INTRODUCTION
Here is the latest summary of research abstracts. Readers are reminded of the upcoming International Cannabinoid Research Society meeting in Paestum, Italy June 22-27th 2004 (http://CannabinoidSociety.org/). The International Association for Cannabis as Medicine is hosting a meeting in Oxford, UK on September 10-11 2004 (http://www.acmed.org/); abstracts are due June 15th 2004.

BASIC SCIENCE

G protein-coupled receptors (GPCRs) and their ligands play a number of important roles in the modulation of acute and chronic pain. Indeed, opioid and cannabinoid ligands are of established therapeutic value for pain management, and further exploitation of the specific GPCR subtypes (delta-opioid, CB1 and CB2) for these ligands may yield more selective, potent analgesics with favorable side effects. More recent identification of a number of other GPCRs involved in pain pathways (eg, sensory neuron specific receptors) and selective ligands that modulate pain transmission, has highlighted further therapeutic opportunities. A further challenge to understanding pain modulation and an additional dimension for targeting analgesia is the discovery of GPCR heteromerization and accessory and regulatory proteins, such as regulator of G protein-signaling proteins, involved in expression and regulation of GPCR.

Antonelli, T., S. Tanganelli, et al. (2004). "Long-term effects on cortical glutamate release induced by prenatal exposure to the cannabinoid receptor agonist (r)-(+)2,3-dihydro-5-methyl-3-(4-morpholinyl-methyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone: an in vivo microdialysis study in the awake rat." Neuroscience 124(2): 367-75.

The aim of the present in vivo microdialysis study was to investigate whether prenatal exposure to the CB(1) receptor agonist WIN55,212-2 mesylate (WIN; (R)-(+)2,3-dihydro-5-methyl-3-(4-morpholinyl-methyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone), at a dose of 0.5 mg/kg (s.c. from the fifth to the 20th day of gestation), that causes neither malformations nor overt signs of toxicity, influences cortical glutamate extracellular levels in adult (90-day old) rats. Dam weight gain, pregnancy length and litter size at birth were not significantly affected by prenatal treatment with WIN. Basal and K(+) -evoked dialysate glutamate levels were lower in the cerebral cortex of adult rats exposed to WIN during gestation than in those born from vehicle-treated mothers. In both group of animals WIN (0.1 mg/kg, i.p.) increased dialysate glutamate levels. However, while the blockade of the CB(1) receptors with the selective receptor antagonist SR141716A completely counteracted the WIN-induced increase in those rats exposed to vehicle during gestation, it failed to antagonise the increase in those born from WIN-treated dams. These findings suggest that prenatal exposure to the CB(1) receptor agonist WIN, at a concentration which is not associated with gross malformations and/or overt signs of toxicity, induces permanent alterations in cortical glutamatergic function. The possibility that these effects might underlie, at least in part, some of the cognitive deficits affecting the offspring of marijuana users is discussed.

The development of an easy and inexpensive immunoassay to measure the limited quantities of endogenous cannabinoids found in the body would be beneficial for both cannabinoid researchers and clinicians. This report describes the hapten design and carrier molecule strategy that we used to generate a panel of monoclonal antibodies (mAB) to the endogenous cannabinoid anandamide (N-arachidonylethanolamide, AEA). We designed and successfully prepared a hapten, N-arachidonyl-7-amino-6-hydroxy-heptanoic acid (AHA), which retained the basic characteristic features of anandamide-the carboxamide, the hydroxyl and the lipophilic arachidonyl moiety with its skipped double bond system, while still allowing attachment to protein. In addition, a secondary alcohol structure was added to reduce the potential for biological hydrolysis of the hapten. Because of the diverse responses obtained after coupling this hapten to four different carriers, we determined that the type of carrier molecule used was particularly important for generating anti-anandamide antibodies. Described in this report are the characteristics of a panel of 11 mAB, generated from four separate fusions, with a range of relative affinities and cross reactivities. Excellent selectivity for anandamide vs. two other endogenous cannabinoids and arachidonic acid was achieved this strategy (cross-reactivities <5%). In addition, at least one mAB maintained specificity for anandamide compared to two very closely related fatty acid amide molecules. However, the IC(50) values in a standard enzyme-linked immunosorbent assay (ELISA) format (ca. 2-3 microM) indicate that improvement in antibody affinities or assay format will be required for an immunoassay to measure endogenous levels. Such work is underway.


Both inhibitory (satiety) and stimulatory (orexigenic) factors from the gastrointestinal tract regulate food intake. In the case of the satiety hormone cholecystokinin (CCK), these effects are mediated via vagal afferent neurons. We now report that vagal afferent neurons expressing the CCK-1 receptor also express cannabinoid CB1 receptors. Retrograde tracing established that these neurons project to the stomach and duodenum. The expression of CB1 receptors determined by RT-PCR, immunohistochemistry and in situ hybridization in rat nodose ganglia was increased by withdrawal of food for > or =12 hr. After refeeding of fasted rats there was a rapid loss of CB1 receptor expression identified by immunohistochemistry and in situ hybridization. These effects were blocked by administration of the CCK-1 receptor antagonist lorglumide and mimicked by administration of CCK to fasted rats. Because CCK is a satiety factor that acts via the vagus nerve and CB1 agonists stimulate food intake, the data suggest a new mechanism modulating the effect on food intake of satiety signals from the gastrointestinal tract.


Cannabinoids induce apoptosis on glioma cells via stimulation of ceramide synthesis de novo while do not affect viability of primary astrocytes. Here we show that incubation with Delta 9-tetrahydrocannabinol did not induce ceramide accumulation on astrocytes although incubation of these cells in a serum-free medium (with or without cannabinoids) led to stimulation of ceramide synthesis de novo and sensitization to oxidative stress. Thus, treatment with H 2O 2 induced apoptosis of 5-day serum-deprived astrocytes and this effect was abrogated by pharmacological blockade of ceramide synthesis de novo. The sensitizing effect of ceramide accumulation may depend on p38 MAPK activation rather than on other ceramide targets. Finally, a protective role of cannabinoids on astrocytes is shown as long-term incubation with cannabinoids prevented H 2O 2-induced loss of viability in a CB 1 receptor-dependent manner. In summary, our data show that while challenge of glioma cells with cannabinoids induce accumulation of de novo-synthesized ceramide and apoptosis, long-term treatment of astrocytes with these compounds not only does not stimulate this pathway but abrogates the sensitizing effects of ceramide accumulation.

Delta(9)-tetrahydrocannabinol (THC) inhibits several immunologic functions of macrophages. THC's impact on peritoneal macrophages to deliver costimulatory signals to a helper T cell hybridoma was investigated by T cell interleukin-2 production stimulated with immobilized anti-CD3 antibody. The drug's inhibition of costimulatory activity depended on the macrophages. THC decreased costimulation provided by peritoneal cells elicited with polystyrene beads and thioglycollate, but the drug had no influence with macrophages elicited with thioglycollate alone. Bead administration induced CB2 mRNA expression in macrophages, while CB1 mRNA was not detected. Although inhibition was associated with functional heat-stable antigen, a costimulatory molecule, on macrophages, THC exposure did not alter cell surface heat-stable antigen expression. Inhibition by THC and anti-heat-stable antigen antibody was not additive suggesting the inhibitory mechanisms may overlap. Cannabinoid suppression was stereoselective; low affinity synthetic isomer CP56,667 did not diminish the T cell response. CB1-selective antagonist SR141716A completely reversed, and CB2-selective antagonist SR144528 partially blocked THC's inhibition. Both antagonists appeared to behave as inverse agonists in a receptor-selective manner. Although T cells expressed a low level of CB2 mRNA, neither THC nor SR141716A affected T cell activation in a system independent of macrophages, while SR144528 was inhibitory. High affinity synthetic agonist CP55,940, but not partial agonist THC, impaired costimulation by macrophages from mice lacking CB2 receptor. Although CB1 mRNA was not detected in CB2 null macrophages, CP55,940 reversed the inverse agonist activity of SR141716A. Hence, CB2 and possibly another receptor subtype may be involved in mediating cannabinoid suppression of macrophage costimulation.


In the present research the interaction between the endogenous ligand for the cannabinoid CB1 receptor anandamide (arachidonylethanolamide) and morphine in memory consolidation was investigated. Four sets of experiments were carried out with CD1 mice tested in a one-trial inhibitory avoidance task. The drugs were administered intraperitoneally after training of the animals in the apparatus. In the first set of experiments morphine (0.3 or 0.5, but not 0.15mg/kg) or anandamide (3 or 6 but not 1.5 mg/kg) dose-dependently impaired memory consolidation. In the second set of experiments the administration of an otherwise ineffective dose of anandamide (1.5mg/kg) enhanced the memory impairment exerted by morphine (0.3 and 0.5mg/kg) when the drugs were injected immediately after training. In the third set of experiments the combined treatments of anandamide (1.5mg/kg) and morphine (0.5mg/kg) 2h after training were ineffective showing that the effects observed on performance following immediate postraining administration of anandamide and morphine combinations were reflecting direct influences on memory consolidation. In the fourth set of experiments otherwise ineffective doses of the D1 DA receptor agonist SKF 38393 or the D2 DA receptor agonist LY 171555 antagonized the memory impairment produced by anandamide and morphine in combination, suggesting a possible involvement of dopaminergic mechanisms.


Activation of CB1 cannabinoid receptors in the cerebellum acutely depresses excitatory synaptic transmission at parallel fibre-Purkinje cell synapses by decreasing the probability of glutamate release. This depression involves the activation of presynaptic 4aminopyridine-sensitive K+ channels by CB1 receptors, which in turn inhibits presynaptic Ca2+ influx controlling glutamate release at these synapses. Using rat cerebellar frontal slices and fluorometric measures of presynaptic Ca2+ influx evoked by stimulation of parallel fibres with the fluorescent dye-Fluo4FF, we tested whether the CB1 receptor-mediated inhibition of these influx also involves a direct inhibition of presynaptic voltage gated calcium channels. Since various physiological effects of CB1 receptors appear to be mediated through the activation of PTX-sensitive proteins, including inhibition of adenylate cyclases, activation of mitogen-activated
protein kinases (MAPK) and activation of G protein-gated inwardly rectifying K+ channels, we also studied the potential involvement of these intracellular signal transduction pathways in the cannabinoid-mediated depression of presynaptic Ca2+ influx. The present study demonstrates that the molecular mechanisms underlying the CB1 inhibitory effect involve the activation of the PTX-sensitive Gi/Go subclass of G proteins, independently of any direct effect on presynaptic Ca2+ channel (N-, P/Q- and R-(SNX-482 sensitive) types) or on adenylate cyclase or MAPK activity, but do require the activation of G protein-gated inwardly rectifying (Ba2+ and tertiapine Q-sensitive) K+ channels, in addition to 4 aminopyridine-sensitive K+ channels.


Modulation of the endocannabinoid system might be useful in treating Parkinson's disease. Here, we show that systemic administration of N-(4-hydroxyphenyl)-arachidonamide (AM404), a cannabinoid modulator that enhances anandamide (AEA) availability in the biophase, exerts antiparkinsonian effects in 6-hydroxydopamine-lesioned rats. Local injections of AM404 into denervated striata reduced parkinsonian motor asymmetries, these effects being associated with the reduction of D(2) dopamine receptor function together with a positive modulation of 5-HT(1B) serotonin receptor function. Stimulation of striatal 5-HT(1B) receptors alone was observed to ameliorate parkinsonian deficits, supporting the fact that AM404 exerts antiparkinsonian effects likely through stimulation of striatal 5-HT(1B) serotonin receptor function. Hence, modulation of cannabinoid function leading to enhancement of AEA in the biophase might be of therapeutic value in the control of symptoms of Parkinson's disease. On the other hand, reduced levels of N-acyl-transferase (AEA precursor synthesizing enzyme), without changes in fatty acid amidohydrolase (AEA degradative enzyme), were detected in denervated striata in comparison with intact striata. This finding reveals the presence of a homeostatic striatal mechanism emerging after dopaminergic denervation likely tending to enhance low dopamine tone. *Neuropsychopharmacology* advance online publication, 10 March 2004; doi:10.1038/sj.npp.1300407


We hypothesized that ethanol (EtOH) might act through the endocannabinoid system to inhibit luteinizing hormone-releasing hormone (LHRH) release. Therefore, we examined the mechanism by which EtOH and anandamide (AEA), an endogenous cannabinoid, inhibit LHRH release from incubated medial basal hypothalamic explants. In previous work, we demonstrated that EtOH inhibits the N-methyl-d-aspartic acid-stimulated release of LHRH by increasing the release of two neurotransmitters: beta-endorphin and gamma-aminobutyric acid (GABA). In the present work, bicuculline, a GABAergic antagonist, completely prevented the inhibition of AEA (10(-9)M) on N-methyl-d-aspartic acid-induced LHRH release, but naltrexone, a micro-opioid receptor antagonist, had no effect. AEA also significantly increased GABA release but had no effect on beta-endorphin release. Therefore, AEA could inhibit LHRH release by increasing GABA but not beta-endorphin release. Because EtOH and AEA acted similarly to inhibit LHRH release, we investigated whether both substances would affect the adenylate cyclase activity acting through the same GTP-coupled receptors, the cannabinoid receptors 1 (CB1-rs). AEA and EtOH (10(-1)M) reduced the forskolin-stimulated accumulation of cAMP, but AM251, a specific antagonist of CB1-r, significantly blocked that inhibition. Additionally we investigated whether CB1-r is involved in the inhibition of LHRH by EtOH and AEA. AEA and EtOH reduced forskolin-stimulated LHRH release, but AM251 significantly blocked that inhibition. Also, we demonstrated that EtOH did not act by increasing AEA synthase activity to inhibit LHRH release in our experimental conditions. Therefore, our results indicate that EtOH inhibits the release of LHRH acting through the endocannabinoid system.

The antinociceptive effects of Delta9-tetrahydrocannabinol (Delta9-THC) have been widely described; however, its therapeutic potential may be limited by secondary effects. We investigated whether coadministration of low doses of cannabinoids or cannabinooids and morphine produced antinociception in the absence of side-effects. Effects of preadministration (i.p.) of Delta9-THC (1 or 2.5 mg/kg), cannabidiol (5 mg/kg), morphine (2 mg/kg), Delta9-THC + morphine, Delta9-THC + cannabidiol or vehicle on formalin-evoked nociceptive behaviour were studied over 60 min. Trunk blood and brains were collected 60 min after formalin injection and assayed for corticosterone and tissue levels of monoamines and metabolites, respectively. Drug effects on locomotor activity, core body temperature and grooming were assessed. Delta9-THC reduced both phases of formalin-evoked nociceptive behaviour, enhanced the formalin-evoked corticosterone response and increased the 4-hydroxy-3-methoxyphenylglycol : noradrenalin ratio in the hypothalamus. Cannabidiol alone had no effect on these indices and did not modulate the effects of Delta9-THC. Morphine reduced both phases of formalin-evoked nociceptive behaviour. Coadministration of Delta9-THC and morphine reduced the second phase of formalin-evoked nociceptive behaviour to a greater extent than either drug alone, and increased levels of thalamic 5-hydroxytryptamine. While the antinociceptive effects of Delta9-THC and morphine alone occurred at doses devoid of effects on locomotor activity, coadministration of Delta9-THC and morphine inhibited locomotor activity. In conclusion, coadministration of a low dose of morphine, but not cannabidiol, with Delta9-THC, increased antinociception and 5-hydroxytryptamine levels in the thalamus in a model of persistent nociception. Nevertheless, these enhanced antinociceptive effects were associated with increased secondary effects on locomotor activity.


The use of cannabis is illicit in numerous countries, and the increasing consumption has led to a multiplication of scientific studies. New methods of planar chromatography such as automated multiple development (AMD) and optimum performance laminar chromatography (OPLC) techniques can be used as a substitute for the traditional thin-layer chromatography for the identification and quantitation of the Indian hemp components. Each method offers its own advantage: high resolution with neither diffusion nor spot stretching for AMD and speed, efficiency, and the possibility of working in the semipreparative mode for OPLC.


In spite of the addictive properties of cannabinoids, under certain circumstances, they can evoke strong anxiogenic and aversive responses in humans and in animal tests of anxiety. Effects of different doses of CP 55,940 (10, 20, and 40 microg/kg) were tested in the low-light, familiar (LF) apparatus test condition of the social interaction test. The 40-microg/kg dose of CP 55,940 significantly decreased the time spent in social interaction, indicating an anxiogenic effect. This dose also had an independent effect of reducing locomotor activity. In rats tested undrugged 24 h after testing with 40 microg/kg, there was a significant anxiogenic effect, indicating conditioned anxiety. The group of rats injected with 40 microg/kg immediately after the social interaction test showed an unexpected significant anxiolytic effect when tested undrugged 24 h later. In an additional experiment, rats were tested in the high-light, familiar (HF) apparatus test condition after 10 or 40 microg/kg, and only those that were tested after 40 microg/kg showed an anxiogenic effect on the test day and a conditioned anxiogenic effect when tested undrugged 24 h later. Once again, those injected with 40 microg/kg after the social interaction test displayed an anxiolytic effect when tested undrugged 24 h later. We provide the first evidence for unconditioned and conditioned anxiogenic-like responses to a cannabinoid agonist in the social interaction test.

In the current study, a possible interaction between spinal cord dorsal horn cannabinoid and mGlu5 receptors was evaluated in rats with a peripheral nerve injury. Following unilateral loose ligation of a sciatic nerve, rats developed decreased withdrawal thresholds to noxious pressure (mechanical hyperalgesia) of the ligated but not the unoperated contralateral hind paw. Systemic (subcutaneous) injection of synthetic cannabinoid agonist WIN55,212-2 increased withdrawal thresholds of both the ligated and the unoperated hind paw. Systemic injection of 2-methyl-6-(phenylethynyl)pyradine (MPEP), an antagonist selective for the mGlu5 receptor, did not alter the antinociceptive and antihyperalgesic effects of systemic WIN55,212-2. Intrathecal (i.t.) injection of WIN55,212-2 increased thresholds of the ligated but not the unoperated hind paw. Intrathecal injection of MPEP reversed the antihyperalgesic effect of i.t. WIN55,212-2. Neither systemic nor i.t. injection of MPEP alone altered withdrawal thresholds. These data suggest that the antihyperalgesic effect of WIN55,212-2 is mediated through an interaction with spinal mGlu5 receptors.


Cannabinoids, the active components of marijuana and their endogenous counterparts were reported as useful analgetic agents to accompany primary cancer treatment by preventing nausea, vomiting, and pain and by stimulating appetite. Moreover, they have been shown to inhibit cell growth and to induce apoptosis in tumor cells. Here, we demonstrate that anandamide, Delta(9)-tetrahydrocannabinol (THC), HU-210, and Win55,212-2 promote mitogenic kinase signaling in cancer cells. Treatment of the glioblastoma cell line U373-MG and the lung carcinoma cell line NCI-H292 with nanomolar concentrations of THC led to accelerated cell proliferation that was completely dependent on metalloprotease and epidermal growth factor receptor (EGFR) activity. EGFR signal transactivation was identified as the mechanistic link between cannabinoid receptors and the activation of the mitogen-activated protein kinases extracellular signal-regulated kinase 1/2 as well as prosurvival protein kinase B (Akt/PKB) signaling. Depending on the cellular context, signal cross-communication was mediated by shedding of proAmphiregulin (proAR) and/or proHeparin-binding epidermal growth factor-like growth factor (proHB-EGF) by tumor necrosis factor alpha converting enzyme (TACE/ADAM17). Taken together, our data show that concentrations of THC comparable with those detected in the serum of patients after THC administration accelerate proliferation of cancer cells instead of apoptosis and thereby contribute to cancer progression in patients.


Cannabinoids include not only plant-derived compounds (of which delta9-tetrahydrocannabinol is the primary psychoactive ingredient of cannabis), but also synthetic agents and endogenous substances termed endocannabinoids which include anandamide (2-arachidonoylethanolamide) and 2-arachidonoylglycerol. Cannabinoids act on specific, G-protein-coupled, receptors which are currently divided into two types, CB1 and CB2. Relatively selective agonists and antagonists for these receptors have been developed, although one agent (SR141716A) widely used as an antagonist at CB1 receptors has non-cannabinoid receptor-mediated effects at concentrations which are often used to define the presence of the CB1 receptor. Both cannabinoid receptors are primarily coupled to Gi/o proteins and act to inhibit adenylly cyclase. Stimulation of CB1 receptors also modulates the activity of K+ and Ca2+ channels and of protein kinase pathways including protein kinase B (Akt) which might mediate effects on apoptosis. CB1 receptors may activate the extracellular signal-regulated kinase cascade through ceramide signalling. Cannabinoid actions on the cardiovascular system have been widely interpreted as being mediated by CB1 receptors although there are a growing number of observations, particularly in isolated heart and blood vessel preparations, that suggest
that other cannabinoid receptors may exist. Interestingly, the currently identified cannabinoid receptors appear to be related to a wider family of lipid receptor, those for the lysophospholipids, which are also linked to Gi/o protein signalling. Anandamide also activates vanilloid VR1 receptors on sensory nerves and releases the vasoactive peptide, calcitonin gene-related peptide (CGRP), which brings about vasodilatation through its action on CGRP receptors. Current evidence suggests that endocannabinoids have important protective roles in pathophysiological conditions such as shock and myocardial infarction. Therefore, their cardiovascular effects and the receptors mediating them are the subject of increasing investigative interest.


This investigation examined the effects, in female rats, of a Pavlovian conditioning paradigm on the development of tolerance to hypolocomotion induced by the cannabinoid agonist HU-210. Rats were administered HU-210 and placebo in either an associative or a nonassociative fashion. The results indicated that rats in the associative paradigm developed tolerance significantly faster than those in the nonassociative group (p < 0.03). Subsequently, once tolerance had developed, the associative group of rats was administered HU-210 and placebo in the opposite environments. There were no differences found in locomotion between the CS+ and CS- environments following administration of HU-210. However, when the placebo was administered in the CS+ environment, there was a trend towards increased activity levels (p = 0.06), suggesting withdrawal-like behavior. These findings indicate that the underlying physiological mechanisms of tolerance development in the cannabinoid system are hastened by conditioning, but that these physiological alterations are not contingent upon the associative parameters used for drug administration.


Abstract Alzheimer's disease is widely held to be associated with oxidative stress due, in part, to the membrane action of beta-amyloid peptide aggregates. Here, we studied the effect of cannabidiol, a major non-psychoactive component of the marijuana plant (Cannabis sativa) on beta-amyloid peptide-induced toxicity in cultured rat pheochromocytoma PC12 cells. Following exposure of cells to beta-amyloid peptide (1 micro g/mL), a marked reduction in cell survival was observed. This effect was associated with increased reactive oxygen species (ROS) production and lipid peroxidation, as well as caspase 3 (a key enzyme in the apoptosis cell-signalling cascade) appearance, DNA fragmentation and increased intracellular calcium. Treatment of the cells with cannabidiol (10(-7)-10(-4)m) prior to beta-amyloid peptide exposure significantly elevated cell survival while it decreased ROS production, lipid peroxidation, caspase 3 levels, DNA fragmentation and intracellular calcium. Our results indicate that cannabidiol exerts a combination of neuroprotective, anti-oxidative and anti-apoptotic effects against beta-amyloid peptide toxicity, and that inhibition of caspase 3 appearance from its inactive precursor, pro-caspase 3, by cannabidiol is involved in the signalling pathway for this neuroprotection.

migration of colon carcinoma cells is inhibited by the CB(1)-R. The SDF-1-induced migration of CD8(+) T lymphocytes was, however, inhibited via the CB(2)-R, as shown by using the specific agonist JWH 133. Therefore, specific inhibition of tumor cell migration via CB(1)-R engagement might be a selective tool to prevent metastasis formation without depreciatory effects on the immune system of cancer patients.


Cannabinoids inhibit excitatory synaptic transmission between hippocampal neurons in culture. Delta(9)-tetrahydrocannabinol (THC), the principal psychoactive component in marijuana, acts as a partial agonist at these synapses. Thus, THC inhibited but did not block synaptic transmission when applied alone and, when applied in combination with WIN552212-2, it partially reversed the effects of this full agonist. Here, we address the question of how THC might interact with endocannabinoid signaling. Reducing the extracellular Mg(2+) concentration to 0.1 mM elicited a repetitive pattern of glutamatergic synaptic activity that produced intracellular Ca(2+) concentration spikes that were measured by indo-1-based microfluorimetry. The endocannabinoid, 2-arachidonyl glycerol (2-AG) produced a concentration-dependent and complete inhibition of spike frequency with an EC(50) of [Formula: see text]. 2-AG (1 microM) inhibition of spiking was blocked by SR141716A (1 microM). THC (100 nM) antagonized the actions of 2-AG producing a parallel shift in the concentration-response relationship for 2-AG (EC(50) of [Formula: see text]). The attenuation of 2-AG (1 microM) inhibition of synaptic activity by THC was concentration-dependent with an IC(50) of [Formula: see text]. These results demonstrate that THC can antagonize endocannabinoid signaling. Thus, the effects of THC on synaptic transmission are predicted to depend on the level of endocannabinoid tone.


Anandamide (N-arachidonylethanolamine, AEA) is a major endocannabinoid, known to impair mouse pregnancy and embryo development and to induce apoptosis in blastocysts. Here we show that mouse blastocysts rapidly (within 30 min of culture) release a soluble compound, that increases by approximately 2.5-fold the activity of AEA hydrolase (fatty acid amide hydrolase, FAAH) present in the mouse uterus, without affecting FAAH gene expression at the translational level. This 'FAAH activator' was produced by both trophoblast and inner cell mass cells, and its initial biochemical characterization showed that it was fully neutralized by adding lipase to the blastocyst-conditioned medium (BCM), and was potentiated by adding trypsin to BCM. Other proteases, phospholipases A2, C or D, DNase I or RNAse A were ineffective. BCM did not affect the AEA-synthesizing phospholipase D, the AEA-binding cannabinoid receptors, or the selective AEA membrane transporter in mouse uterus. The FAAH activator was absent in uterine fluid from pregnant mice and could not be identified with any factor known to be released by blastocysts. In fact, platelet-activating factor inhibited non-competitively FAAH in mouse uterus extracts, but not in intact uterine horns, whereas leukotriene B4 or prostaglandins E2 and F2alpha had no effect. Overall, it can be suggested that blastocysts may protect themselves against the noxious effects of uterine endocannabinoids by locally releasing a lipid able to cross the cell membranes and to activate FAAH. The precise molecular identity of this activator, the first ever reported for FAAH, remains to be elucidated.


It has been suggested that cannabimimetic drugs could be of interest in the treatment of several nervous disorders. Thus, it is important to analyse the distribution and properties of cannabinoid (CB) receptors directly in human brain. As postmortem human tissue is subjected to the effects of several biological variables, we have analyzed by autoradiography the influence of age, postmortem delay and freezing storage period (at -25 degrees C) on two parameters corresponding to cannabinoid CB(1) receptors in human frontal cortex: receptor density and
A significant decrease in the amount of both receptor density and agonist-stimulated G-protein activity was observed with age, revealing a mean reduction of about 10% per decade. In contrast, no significant correlations were found with postmortem delay either for CB(1) receptors density or functionality. Finally, both parameters (receptor density and [(35)S]GTPgammaS response) were significantly reduced with freezing storage period at -25 degrees C in frontal cortical layers. Non-linear analysis of these data yielded values between 12 and 24 months of storage for a 50% reduction. In conclusion, when studying CB(1) receptor properties in human brain samples, a careful analysis (and matching) for variables such as age and freezing storage period has to be carried out.


Systemic administration of a cannabinoid agonist produces antinociception through the activation of pain modulating neurons in the rostral ventromedial medulla (RVM). The aim of the present study was to determine how a cannabinoid receptor agonist acting directly within the RVM affects neuronal activity to produce behaviorally measurable antinociception. In lightly anesthetized rats, two types of RVM neurons have been defined based on changes in tail flick-related activity. On-cells increase firing (on-cell burst), whereas off-cells cease firing (off-cell pause), just prior to a tail flick. The cannabinoid receptor agonist WIN55,212-2 was microinfused directly into the RVM while monitoring tail flick latencies and on- and off-cell activity. Microinfusion of WIN55,212-2 (2.0 microg/microl and 0.4 microg/microl) reduced the tail flick-related on-cell burst, decreased the duration of the off-cell pause, and increased off-cell ongoing activity. These changes were prevented by co-infusing the CB1 receptor antagonist, SR141716A (0.35 microg/microl), with WIN55,212-2 (0.4 microg/microl). Furthermore, 2.0 microg/microl WIN55,212-2 delayed the onset of the off-cell pause and increased tail flick latencies. Microinfusion of WIN55,212-2 to brain regions caudal or lateral to the RVM had no effect on RVM neuronal activity or tail flick latencies. These results indicate that cannabinoids act directly within the RVM to affect off-cell activity, providing one mechanism by which cannabinoids produce antinociception.


Cannabinoids have been shown to influence food intake, and until recently, the neural pathways mediating these effects have remained obscure. It has been previously shown that intracerebroventricular injection of delta-9-tetrahydrocannabinol (Delta(9)-THC) causes increased consumption of palatable foods in rats, and we postulated the involvement of the hindbrain in this cannabinoid-induced food intake. Cannulated rats (both female and male groups) trained to consume sweetened condensed milk received either lateral or fourth ventricle injections of CP 55,940 and were presented with sweetened condensed milk 15 min after injection. Rats were injected over a range of doses between 100 pg and 10 microg per rat. Milk intake was recorded for a total of 3 h. Lateral ventricle injection of CP 55,940 increased milk intake at doses in the microgram range. However, CP 55,940 was effective in increasing food intake at nanogram doses when injected into the fourth ventricle. Finally, male rats appeared to be more sensitive to CP 55,940 than female rats inasmuch as milk consumption was increased at the 1 ng dose in male rats, whereas only the 10 ng dose was effective in females. These results indicate that CP 55,940 may act in the hindbrain to influence feeding behavior in rats.


**AIMS:** The aim of this study was to examine the effects of chronic ethanol consumption in cannabinoid CB(1) receptor gene expression in Wistar rats. **METHODS:** Rats were exposed to a bottle containing a solution of ethanol (10% v/v) and saccharin (0.25% w/v) for 52 days. At the end of this period, rats were killed by decapitation and cannabinoid CB(1) receptor gene expression was measured by in situ hybridization histochemistry. **RESULTS:** Our results indicated that chronic ethanol consumption reduced cannabinoid CB(1) receptor gene expression in caudate-putamen (CPU) (24%), ventromedial nucleus of the hypothalamus (VMN) (43%), CA1...
(27%) and CA2 (22%) fields of hippocampus and increased dentate gyrus (DG) (30%).

CONCLUSIONS: These results reveal for the first time that prolonged exposure to ethanol produces marked alterations in cannabinoid CB(1) receptor gene expression in selected regions of the rat brain, supporting an interaction between ethanol consumption and the endogenous cannabinoid receptor. Furthermore, these findings suggest that cannabinoid CB(1) receptor may be considered as a new pharmacological target for treating ethanol dependence.


Peripheral cannabinoids have been shown to suppress nociceptive neurotransmission in a number of behavioral and neurophysiological studies. It is not known, however, whether cannabinoids exert this action through direct interactions with nociceptors in the periphery and/or if other processes are involved. To gain a better understanding of the direct actions of cannabinoid-vanilloid agonists on sensory neurons, we examined the effects of these compounds on trigeminal ganglion (TG) neurons in vitro. AEA (EC50=11.0 micro M), NADA (EC50=857 nM) and arachidonyl-2-chloroethylamide ACEA (EC50=14.0 micro M) each evoked calcitonin gene-related peptide (CGRP) release from TG neurons. The TRPV1 antagonists iodo-resiniferatoxin (I-RTX) and capsazepine (CPZ) each obtunded AEA-, NADA-, ACEA- and capsaicin (CAP)-evoked CGRP release with individually equivalent IC50's for each of the compounds (I-RTX IC50 range=2.6-4.0 nM; CPZ IC50 range=523-1140 micro M). The pro-inflammatory mediator prostaglandin E2 significantly increased the maximal effect of AEA-evoked CGRP release without altering the EC50. AEA, ACEA and CAP stimulated cAMP accumulation in TG neurons in a calcium- and TRPV1-dependent fashion. Moreover, the protein kinase inhibitor staurosporine significantly inhibited AEA- and CAP-evoked CGRP release. The pungency of AEA, NADA, ACEA and CAP in the rat eye-wipe assay was also assessed. Interestingly, when applied intraocularly, NADA or CAP each produced nocifensive responses, while AEA or ACEA did not. Finally, the potential inhibitory effects of these cannabinoids on TG nociceptors were evaluated. Neither AEA nor ACEA decreased CAP-evoked CGRP release. Furthermore, neither of the cannabinoid receptor type 1 antagonists SR141716A nor AM251 had any impact on either basal or CAP-evoked CGRP release. AEA also did not inhibit 50 mM K(+) evoked CGRP release and did not influence bradykinin-stimulated inositol phosphate accumulation. We conclude that the major action of AEA, NADA and ACEA on TG neurons is excitatory, while, of these, only NADA is pungent. These findings are discussed in relation to our current understanding of interactions between the cannabinoid and vanilloid systems and nociceptive processing in the periphery.


Acute Delta(9)-tetrahydrocannabinol (THC) injection increased ERK pathway (ERK, pCREB, and c-fos) mostly in the caudate putamen and cerebellum. This effect underwent to homeostatic adaptation after chronic treatment. Moreover, chronic THC exposure induced increases in the ERK cascade (ERK, pCREB, and Fos B) in the prefrontal cortex and hippocampus, suggesting that different neuronal circuits seem to be involved in the early phase and late phase of exposure. The involvement of ERK pathway in cannabinoid chronic exposure was also confirmed in Ras-GRF1 knock out mice, a useful model where cannabinoid-induced ERK activation is lost. In fact, Ras-GRF1 ko mice did not develop tolerance to THC analgesic and hypolocomotor effect. Our data suggest that ERK cascade could play a pivotal role in the induction of synaptic plasticity due to cannabinoid chronic exposure.


2-Arachidonoylglycerol (2-AG) is an endogenous cannabinoid that binds to CB1 and CB2 cannabinoid receptors, inducing cannabimimetic effects. However, the cannabimimetic effects of 2-AG are weak in vivo due to its rapid enzymatic hydrolysis. The enzymatic hydrolysis of 2-AG has been proposed to mainly occur by monoglyceride lipase (monoacylglycerol lipase). Fatty acid
amide hydrolase (FAAH), the enzyme responsible for the hydrolysis of N-arachidonoyl ethanolamide (AEA), is also able to hydrolyse 2-AG. In the present study, we investigated the hydrolysis of endocannabinoids in rat cerebellar membranes and observed that enzymatic activity towards 2-AG was 50-fold higher than that towards AEA. Furthermore, various inhibitors for 2-AG hydrolase activity were studied in rat cerebellar membranes. 2-AG hydrolysis was inhibited by methyl arachidonoylfluorophosphonate, hexadecylsulphonyl fluoride and phenylmethylsulphonyl fluoride with IC(50) values of 2.2nM, 241nM and 155microM, respectively. Potent FAAH inhibitors, such as OL-53 and URB597, did not inhibit the hydrolysis of 2-AG, suggesting that 2-AG is inactivated in rat cerebellar membranes by an enzyme distinct of FAAH. The observation that the hydrolysis of 1(3)-AG and 2-AG occurred at equal rates supports the role of MGL in 2-AG inactivation. This enzyme assay provides a useful method for future inhibition studies of 2-AG degrading enzyme(s) in brain membrane preparation having considerably higher MGL-like activity when compared to FAAH activity.


Preanalytical stability of a drug and its major metabolites is an important consideration in pharmacokinetic studies or whenever the analyte pattern is used to estimate drug habits. Firstly, the stability of free and glucuronidated 11-nor-delta9-tetrahydrocannabinol-9-carboxylic acid (THCCOOH, THCCOOglu) in authentic urine samples was investigated. Random urine samples of cannabis users (n = 38) were stored at -20, 4, and 20 degrees C up to 15 days and up to 5 days at 40 degrees C, and alterations of the analyte pattern during storage were followed by liquid chromatography-tandem mass spectrometry. Secondly, the influence of pH (range 5.0-8.0) on the stability of the analytes was studied using spiked urine to elucidate the results obtained from authentic samples. In authentic urine samples, the initial pH ranged from 5.1 to 8.8. The glucuronide was found to be highly labile at a storage temperature of 4 degrees C and above. Initially, 18 urine samples tested positive for THCCOOH. After 2 days storage at 20 degrees C, THCCOOH was detectable in a further 4 samples, and 7 more samples tested positive for THCCOOH (5-81 ng/mL) after 15 days. Depending on time and temperature, the glucuronide concentration decreased, resulting in an increase of THCCOOH concentration. However, a loss in mean total THCCOOH concentration was found, which was significantly higher in deteriorated samples than in samples without signs of deterioration after 15 days of storage at 20 degrees C. In the drug-free urine sample separately spiked with THCCOOglu or THCCOOH, the investigations on the stability of the target analytes at various pH values revealed that THCCOOH was stable at pH 5.0. At higher pH values, its concentration slightly decreased with time, and about 69% of the initial THCCOOH concentration was still present at pH 8.0 on day 5. THCCOOglu concentrations rapidly decreased with increasing pH value. For example, only 72% of the initial THCCOOglu concentration could be detected at pH 5.0 on day 1. Degradation of the glucuronide resulted in formation of THCCOOH, which was observed even at pH 5.0. In light of the present findings, advanced forensic interpretations based on the presence of THCCOOH or the pattern of THCCOOH and THCCOOglu in stored urine samples seems questionable.

antagonist AM251. However, ([3]H)-DA release was not influenced in rat neocortex. In human tissue, the estimated endocannabinoid concentration in the biophase of the release-modulating CB1 receptors was 1.07 nM, expressed in CP55.940 units. K(+-)evoked ([3]H)-DA release in the presence of tetrodotoxin (TTX) was strongly inhibited by CP55.940 in humans, but not in rats. In human tissue, CP55.940 inhibited forskolin-stimulated cAMP accumulation (IC50 20.89 nM, Imax 35%). AM251 blocked this effect and per se increased forskolin-stimulated cAMP accumulation by approximately 20%. In conclusion, cannabinoids modulate ([3]H)-DA release and adenylyl cyclase activity in the human neocortex. CB1 receptors are located on dopaminergic nerve terminals and seem to be tonically activated by endocannabinoids.


OBJECTIVE: To explore the antiarthritic potential of a novel synthetic cannabinoid acid, Hebrew University-320 (HU-320), in the DBA/1 mouse model of arthritis, and to investigate in vitro antiinflammatory and immunosuppressive effects of HU-320 on macrophages and lymphocytes. METHODS: DBA/1 mice were immunized with bovine type II collagen (CII) to induce arthritis and then injected intraperitoneally daily with HU-320. The effects of treatment on arthritic changes in hind feet were assessed clinically and histologically, and draining lymph node responses to CII were assayed. Murine splenic and human blood lymphocytes were cultured to study the effect of HU-320 on polyclonal mitogenic stimulation. Macrophage cultures were set up to evaluate in vitro effects of HU-320 on production of tumor necrosis factor alpha (TNF alpha) and reactive oxygen intermediates (ROIs). The effect of HU-320 administration on lipopolysaccharide-induced serum TNF levels was assayed using C57BL/6 mice. Bioactive TNF production was measured using BALB/c clone 7 target cells. Evaluation of HU-320 psychoactivity was performed using established laboratory tests on Sabra mice. RESULTS: Systemic daily administration of 1 and 2 mg/kg HU-320 ameliorated established CII-induced arthritis. Hind foot joints of treated mice were protected from pathologic damage. CII-specific and polyclonal responses of murine and human lymphocytes were down-modulated. HU-320 inhibited production of TNF from mouse macrophages and of ROIs from RAW 264.7 cells and suppressed the rise in serum TNF level following endotoxin challenge. HU-320 administration yielded no adverse psychotropic effects in mice. CONCLUSION: Our studies show that the novel synthetic cannabinoid acid HU-320 has strong antiinflammatory and immunosuppressive properties while demonstrating no psychoactive effects. The profound suppressive effects on cellular immune responses and on the production of proinflammatory mediators all indicate its usefulness as a novel nonpsychoactive, synthetic antiinflammatory product.


Previous experiments with the mouse vas deferens have shown that cannabidiol produces surmountable antagonism of cannabinoid CB(1) receptor agonists at concentrations well below those at which it binds to cannabinoid CB(1) receptors and antagonizes alpha(1)-adrenoceptor agonists insurmountably. It also enhances electrically evoked contractions of this tissue. We have now found that subtle changes in the structure of cannabidiol markedly influence its ability to produce each of these effects, suggesting the presence of specific pharmacological targets for this non-psychoactive cannabinoid. Our experiments were performed with cannabidiol, 6?-azidohex-2?-yne-cannabidiol, abnormal-cannabidiol and 2?-monomethoxy- and 2?,6?-dimethoxy-cannabidiol. Of these, 6?-azidohex-2?-yne-cannabidiol was as potent as cannabidiol in producing surmountable antagonism of (R)-(+)-(2,3-dihydro-5-methyl-3(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1, 4-benzoxazin-6-yl]-1-naphthalenylmethanone (R(+-)WIN55212) in vasa deferentia. However, it produced this antagonism with a potency that matched its cannabinoid CB(1) receptor affinity, suggesting that, unlike cannabidiol, it is a competitive cannabinoid CB(1) receptor antagonist. Moreover, since it did not enhance the amplitude of electrically evoked contractions, it may be a neutral cannabinoid CB(1) receptor antagonist.

RATIONALE. Cannabinoids have been shown to produce greater behavioral effects in female than male rats. Although central nervous system CB(1) receptors are known to mediate cannabinoid-induced behavioral effects in male rats, it is not known whether the same is true for females. OBJECTIVE. To determine if cannabinoid-induced antinociception and catalepsy are similarly mediated by central CB(1) receptors in male and female rats. METHODS. The ability of SR141716A, a CB(1) receptor selective antagonist, administered ICV (1-1000 microg) or IT (1-600 microg) to block 10 mg/kg IP Delta(9)-THC-induced antinociception (paw pressure) and catalepsy (bar test), was compared in male and female rats. RESULTS. Delta(9)-THC alone produced slightly greater antinociception, and significantly greater catalepsy in females than males. When administered ICV, SR141716A partially antagonized Delta(9)-THC-induced antinociception in both females and males. IT SR141716A also antagonized Delta(9)-THC-induced antinociception in both sexes; it was slightly more potent in males but equally effective in males and females. SR141716A antagonized Delta(9)-THC-induced catalepsy in a similar manner in males and females when given ICV or IT. CONCLUSIONS. These results confirm that Delta(9)-THC-induced behavioral effects are mediated by central CB(1) receptors in male and female rats.


Melanocortin receptor 4 (MCR4) and CB1 cannabinoid receptors independently modulate food intake. Although an interaction between cannabinoid and melanocortin systems has been found in recovery from hemorrhagic shock, the interaction between these systems in modulating food intake has not yet been examined. The present study had two primary purposes: (1) to examine whether the cannabinoid and melanocortin systems act independently or synergistically in suppressing food intake and (2) to determine the relative position of the CB1 receptors in the chain of control of food intake in relation to the melanocortin system. Rats were habituated to the test environment and injection procedure, and then received intracerebroventricular (ICV) injections of various combinations of the MCR4 receptor antagonist JKC-363, the CB1 receptor agonist Delta(9)-tetrahydrocannabinol (THC), the MCR4 receptor agonist alpha-MSH, or the cannabinoid CB1 receptor antagonist SR 141716. Food intake and locomotor activity were then recorded for 120 min. When administrated alone, SR 141716 and alpha-MSH dose-dependently attenuated baseline feeding, while sub-anorectic doses of SR 141716 and alpha-MSH synergistically attenuated baseline feeding when combined. THC-induced feeding was not blocked by alpha-MSH, while SR 141716 dose-dependently attenuated JKC-363-induced feeding. Locomotor activity was not significantly affected by any drug treatment, suggesting that the observed effects on feeding were not due to a non-specific reduction in motivated behavior. These findings reveal a synergistic interaction between cannabinoid and melanocortin systems in feeding behavior. These results further suggest that CB1 receptors are located downstream from melanocortin receptors, and CB1 receptor signaling is necessary to prevent the melanocortin system from altering food intake.

**CLINICAL SCIENCE**


Although cannabinoids have anti-hyperalgesic effects in animal models of nerve injury, there are currently very few prospective trials of the efficacy of cannabinoids in neuropathic pain in humans. This open label prospective study investigated the safety, tolerability and analgesic benefit of oral Delta-9-tetrahydrocannabinol (THC) titrated to a maximal dosage of 25 mg/day in 8 consecutive patients with chronic refractory neuropathic pain. Spontaneous ongoing and paroxysmal pain, allodynia and paresthesias were assessed. The sensory and affective components of pain using the McGill pain questionnaire, quality of life, mood, anxiety and functionality were also evaluated. Seven patients suffered from side effects necessitating premature arrest of the drug in 5 of them. THC (mean dosage: 16.6+-6.5 mg/day) did not induce
any significant effects on ongoing and paroxysmal pain, allodynia, quality of life, anxiety/depression scores and functional impact of pain. These results do not support an overall benefit of THC in pain and quality of life in patients with refractory neuropathic pain.


OBJECTIVES: The aim of the study was to compare the treatment of panic disorder in patients with or without cannabis use according to response, relapse and side effects.

MATERIALS AND METHODS: 66 panic disorder (PD) patients were included in our study. All the subjects met the DSM-IV diagnosis of panic disorder (n=45) or panic disorder with agoraphobia (n=21). Twenty four patients experienced their first panic attack within 48 h of cannabis use and then went on to develop PD. All the patients received pharmacologic treatment with paroxetine (gradually increased up to 40 mg/d). A masked rater that was blind to the group allocation, assessed patients in order to rate anxiety symptoms and medication side effects. Relapse was defined as the occurrence of a single panic attack after remission of panic symptoms. The instruments were administered at baseline and also at the 4, 8 and 12 weeks visits and at the 1 year visit. RESULTS: The two groups responded equally well to paroxetine treatment as measured at the 8 weeks and 12 months follow-up visits. There were no significant effects of age, sex and duration of illness as covariates with response rates between the two groups. Also PD or PDA diagnosis did not affect the treatment response in either group. There were no significant differences in weight gain, sexual side effects or relapse rates between patients according to gender or comorbid diagnosis. SUMMARY: Acute cannabis use can be associated with the onset of panic attacks and panic disorder, and panic disorder which develops after cannabis use is responsive to pharmacotherapy.


Growing basic research in recent years led to the discovery of the endocannabinoid system with a central role in neurobiology. New evidence suggests a therapeutic potential of cannabinoids in cancer chemotherapy-induced nausea and vomiting as well as in pain, spasticity and other symptoms in multiple sclerosis and movement disorders. Results of large randomized clinical trials of oral and sublingual Cannabis extracts will be known soon and there will be definitive answers to whether Cannabis has any therapeutic potential. Although the immediate future may lie in plant-based medicines, new targets for cannabinoid therapy focuses on the development of endocannabinoid degradation inhibitors which may offer site selectivity not afforded by cannabinoid receptor agonists.


The purpose of this study was to quantify the in-vitro human skin transdermal flux of Delta8-tetrahydrocannabinol (Delta8-THC), cannabidiol (CBD) and cannabinol (CBN). These cannabinoids are of interest because they are likely candidates for transdermal combination therapy. Differential thermal analysis and in-vitro diffusion studies with human tissue were completed for the compounds. Heats of fusion, melting points and relative thermodynamic activities were determined for the crystalline compounds, CBD and CBN. Flux, permeability, tissue concentration and lag times were measured in the diffusion experiments. CBN had a lower heat of fusion and corresponding higher calculated relative thermodynamic activity than CBD. Ethanol concentrations of 30 to 33% significantly increased the transdermal flux of Delta8-THC and CBD. Tissue concentrations of Delta8-THC were significantly higher than for CBN. Lag times for CBD were significantly smaller than for CBN. The permeabilities of CBD and CBN were 10-fold higher than for Delta8-THC. Combinations of these cannabinoids with ethanol will be further studied in transdermal patch formulations in vitro and in vivo, as significant flux levels of all the
drugs were obtained. CBD, the most polar of the three drugs, and other more polar cannabinoids will also be the focus of future drug design studies for improved transdermal delivery rates.

**BEHAVIOURAL SCIENCE**


Cannabis and other illicit drugs are often used or abused comorbidly. Two competing theories to explain this comorbidity are (i) the phenotypic causation (gateway) model and (ii) the correlated liabilities model. We used data from 1191 male and 934 female same-sex twin pairs to test 13 genetically informative models of comorbidity. Models were fit separately for use and abuse/dependence in both sexes. The correlated liabilities model provided a good fit to the data for cannabis and other illicit drug use, as well as abuse/dependence. The relationship between the use or abuse of cannabis and other illicit drugs is not entirely phenotypic, as depicted by the random multiformity of cannabis model, which is an adaptation of the gateway model. The comorbidity appears to arise from correlated genetic and environmental influences. There is some evidence for a model in which high-risk cannabis users may be at increased risk for other illicit drug use. For abuse/dependence, a model with causal pathways between the liability for cannabis and other illicit drug abuse/dependence also fits well. Overall, our results suggest that the use and abuse/dependence of cannabis and other illicit drugs are strongly linked via common risk factors that jointly influence their individual liabilities.


**BACKGROUND:** Hyperactive/ADHD children are believed to be a greater risk for adolescent and young adult antisocial activity and drug use/abuse, particularly that subset having comorbid conduct problems/disorder. **METHOD:** We report on the lifetime antisocial activities and illegal drug use self-reported at young adult follow-up (mean age 20-21 years; 13+ year follow-up) for a large sample of hyperactive (H; N = 147) and community control (CC; N = 73) children. Parent reports of childhood hyperactivity and conduct problems at study entry, parent and self-reports of ADHD and conduct disorder at adolescence, and parent reports of ADHD at young adulthood are examined for their contribution to antisocial behavior and drug use at adulthood. **RESULTS:** More of the H group committed a variety of antisocial acts and had been arrested for doing so (corroborated through official arrest records) than did the CC group. The H group also committed a higher frequency of property theft, disorderly conduct, assault with fists, carrying a concealed weapon, and illegal drug possession, as well as more arrests. These activities reduced to two dimensions corresponding to predatory-overt and drug-related antisocial conduct. The H group differed from the CC group only on the latter dimension. Childhood, adolescent, and adult ADHD predicted higher drug-related activities, as did childhood conduct problems. The H group with conduct disorder (CD) reported greater use of most substances than did the H only or CC groups, who did not differ from each other. Severity of teen ADHD and especially lifetime CD predicted use of hard drugs while just lifetime CD predicted marijuana/LSD use. Teen drug use seemed to potentiate increased drug-related antisocial activities beyond the contribution made by teen CD. **CONCLUSIONS:** Hyperactive children are at greater risk for antisocial activities and arrests by young adulthood that appear to be principally associated with illegal drug possession, use, and sale. Those having CD, however, appear to engage in greater and more diverse substance use.


This study examined the impact of a school-based preventive intervention on cannabis use in adolescence, using a cluster-randomized trial of a multilevel intervention aimed at improving social relationships within schools by promoting change in school environment. Four waves of data were collected at baseline (1997, Year 8: mean age 13 years) and six, 18, and 30 months later (1999, Year 10: mean age 16 years). Self-reported substance use, school engagement, and sociodemographic data were collected using computer-administered
questionnaires. Some 2,678 (74%) Year 8 students participated (wave 1) with minimal attrition (10% by wave 4). Adjusting for baseline use, weak evidence existed for an intervention effect on the prevalence of any use at Year 10 (OR 0.75, 95% CI 0.54, 1.05) and incident weekly use (OR 0.72, 95% CI 0.39, 1.33). These effects were reduced after adjusting for confounders. Moderate evidence suggested an interaction effect between intervention group and tobacco use (p = 0.04), suggesting the intervention was more effective for non-smokers at baseline (Adj. OR 0.50, 95% CI 0.26, 0.98). This study indicates that a multi-level school-based program may provide an innovative direction for sustainable school interventions with the potential to reduce substance use.


CONTEXT: In order to establish prevention programs regarding psychotropic drug use that are adapted to specific populations it is, first of all, important to have data on the realities of such consumption. Single data points are not enough for drawing up a profile of society in relation to drugs. OBJECTIVE: The aim of this household survey was to determine the incidence of illegal drug, alcohol, tobacco and psychotropic medication use, and thus the number of persons dependent on drugs, alcohol and nicotine, and to evaluate their perception regarding how easy it is to obtain psychotropic drugs. TYPE OF STUDY: Epidemiological survey. SETTING: All of the 24 cities in the State of Sao Paulo with more 200,000 inhabitants participated in the study. METHOD: The sampling was constructed from weighted probabilistic stratified conglomerates obtained via two-stage selection. In each municipality sampled, census sectors (generally 200-300 households) were first selected. Then, households and a respondent were selected to provide information from his/her point of view. The SAMHSA questionnaire (Substance Abuse and Mental Health Services Administration) of the U.S. Department of Public Health was used, after translation and adaptation to Brazilian conditions. RESULTS: A total of 2,411 persons aged 12-65 years old were interviewed, of whom 39.9% were men. Lifetime use of any psychotropic drug other than alcohol and tobacco was 11.6%; much less than in the U.S. (34.8%). The alcohol dependence rate was 6%, similar to findings from other countries. Marijuana was the illegal drug most cited as used daily (6.6%); a prevalence much lower than in the U.S. (32.0%): Inhalant use was next in frequency of use (2.7%); about 10 times less than in the United Kingdom (20%). Cocaine use (2.1%) was about 5 times less than in the U.S. (10.6%). There was no report of heroin use, although there was a surprisingly high perception regarding the case of obtaining heroin: 38.3% sold if was easy to obtain. CONCLUSION: This study supports the implementation of better prevention programs regarding drug abuse in Sao Paulo state.


Item response theory (IRT) is supplanting classical test theory as the basis for measures development. This study demonstrated the utility of IRT for evaluating DSM-IV diagnostic criteria. Data on alcohol, cannabis, and cocaine symptoms from 372 adult clinical participants interviewed with the Composite International Diagnostic Interview--Expanded Substance Abuse Module (CIDI-SAM) were analyzed with Mplus (B. Muthen & L. Muthen, 1998) and MULTILOG (D. Thissen, 1991) software. Tolerance and legal problems criteria were dropped because of poor fit with a unidimensional model. Item response curves, test information curves, and testing of variously constrained models suggested that DSM-IV criteria in the CIDI-SAM discriminate between only impaired and less impaired cases and may not be useful to scale case severity. IRT can be used to study the construct validity of DSM-IV diagnoses and to identify diagnostic criteria with poor performance. ((c) 2004 APA, all rights reserved)


The purpose of this investigation was to determine the substances used, and the attitudes towards doping of high school athletes. A four-page, self-completed questionnaire was designed to determine the drugs used (licit, illicit and doping substances) along with beliefs about
doping and the psychosociological factors associated with their consumption. The questionnaire was distributed to all the high school students enrolled in a school sports association in the Lorraine region in Eastern France. The completed forms were received from 1459 athletes: 4% stated that they had used doping agents at least once in their life (their main source of supply being peers and health professionals). Thirty-four percent of the sample smoked some tobacco, 66% used alcohol, 19% cannabis, 4% ecstasy, 10% tranquilizers, 9% hypnotics, 4% creatine and 41% used vitamins against fatigue. Beliefs about doping did not differ among doping agent users and non-users, except for the associated health risks which were minimized by users. Users of doping agents stated that the quality of the relations that they maintain with their parents is sharply degraded, and they reported that they are susceptible to influence and difficult to live with. More often than non-doping agent users, these adolescents are neither happy, nor healthy, while paradoxically, they seem less anxious and they are more self-confident. Our findings suggest that doping prevention among young athletes cannot be limited uniquely to the list of banned drugs.


Patients with schizophrenia and related psychoses frequently use, abuse and become dependent on psychoactive substances. Local surveys indicate differences in both types and patterns of substances used. A cross-sectional survey was conducted to document abuse in 207 successive outpatients presenting to a psychiatric continuing care facility in a large Canadian city. Nicotine, alcohol and cannabis were the most frequently abused substances in the cohort. Excluding nicotine, 44.9% met criteria for lifetime and 14.0% for current abuse/dependence. Cocaine, heroin, hallucinogen, amphetamine, and inhalant use were rarely reported. Patients with current substance abuse/dependence and a psychotic disorder (dual diagnosis, DD) had significantly higher Positive and Negative Symptom Scale (PANSS) positive scores than lifetime-DD or those with a single diagnosis (SD). Significantly more current-DD (69.0%) patients were depressed (HAM-D score \( \geq 12 \)) compared to SD (45.6%). Furthermore, current-DD (27.6%) patients were more likely than SD (4.5%) to be medication non-compliant. Patients with current-DD were more likely to smoke cigarettes (88.9%) compared to those with SD (49.6%) and they had significantly longer histories of cigarette smoking (19.1 years for DD vs. 11.5 years for SD). The smoking behavior of the DD population is discussed in terms of enhanced risk for alcohol abuse, as well as effects on antipsychotic blood levels and metabolism.


Purpose: To study the relationship between cannabis use, sports practice and other leisure activities during adolescence, as a test for the sociological theory of deviant opportunities. Methods: A sample of 12,512 French adolescents aged 18 responded to an anonymous self-reported questionnaire in March 2001. Three logistic models (for occasional, recent and regular cannabis use) were estimated for girls and boys separately. Results: Outings and other peer-oriented activities were strongly correlated with cannabis use but this relationship depended on which levels of use were considered. Occasional use was more common among respondents who participated in many different outdoor activities. Regular use was associated with a more selective lifestyle, focusing on music-oriented outings and time spent at a friend's home in the evening. Conclusions: Our results provided empirical support for the theory of deviant opportunities. Changing patterns of lifestyle associated with transition from initiation to higher levels of use may reveal a shift from opportunities of cannabis use provided by a wide range of activities to specific activities chosen for their convenience to cannabis use. Further research will need to investigate how drug use is shaped by lifestyle, and conversely, how drug use reshapes lifestyle.

The authors investigated relationships between marijuana and inhalant use and several cultural and demographic factors in Anglo American and Hispanic American adolescents (N=1,094). Outcome measures assessed lifetime and 30-day marijuana and inhalant use. Predictors and covariates used in logistic regression analyses were region, grade, gender, knowledge, acculturation, familism, and parental monitoring. Hispanic Americans exhibited higher usage across all measures. In this group, high acculturation was associated with low marijuana, but high inhalant, use. Across all participants, positive family relations and parental monitoring were strongly associated with attenuated marijuana use but only among those most knowledgeable about drugs. Familism and monitoring were not associated with diminished usage among the less knowledgeable. For inhalants, monitoring combined with high knowledge or high familism was associated with diminished usage. ((c) 2004 APA, all rights reserved)


This article compares the performance of multiple logistic regression (MLR) with feed-forward, artificial neural network (ANN) models for the assessment of adolescent marijuana use and clinical features of dependence based on self-evaluation from recent National Household Surveys on Drug Abuse (NHSDA). The effect of training and testing the neural networks with randomly selected data was compared to data selected as a function of survey year. The technical aim of the study was to account for adolescent marijuana use and features of marijuana dependence based on experiences with alcohol and tobacco. Similarities observed in MLR and ANN model performance may indicate no major complex or nonlinear relationships in cross-sectional epidemiological data selected to model adolescent drug use and dependence in this specific application. We concluded that ANNs should be further studied in future longitudinal research, perhaps with modeling of recursive networks, allowing feedback from drug dependence to levels of marijuana use. The ANN models also have the potential to model drug use and dependence based on input parameters with no obvious direct link to drug involvement—e.g., polymorphisms associated with “openness to experience” or other personality traits hypothesized to function as distal antecedents, and could thus be implemented to identify higher risk youths using assessments indirectly related or nonlinearly associated to adolescent drug use and dependence but less sensitive to survey-related response tendencies.


OBJECTIVE: The purpose of the study was to assess the independent influences of gender and cannabis use on milestones of early course in schizophrenia. METHOD: In this population-based, first-contact incidence study conducted in The Hague, the Netherlands, patients (N=133) were interviewed with the Comprehensive Assessment of Symptoms and History, and key informants were interviewed with the Instrument for the Retrospective Assessment of the Onset of Schizophrenia. Milestones of early course were 1) first social and/or occupational dysfunction, 2) first psychotic episode, and 3) first negative symptoms. RESULTS: Male patients were significantly younger than female patients at first social and/or occupational dysfunction, first psychotic episode, and first negative symptoms. Cannabis-using patients were significantly younger at these milestones than were patients who did not use cannabis. Multivariate analyses showed that cannabis use, but not gender, made an independent contribution to the prediction of age at first psychotic episode: male cannabis users were a mean of 6.9 years younger at illness onset than male nonusers. In contrast, age at first social and/or occupational dysfunction and the risk of developing negative symptoms before the first contact with a physician for treatment of possible psychotic disorder were predicted by gender, but not by cannabis use. CONCLUSIONS: The results indicate a strong association between use of cannabis and earlier age at first psychotic episode in male schizophrenia patients. Additional studies examining this possibly causal relationship are needed.
This newsletter is supported by an unrestricted educational grant Valeant Pharmaceuticals