general, as well as understanding the enhanced memory of food-storing birds.


Abstract A(2A) adenosine and CB1 cannabinoid receptors are highly expressed in the central nervous system, where they modulate numerous physiological processes including adaptive responses to drugs of abuse. Both purinergic and cannabinoid systems interact with dopamine neurotransmission (through A(2A) and CB1 receptors, respectively). Changes in dopamine neurotransmission play an important role in addictive-related behaviours. In this study, we investigated the contribution of A(2A) adenosine receptors in several behavioural responses of Delta(9)-tetrahydrocannabinol (THC) related to its addictive properties, including tolerance, physical dependence and motivational effects. For this purpose, we first investigated acute THC responses in mice lacking A(2A) adenosine receptors. Antinociception, hypolocomotion and hypothermia induced by acute THC administration remained unaffected in mutant mice. Chronic THC treatment developed similar tolerance to these acute effects in wild-type and A(2A)-knockout mice. However, differences in the body weight pattern were found between genotypes during such chronic treatment. Interestingly, the somatic manifestations of SR141716A-precipitated THC withdrawal were significantly attenuated in mutant mice. The motivational responses of THC were also evaluated by using the place-conditioning paradigm. A significant reduction of THC-induced rewarding and aversive effects was found in mice lacking A(2A) adenosine receptors in comparison with wild-type littermates. Binding studies revealed that these behavioural changes were not associated with any modification in the distribution and/or functional activity of CB1 receptors in knockout mice. Therefore, this study shows, for the first time, a specific involvement of A(2A) receptors in the addictive-related properties of cannabinoids.


We recently provided evidence for a functional link between cannabinoid and opioid endogenous systems in relapse to heroin-seeking behaviour in rats. In the present study, we aimed at investigating whether the previously observed cross-talk between cannabinoids and opioids could be extended to mechanisms underlying relapse to cannabinoid-seeking behaviour after a prolonged period of abstinence. In rats previously trained to intravenously self-administer the synthetic cannabinoid receptor (CB1) agonist WIN 55,212-2 (12.5 micro g kg(-1) inf(-1)) under a fixed ratio (FR1) schedule of reinforcement, noncontingent nonreinforced intraperitoneal (i.p.) priming injections of the previously self-administered CB1 agonist (0.25 and 0.5 mg kg(-1)) as well as heroin (0.5 mg kg(-1)), but not cocaine (10 mg kg(-1)), effectively reinstate cannabinoid-seeking behaviour following 3 weeks of extinction. The selective CB1 receptor antagonist SR 141716A (0.3 mg kg(-1) i.p.) does not reinstate responding when given alone, but completely prevents the cannabinoid-seeking behaviour triggered by WIN 55,212-2 or heroin primings. The nonselective opioid antagonist naloxone (1 mg kg(-1) i.p.) has no effect on operant behaviour per se, but significantly blocks cannabinoid- and heroin-induced reinstatement of cannabinoid-seeking behaviour. These results provide the first evidence of drug-induced reinstatement of
cannabinoid-seeking behaviour, and further strengthen previous findings on a cross-talk between
the endogenous cannabinoid and opioid systems in relapse mechanisms to drug-seeking.


The cannabinoid signaling system is composed of cannabinoid (CB) receptors, their
endogenous ligands, the endocannabinoids, and the enzymes that produce and inactivate them.
It is well known that neurons communicate between each other through this signaling system.
Delta(9)-tetrahydrocannabinol, the main psychoactive compound of marijuana, interacts with CB
receptors, impinging on this communication and inducing profound behavioral effects such as
memory impairment and analgesia. Recent evidence suggests that glial cells also express
components of the cannabinoid signaling system and marijuana-derived compounds act at CB
receptors expressed by glial cells, affecting their functions. This review summarizes this
evidence, discusses how glial cells might use the cannabinoid signaling system to communicate
with neighboring cells, and argues that nonpsychotropic cannabinoids, both marijuana-derived
and synthetic, likely constitute lead compounds for therapy aimed at reducing acute and chronic
neuroinflammation, such as occurs in multiple sclerosis. Copyright 2004 Wiley-Liss, Inc.


Delta(9)-Tetrahydrocannabinol (THC) and 11-nor-Delta(9)-tetrahydrocannabinol-9-
carboxylic acid (THCA) are equally used to indicate consumption of cannabis (hashish and
marijuana). Publications of the early 90's demonstrate the possibilities of determining THC,
cannabinol (CBN), and cannabidiol (CBD). All these substances are present in cannabis smoke
and can be incorporated into the hair only by contamination. Generally, washing procedures
should prevent false positive results, but finally it cannot be excluded that traces of THC may be
found in hair after mere passive cannabis smoke exposure. Three authentic cases illustrate the
problems originating in the exclusive determination of THC/CBN. The first example is the case of
a couple living together in an apartment. Both persons' hair samples had been taken and gave
positive results for THC and CBN. The male subject admitted smoking cannabis several times per
day, but the female mate denied any consumption. Examination of the hair for THCA showed a
high level (>6.6pg/mg) in the sample of the male person and negative results (LOQ 0.1pg/mg) in
the sample of his mate. The second case hair is of a self admitted cannabis user's hair and was
tested first by an immunoassay and GC/MS with a negative result. Nevertheless, the THCA
concentration quantified in his sample was 2.7pg/mg hair. The third hair sample is of a 2-year-old
child that was tested positive for cannabis by using an immunochemical test. No THC and CBN
were detectable by GC/MS, however, trace amounts of THCA using GC/MS/MS. A comparative
study of hair samples (screening for cannabinoids using ELISA test, THC determination by
GC/MS, THCA by GC/MS/MS) showed that only 26 segments of 66 were positive for both THC
and THCA. Thirteen were negative for THC and positive for THCA, and six were positive for THC
but negative for THCA. The cases were selected by an ELISA test or re-examined when the
blood/urine results or the statement of the accused did not match with a THC outcome. The most
appropriate strategy to prove cannabis consumption is immunochemical initial test followed by a
GC/MS/MS confirmation of THCA.

embryos." Nat Med.

Ectopic pregnancy is a major reproductive health issue. Although other underlying
causes remain largely unknown, one cause of ectopic pregnancy is embryo retention in the
fallopian tube. Here we show that genetic or pharmacologic silencing of cannabinoid receptor
CB1 causes retention of a large number of embryos in the mouse oviduct, eventually leading to
pregnancy failure. This is reversed by isoproterenol, a beta-adrenergic receptor agonist. Impaired
oviductal embryo transport is also observed in wild-type mice treated with methanandamide.
Collectively, the results suggest that aberrant cannabinoid signaling impedes coordinated
oviductal smooth muscle contraction and relaxation crucial to normal oviductal embryo transport.
Colocalization of CB1 and beta2-adrenergic receptors in the oviduct muscularis implies that a
basal endocannabinoid tone in collaboration with adrenergic receptors coordinates oviductal
motility for normal journey of embryos into the uterus. Besides uncovering a new regulatory mechanism, this study could be clinically relevant to ectopic pregnancy.

**CLINICAL SCIENCE**


**CONTEXT:** Hepatotoxicity is a potential complication from the usage of various illicit drugs, possibly consequent to their liver metabolism, but information on this is scarce in the medical literature. **OBJECTIVE:** To study the occurrence of clinical and laboratory hepatic alterations in chronic marijuana users, from the use of marijuana on its own or in association with other legal or illicit drugs. **TYPE OF STUDY:** transversal study **SETTING:** Hospital Espirita de Marilia, Marilia, Sao Paulo, Brazil **PARTICIPANTS:** The study was made among 123 patients interned in the Hospital Espirita de Marilia from October 1996 to December 1998, divided into 3 groups: 26 (21%) using only marijuana, 83 (67.5%) using marijuana and crack, and 14 (11.4%) consuming marijuana and alcohol. **PROCEDURES AND MAIN MEASUREMENTS:** Patients were examined clinically with special emphasis on types of drugs used, drug intake route, age when consumption began, length and pattern of usage, presence of tattooing, jaundice, hepatomegaly and splenomegaly. Serum determinations of total proteins, albumin, globulin, total and fractions of bilirubin, aspartate (AST) and alanine (ALT) aminotransferases, alkaline phosphatase (AP), gamma-glutamyltransferase and prothrombin activity were performed. **RESULTS:** Among users of only marijuana, hepatomegaly was observed in 57.7% and splenomegaly in 73.1%, and slightly elevated AST (42.3%), ALT (34.6%) and AP (53.8%). The three groups did not differ significantly in the prevalence of hepatomegaly, splenomegaly and hepatosplenomegaly. The group using both marijuana and alcohol showed the highest prevalence of alterations and highest levels of aminotransferases. Mean AP levels were above normal in all groups. **CONCLUSIONS:** Chronic marijuana usage, on its own or in association with other drugs, was associated with hepatic morphologic and enzymatic alterations. This indicates that cannabinoids are possible hepatotoxic substances.


The majority of patients with multiple sclerosis (MS) develop troublesome lower urinary tract symptoms (LUTS). Anecdotal reports suggest that cannabis may alleviate LUTS, and cannabinoid receptors in the bladder and nervous system are potential pharmacological targets. In an open trial we evaluated the safety, tolerability, dose range, and efficacy of two whole-plant extracts of Cannabis sativa in patients with advanced MS and refractory LUTS. Patients took extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension. Assessments included urinary frequency and volume charts, incontinence pad weights, cystometry and visual analogue scales for secondary troublesome symptoms. Twenty-one patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment (P <0.05, Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly (P <0.05, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks. There were few troublesome side effects, suggesting that cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS.


The effect of marijuana use on cognitive function is controversial. Although marijuana use is common in HIV-infected individuals for recreational and medicinal purposes, there have been no studies of the impact of marijuana on cognitive function in these subjects. Marijuana also has
known immunologic effects, which increases the relevance in HIV-infected patients. We examined the interaction of HIV disease-stage and marijuana use in 282 subjects, stratified by disease stage and frequency of marijuana use. After controlling for the effects of depression, anxiety, and alcohol use, a significant interaction was observed on an overall measure of cognitive impairment. The effect of marijuana use was greatest in subjects with symptomatic HIV infection. Further inspection suggested that this effect was due primarily to performance on memory tasks. These data suggest that although there is minimal impact of marijuana on uninfected individuals or those at early stages of HIV infection, there is a synergistic effect of HIV and marijuana use in patients with advanced HIV disease. This is consistent with other data suggesting that the subtle effects of some conditions may become more manifest in the setting of immunocompromise.


Recent research has clarified a number of important questions concerning adverse effects of cannabis on health. A causal role of acute cannabis intoxication in motor vehicle and other accidents has now been shown by the presence of measurable levels of Delta(9)-tetrahydrocannabinol (THC) in the blood of injured drivers in the absence of alcohol or other drugs, by surveys of driving under the influence of cannabis, and by significantly higher accident culpability risk of drivers using cannabis. Chronic inflammatory and precancerous changes in the airways have been demonstrated in cannabis smokers, and the most recent case-control study shows an increased risk of airways cancer that is proportional to the amount of cannabis use. Several different studies indicate that the epidemiological link between cannabis use and schizophrenia probably represents a causal role of cannabis in precipitating the onset or relapse of schizophrenia. A weaker but significant link between cannabis and depression has been found in various cohort studies, but the nature of the link is not yet clear. A large body of evidence now demonstrates that cannabis dependence, both behavioral and physical, does occur in about 7-10% of regular users, and that early onset of use, and especially of weekly or daily use, is a strong predictor of future dependence. Cognitive impairments of various types are readily demonstrable during acute cannabis intoxication, but there is no suitable evidence yet available to permit a decision as to whether long-lasting or permanent functional losses can result from chronic heavy use in adults. However, a small but growing body of evidence indicates subtle but apparently permanent effects on memory, information processing, and executive functions, in the offspring of women who used cannabis during pregnancy. In total, the evidence indicates that regular heavy use of cannabis carries significant risks for the individual user and for the health care system.


Background: This case-control study aimed to identify the risk factors for oral cancer in patients aged 45 years and under. Methods: Patients were recruited over a 3-year period between 1999 and 2001 from 14 hospitals in the southeast of England, UK. Results: Fifty-three (80%) newly diagnosed patients with squamous cell carcinoma (SCC) of the oral cavity participated. The mean age of cases at diagnosis was 38.5 years (SD = 7.0) and 53% were male. Patients were interviewed about main risk factors of tobacco, alcohol, cannabis and their consumption of fresh fruit and vegetables in the past. Ninety-one matched control patients were also recruited. Odds ratios (ORs) and 95% confidence intervals (CI) were obtained from adjusted conditional logistic analyses. Significantly elevated ORs were evidenced amongst males who had started to smoke under the age of 16 years (OR = 14.3; 95% CI: 1.1-178.8). A significant
reduction in risk was also shown for ex-smokers (OR = 0.2; 95% CI: 0.5-0.8). Consumption of alcohol in excess of recommended amounts also produced an eightfold risk in males (OR = 8.1; 95% CI: 1.6-40.1) and over a fourfold risk of oral cancer from the consumption of excessive amounts of alcohol and having ever smoked (OR = 4.4; 95% CI: 1.1-17.7). Conclusion: The study shows that the traditional behavioural risk factors are present in younger people diagnosed with oral cancer. The relatively short duration of exposure and the substantial number of cases without any known risk factors, particularly amongst females, however, suggest that factors other than tobacco and alcohol may also be implicated in the development of oral cancer in a proportion of these younger patients. J Oral Pathol Med (2004) 33: 525-32


Many patients with life-threatening diseases such as cancer experience severe symptoms that compromise their health status and deny them quality of life. Patients with cancer often experience cachexia, pain, and depression, which translate into an unacceptable quality of life. The discovery of the endocannabinoid system has led to a renewed interest in the use of cannabinoids for the management of nausea, vomiting, and weight loss arising either from cancer or the agents used to treat cancer. The endocannabinoid system has been found to be a key modulator of systems involved in pain perception, emesis, and reward pathways. As such, it represents a target for development of new medications for controlling the symptoms associated with cancer. Although the cannabinoid receptor agonist tetrahydrocannabinol and one of its analogs are currently the only agents approved for clinical use, efforts are under way to devise other strategies for activating the endocannabinoid system for therapeutic uses.


We review health of marijuana since 1998, when The Lancet published the article dealing with this subject.


A 6-year-old boy accidentally became intoxicated with marijuana secondary to ingesting cookies laced with marijuana. He presented with retentive memory deficit of sudden onset that was later diagnosed as transient global amnesia. Transient global amnesia as a result of marijuana intoxication is an extremely rare event.


A patient with generalized dystonia due to Wilson's disease obtained marked improvement in response to smoking cannabis. Copyright 2004 Movement Disorder Society


OBJECTIVE: Cannabis may alleviate some symptoms associated with multiple sclerosis (MS). This study investigated the effect of an orally administered standardized Cannabis sativa plant extract in MS patients with poorly controlled spasticity. METHODS: During their inpatient rehabilitation programme, 57 patients were enrolled in a prospective, randomized, double-blind, placebo-controlled crossover study of cannabis-extract capsules standardized to 2.5 mg tetrahydrocannabinol (THC) and 0.9 mg cannabidiol (CBD) each. Patients in group A started with a drug escalation phase from 15 to maximally 30 mg THC by 5 mg per day if well tolerated, being on active medication for 14 days before starting placebo. Patients in group B started with placebo for seven days, crossed to the active period (14 days) and closed with a three-day placebo period (active drug dose escalation and placebo sham escalation as in group A). Measures used included daily self-report of spasm frequency and symptoms, Ashworth Scale, Rivermead Mobility Index, 10-m timed walk, nine-hole peg test, paced auditory serial addition test (PASAT), and the
digit span test. RESULTS: In the 50 patients included into the intention-to-treat analysis set, there were no statistically significant differences associated with active treatment compared to placebo, but trends in favour of active treatment were seen for spasm frequency, mobility and getting to sleep. In the 37 patients (per-protocol set) who received at least 90% of their prescribed dose, improvements in spasm frequency ($P = 0.013$) and mobility after excluding a patient who fell and stopped walking were seen ($P = 0.01$). Minor adverse events were slightly more frequent and severe during active treatment, and toxicity symptoms, which were generally mild, were more pronounced in the active phase. CONCLUSION: A standardized Cannabis sativa plant extract might lower spasm frequency and increase mobility with tolerable side effects in MS patients with persistent spasticity not responding to other drugs.


An anonymous questionnaire sent to all patients attending the Prague Movement Disorder Centre revealed that 25% of 339 respondents had taken cannabis and 45.9% of these described some form of benefit. Copyright 2004 Movement Disorder Society


The objective was to determine whether a cannabis-based medicinal extract (CBME) benefits a range of symptoms due to multiple sclerosis (MS). A parallel group, double-blind, randomized, placebo-controlled study was undertaken in three centres, recruiting 160 outpatients with MS experiencing significant problems from at least one of the following: spasticity, spasms, bladder problems, tremor or pain. The interventions were oromucosal sprays of matched placebo, or whole plant CBME containing equal amounts of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) at a dose of 2.5-120 mg of each daily, in divided doses. The primary outcome measure was a Visual Analogue Scale (VAS) score for each patient's most troublesome symptom. Additional measures included VAS scores of other symptoms, and measures of disability, cognition, mood, sleep and fatigue. Following CBME the primary symptom score reduced from mean (SE) 74.36 (11.1) to 48.89 (22.0) following CBME and from 74.31 (12.5) to 54.79 (26.3) following placebo [ns]. Spasticity VAS scores were significantly reduced by CBME (Sativex) in comparison with placebo (P = 0.001). There were no significant adverse effects on cognition or mood and intoxication was generally mild.

BEHAVIOURAL SCIENCE


The effectiveness of adolescent substance abuse treatment has been repeatedly demonstrated, but specific treatment approaches have rarely been sufficiently documented to permit replication. This study evaluated the effectiveness of a manual-guided, outpatient, group-based treatment program for adolescents (N = 194) who were mild-to-moderate substance abusers. In addition to evaluating the group-based treatment model, the study was designed to compare the effectiveness of two approaches to preparing youth to engage in treatment, whereby adolescents received one of two types of treatment induction, either motivational interviewing or counseling overview. Self-reported pretreatment substance use and criminal behaviors were compared with these behaviors 6 and 12 months following treatment entry using a General Linear Mixed Model analytic approach that controlled for the effects of potential confounding variables and examined individual and program factors that might explain treatment response. Participants significantly reduced marijuana use at 6 months, and these reductions were largely sustained at 12 months. No changes in alcohol use or criminal involvement were obtained. Further examination of marijuana use indicated differential treatment response based on participants' emotional abuse history, family satisfaction, school adjustment, and pretreatment substance use frequency. This treatment approach appears promising for marijuana-abusing youth.

Defence lawyers sometimes argue that the presence of cannabinoid metabolites in the defendant's blood or urine resulted from passive unintentional inhalation of environmental cannabis smoke. It would be useful to be able to differentiate passive inhalation from active use so as to discourage the potential abuse of this phenomenon by the defence. Four cases from two jurisdictions in which passive cannabis smoking was used as a defence are presented to illustrate this dilemma. It remains impossible to define objectively an upper limit for blood and urine levels in cases of passive inhalation of cannabis from the environment. However, a claim of passive inhalation, or indeed 'deliberate passive exposure' could be discouraged by making it an offence to place oneself in a position of being 'concerned' in the use of the drug. The onus should be on the defendant to prove that he had not attempted to extricate himself from the situation, being aware of the smoking of cannabis in his immediate vicinity; ignorance would not be an excuse.


This study was conducted to identify factors associated with alcohol use among early adolescents. A survey was administered to all Grade 7 and 8 students in 16 Vermont school districts. The questionnaire covered demographics, alcohol, tobacco, and marijuana use, and measures of psychosocial mediators of alcohol use drawn from social cognitive theory. These included positive and negative expectancies about alcohol effects, perceived peer and parent alcohol norms, perceived prevalence of adolescent alcohol use, and confidence in ability to refuse alcohol. Of the 2919 respondents, 29% reported having at least one drink of beer in the preceding 30 days. In logistic regression, factors independently related to risk of drinking beer in the past 30 days were smoking (odds ratio [OR]=2.3, 95% confidence interval [CI] 1.8-3.0), marijuana use (OR 3.9, 95% CI 3.0-5.2), negative expectancies (OR 0.4, 95% CI 0.3-0.6), parent norms (OR 1.4, 95% CI 1.1-1.7), and estimated percentage of high school students who drink (OR 1.3, 95% CI 1.1-1.5). Gender, positive alcohol expectancies, and lack of confidence in ability to refuse alcohol all significantly interacted with peer norm, with these items more strongly associated with alcohol use when peer norm is toward "shouldn't drink." Modifiable perceptions of alcohol use were strongly associated with actual use in this adolescent sample, providing a basis for intervention program design.


Substance use disorders, especially cannabis abuse and dependence, are common comorbid diagnoses among patients in the early course of schizophrenia. Some prior research suggests that individuals with schizophrenia and related disorders and comorbid substance abuse may have fewer negative symptoms than those without substance abuse. This pilot study examined the association between cannabis dependence and negative symptoms in a relatively homogenous sample of 18 African American first-episode, first-hospitalization patients. Those with cannabis dependence had significantly lower Positive and Negative Syndrome Scale (PANSS) negative subscale scores compared to those without cannabis dependence (p<0.012). The two groups did not differ on PANSS positive and general psychopathology subscale scores. Additional research is needed on the correlates of substance abuse among first-episode patients, including socially disadvantaged African American patients.


The existing literature on the prevalence of drug driving, the effects of drugs on driving performance, risk factors and risk perceptions associated with drug driving was reviewed. The 12-month prevalence of drug driving among the general population is approximately 4%. Drugs are detected commonly among those involved in motor vehicle accidents, with studies reporting up to 25% of accident-involved drivers positive for drugs. Cannabis is generally the most common drug detected in accident-involved drivers, followed by benzodiazepines, cocaine, amphetamines and opioids. Polydru use is common among accident-involved drivers. Studies of impairment indicate an undeniable association between alcohol and driving impairment. There is also evidence that cannabis and benzodiazepines increase accident risk. The most equivocal evidence surrounds opioids and stimulants. It is apparent that drugs in combination with alcohol, and multiple drugs, present an even greater risk. Demographically, young males are over-represented among drug drivers. Although there is an association between alcohol use problems and drink driving, it is unclear whether such an association exists between drug use problems and drug driving. Evidence surrounding psychosocial factors and driving behaviour is also equivocal at this stage. While most drivers perceive drug driving to be dangerous and unacceptable, there is less concern about impaired driving among drug drivers and drink drivers than from those who have not engaged in impaired driving. Risk perceptions differ according to drug type, with certain drugs (e.g. cannabis) seen as producing less impairment than others (e.g. alcohol). It is concluded that drug driving is a significant problem, both in terms of a general public health issue and as a specific concern for drug users. [Kelly E, Darke S, Ross J. A review of drug use and driving: epidemiology, impairment, risk factors and risk perceptions. Drug Alcohol Rev 2004;23:319-344]


The present study examined substance use rates among adolescents in Grades 7-12 in Puerto Rico. Nine hundred eighty-nine students completed the Spanish version of the International Survey of Adolescent Health. More than 50% of middle school youths and 75% of high-school youths reported lifetime alcohol use. Female gender was associated with tobacco use in middle school while male gender was associated with marijuana use in high school. High-school females reported lower rates of tobacco use and marijuana use than middle-school females. High-school males exhibited substantially higher drug-use rates than middle-school males for each substance. These findings may suggest that universal drug prevention interventions may be needed for females in Puerto Rico before they enter middle school, while targeted interventions aimed at high-risk females who continue to smoke tobacco or marijuana may be more effective during high school. In contrast, targeted drug prevention interventions for males probably need to begin in middle school and be maintained if not increased in intensity throughout the high-school years.


A comprehensive review of 75 samples of both blood and urine specimens submitted to the Lothian and Borders Police Forensic Laboratory. The police reports, analytical results and criminal conviction records relating to each of the drivers were examined. This provided useful information concerning differences in laboratory procedures and produced a profile of the average drugged driver. The average age of the drivers was 23 years. Only two females were within the sample. Drugs were found in 65 cases (86.7%). Polydru ge use was found in seven cases (9.3%). The drugs found, in order of frequency, were benzodiazepines (40%), cannabinoids (24%), alcohol (16%), methadone (12%), d Nhydrocodeine (9.3%), ecstasy (5.3%), amphetamine (2.7%), volatiles (1.3%) and morphine (1.3%). 90.3% of the drivers had previous convictions for criminal offences and 47.2% had convictions for drugs-related offences. Recommendations concerning police and medical training are discussed with particular reference to the Drug Recognition Expert program.

Windows of opportunity for changing drug laws open infrequently and they often close without legislative change being affected. In this paper the author, who has been intimately involved in the process, describes how evidence-based recommendations to 'decriminalize' cannabis have recently been progressed through public debate and the political process to become law in Western Australia (WA). The Cannabis Control Bill 2003 passed the WA Parliament on 23 September. The Bill, the legislative backing behind the Cannabis Infringement Notice (CIN) Scheme, came into effect on 22 March 2004. This made WA the fourth Australian jurisdiction, after South Australia, the Australian Capital Territory and the Northern Territory, to adopt a prohibition with civil penalties scheme for minor cannabis offences. This paper describes some of the background to the scheme, the process by which it has become law, the main provisions of the scheme and its evaluation. It includes reflections on the role of politics and the press in the process. The process of implementation and evaluation are outlined by the author, foreshadowing an ongoing opportunity to understand the impact of the change in legislation.


The prevalence and the clinical meaning of cannabis use in patients with chronic psychosis has not been systematically explored. The authors have compared the diagnostic and symptomatological characteristics of 111 male patients affected by chronic psychosis with and without past or current use of cannabis. Sixty-six patients were still using or had used cannabis; in all cases the use preceded the onset of psychotic symptoms. Forty-three patients were cannabis-positive on urinary screening at the moment of hospitalization and 23 were currently cannabis-free but reported the use of cannabis in the past. Forty-five patients were negative on urinary screening and reported no past history of cannabis use. In evaluating the psychopathological features, the Brief Psychiatric Rating Scale (BPRS) and the Overt Aggression Rating Scale (AORS) were used. The three groups showed similar demographic data, except for age, which was lower in current cannabis users than in nonusers; no differences were found between current and past users. As regards diagnostic features, "mood cluster" was significantly better represented in cannabis users and "schizophrenic cluster" in nonusers; bipolar spectrum disorders were more frequently reported than unipolar ones. When past and current users were grouped together, only blunted affect score was significantly higher in nonusers than in users, while clastic violence showed higher scores in users. These data indicate that chronic, psychosis, whether associated with past or with current use of cannabis, is frequently associated with bipolar spectrum disorders and tends to display less blunted affect and more clastic behavior.


OBJECTIVE: Substance abuse remains one of the major threats to adolescent health in Western cultures. The study aim was to ascertain the extent of association between pubertal development and early adolescent substance use. METHODS: The design was a cross-sectional survey of 10- to 15-year-old subjects in the states of Washington, United States, and Victoria, Australia. Participants were 5769 students in grades 5, 7, and 9, drawn as a 2-stage cluster sample in each state, and the questionnaire was completed in the school classrooms. The main outcomes of the study were lifetime substance use (tobacco use, having been drunk, or cannabis use), recent substance use (tobacco, alcohol, or cannabis use in the previous month), and substance abuse (daily smoking, any binge drinking, drinking at least weekly, or cannabis use at least weekly). RESULTS: The odds of lifetime substance use were almost twofold higher (odds ratio [OR]: 1.7; 95% confidence interval [CI]: 1.4-2.1) in midpuberty (Tanner stage III) and were threefold higher (OR: 3.1; 95% CI: 2.4-4.2) in late puberty (Tanner stage IV/V), after adjustment for age and school grade level. Recent substance use was moderately higher (OR: 1.4; 95% CI: 1.0-1.9) in midpuberty and more than twofold higher (OR: 2.3; 95% CI: 1.7-3.3) in late puberty.
The odds of substance abuse were twofold higher (OR: 2.0; 95% CI: 1.2-3.2) in midpuberty and more than threefold higher (OR: 3.5; 95% CI: 2.2-5.4) in late puberty. Reporting most friends as substance users was more likely in the later stages of pubertal development, a relationship that accounted in part for the association found between later pubertal stage and substance abuse.

CONCLUSIONS: Pubertal stage was associated with higher rates of substance use and abuse independent of age and school grade level. Early maturers had higher levels of substance use because they entered the risk period at an earlier point than did late maturers. The study findings support prevention strategies and policies that decrease recreational substance use within the peer social group in the early teens.


Gay, lesbian, and bisexual (GLB) youths report elevated levels of substance use relative to heterosexual youths, but reasons for this disparity have received scant attention. This report longitudinally examined three hypothesized explanations for cigarette, alcohol, and marijuana use among 156 GLB youths. Counter to two hypotheses, neither a history of childhood sexual abuse nor recent experiences of gay-related stressful life events were associated with increased substance use over time. However, the hypothesis concerning the coming-out process was supported by significant nonlinear associations of involvement in gay-related (recreational and social) activities with changes in alcohol use at 12 months and changes in marijuana use at 6 months and 12 months. Specifically, as involvement in gay-related activities increased, alcohol and marijuana use was found to initially increase, but then, substance use declined as involvement in gay-related activities continued to increase. These findings offer a potential explanation for high levels of substance use among GLB youths and suggest potential areas for intervention to prevent or decrease substance use among these youths.


ABSTRACT Aims To investigate the effect of exposure to cannabis early in adolescence on subclinical positive and negative symptoms of psychosis. Design Cross-sectional survey in the context of an ongoing cohort study. Setting Government-supported general population cohort study. Participants A total of 3500 representative 19-year olds in Greece. Measurements Subjects filled in the 40-item Community Assessment of Psychic Experiences, measuring subclinical positive (paranoia, hallucinations, grandiosity, first-rank symptoms) and negative psychosis dimensions and depression. Drug use was also reported on. Findings Use of cannabis was associated positively with both positive and negative dimensions of psychosis, independent of each other, and of depression. An association between cannabis and depression disappeared after adjustment for the negative psychosis dimensions. First use of cannabis below age 16 years was associated with a much stronger effect than first use after age 15 years, independent of lifetime frequency of use. The association between cannabis and psychosis was not influenced by the distress associated with the experiences, indicating that self-medication may be an unlikely explanation for the entire association between cannabis and psychosis. Conclusions These results add credence to the hypothesis that cannabis contributes to the population level of expression of psychosis. In particular, exposure early in adolescence may increase the risk for the subclinical positive and negative dimensions of psychosis, but not for depression.


ABSTRACT Aims A brief intervention called the Marijuana Check-up (MCU) was designed to attract adult marijuana users who were experiencing adverse consequences, but who were ambivalent about change and would be unlikely to seek treatment. Our objective was to determine whether the MCU would reach the target population. Design Comparisons were made between those who enrolled in the MCU versus those who were screened but failed to follow through with enrollment on demographic, drug use and stage of change variables. Comparisons were also made between participants in the MCU and participants in a concurrently offered treatment project that targeted marijuana users who wanted to quit. Setting The study took place...
at the University of Washington in Seattle. Participants were adult marijuana users who telephoned and expressed interest in the MCU (n = 587). Measurement variables included stage of change, frequency and duration of drug use, DSM-IV cannabis dependence and abuse diagnoses and negative consequences of marijuana use assessed via interviews and questionnaires. Findings Callers to the MCU were near-daily marijuana users, two-thirds of whom were in the pre-contemplation or contemplation stage of change. Participants who enrolled in the MCU reported fewer problems related to marijuana use and less readiness to make changes compared to those enrolled in the treatment study, despite similar levels of drug use. Conclusions The MCU attracted and enrolled near-daily users of marijuana who experienced negative consequences but were ambivalent about making changes. The MCU potentially has a role in the continuum of care for substance abuse problems.


Previous research has shown that the recent tightening of college alcohol policies has been effective at reducing college students' drinking. Over the period in which these stricter alcohol policies have been put in place, marijuana use among college students has increased. This raises the question of whether current policies aimed at reducing alcohol consumption are inadvertently encouraging marijuana use. This paper begins to address this question by investigating the relationship between the demands for alcohol and marijuana for college students using data from the 1993, 1997 and 1999 waves of the Harvard School of Public Health's College Alcohol Study (CAS). We find that alcohol and marijuana are economic complements and that policies that increase the full price of alcohol decrease participation in marijuana use. Copyright 2004 John Wiley & Sons, Ltd.


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