INTRODUCTION
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BASIC SCIENCE

Recent behavioral and pharmacological research shows extensive interplay between cannabinoid and opioid neurochemical systems. Here we examined the neuroanatomical basis of this interaction using c-fos immunohistochemistry. We compared Fos immunoreactivity in groups of male albino Wistar rats treated with vehicle, Delta(9)-tetrahydrocannabinol (THC, 10 mg/kg, i.p.), naloxone (10 mg/kg, i.p.) or THC and naloxone in combination. Locomotor activity was depressed in both THC treatment groups and moderately inhibited in rats given naloxone alone. Results showed that naloxone inhibited THC-induced Fos immunoreactivity in several key brain regions including the ventral tegmental area, ventromedial and dorsomedial hypothalamus, central caudate-putamen and ventrolateral periaqueductal grey. Conversely, naloxone and THC had an additive effect on Fos immunoreactivity in the central nucleus of the amygdala, the bed nucleus of the stria terminalis (lateral division), the insular cortex, and the paraventricular nucleus of the thalamus. These findings complement earlier pharmacological results showing potent modulation of cannabinoid-induced analgesia, appetite and reward by opioids. The inhibitory effects of naloxone on THC-induced ventral tegmentum, hypothalamic and periaqueductal grey Fos expression point to these structures as key sites involved in cannabinoid-opioid interactions.


The present study aimed to clarify the role of the arachidonic acid cascade in mediating the expression of withdrawal signs in cannabinoid-dependent mice. Mice were injected with Delta(8)-tetrahydrocannabinol (THC) at 20 mg/kg (i.p.) every 12 h, 11 times. When SR141716A, a specific cannabinoid CB1 receptor antagonist, at 10 mg/kg (i.p.) was given 4 h after the last THC injection, withdrawal signs such as forepaw licking, facial preening, grooming, forepaw tremor, head shakes and weight loss were clearly observed. PGE(2) at 0.1, 1.0 and 3.2 &mgr;g (per animal; i.c.v.) given prior to SR141716A (10 mg/kg, i.p.) dose-dependently decreased the number of forepaw licking, facial preening, grooming and forepaw tremor episodes. Instead of SR141716A, a cyclooxygenase inhibitor diclofenac at 10 mg/kg (i.p.) also precipitated these withdrawal signs. The results suggest that the expression of THC withdrawal is due to a decrease in prostaglandin levels through inactivation of the arachidonic acid cascade in the brain.


At proximal synapses from layer V pyramidal neurons from the rat prefrontal cortex, activation of group II metabotropic glutamate receptors (group II mGlur) by (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl) glycine (DCG IV) induced a long-lasting depression of excitatory postsynaptic currents. Paired-pulse experiments suggested that the depression was expressed
Activation of type 1 cannabinoid receptors (CB1) by WIN 55,212-2 occluded the DCG IV-induced depression in a mutually occlusive manner. At the postsynaptic level, WIN 55,212-2 and DCG IV were also occlusive for the activation of extracellular signal-regulated kinase. The postsynaptic localization of active extracellular signal-regulated kinase was confirmed by immunocytochemistry after activation of CB1 receptors. However, phosphorylation of extracellular signal-regulated kinase in layer V pyramidal neurons was dependent on the activation of N-methyl-d-aspartate receptors, consequently to a release of glutamate in the local network. Group II mGlu were also shown to be involved in long-term changes in synaptic plasticity induced by high frequency stimulations. The group II mGlu antagonist (RS)-alpha-methylserine-O-phosphate monophenyl ester (MSOPPE) favoured long-term depression. However, no interaction was found between MSOPPE, WIN 55,212-2 and the CB1 receptor antagonist SR 141716A on the modulation of long-term depression or long-term potentiation and the effects of these drugs were rather additive. We suggest that CB1 receptor and group II mGlu signalling may interact through a presynaptic mechanism in the induction of a DCG IV-induced depression. Postsynaptically, an indirect interaction occurs for activation of extracellular signal-regulated kinase. However, none of these interactions seem to play a role in synaptic plasticities induced with high frequency stimulations.


Cannabinoids are neurodepressive drugs that convey their cellular action through G(i/o) GTP-binding proteins which reduce cAMP formation and Ca(2+) influx. However, a growing body of evidence indicates that the stimulatory effects of cannabinoids include the elevation in cAMP and cytosolic Ca(2+) concentration. The present study expands our previous findings and demonstrates that, in N18TG2 neuroblastoma cells, the cannabinoid agonist desacetyllevonantradol (DALN) stimulates both cAMP formation and Ca(2+) uptake. The stimulatory effect of DALN on cAMP formation was not eliminated by blocking Ca(2+) entry to the cells, while its stimulatory effect on Ca(2+) uptake was abolished by blocking cAMP-dependent protein kinase. Furthermore, elevating cAMP by forskolin stimulated calcium uptake, while elevating the intracellular Ca(2+) concentration by ionomycin or KCl failed to stimulate cAMP formation. These findings suggest that cAMP production precedes the influx of Ca(2+) in the cannabinoid stimulatory cascade. The stimulatory effect of DALN on calcium uptake resisted pertussis toxin treatment, and was completely blocked by introducing anti-G(s) antibodies into the cells, indicating that the stimulatory activity of cannabinoids is mediated by G(s) GTP-binding proteins. The relevance of the cellular stimulatory activity of DALN to the pharmacological profile of cannabinoid drugs is discussed. Copyright 2003 S. Karger AG, Basel


This study investigates the effects of SR141716, a selective CB(1) receptor antagonist that reduces food intake and body weight of rodents, on Acrp30 mRNA expression in adipose tissue. Acrp30, a plasma protein exclusively expressed and secreted by adipose tissue, has been shown to induce free fatty acid oxidation, hyperglycemia and hyperinsulinemia decrease, and body weight reduction. We report that N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-p yrazole-3-carboximide hydrochloride (SR141716) treatment once daily (10 mg/kg/d, i.p.) from 2 to 14 days reduced body weight and stimulated Acrp30 mRNA expression in adipose tissue of obese Zucker (fa/fa) rats. In parallel, the hyperinsulinemia associated with this animal model was reduced by SR141716 treatment. In cultured mouse adipocytes (3T3 F442A), SR141716 (25 to 100 nM) also induced an overexpression of Acrp30 mRNA and protein. In addition, in adipose tissue of CB(1)-receptor knockout mice, SR141716 had no effect on Acrp30 mRNA expression, demonstrating a CB(1) receptor mediating effect. Furthermore, RT-PCR analysis revealed that rat adipose tissue and 3T3 F442A adipocytes expressed CB(1) receptor mRNA. Relative quantification of this expression revealed an up-regulation (3- to 4-fold) of CB(1) receptor mRNA expression in adipose tissue of obese (fa/fa) rats and in differentiated 3T3 F442A adipocytes compared with lean rats and undifferentiated adipocytes, respectively. Western blot
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analysis revealed the presence of CB(1) receptors in 3T3 F442A adipocytes, and their expression was up-regulated in differentiated cells. These results show that SR141716 stimulated Acrp30 mRNA expression in adipose tissue by an effect on adipocytes, and reduced hyperinsulinemia in obese (fa/fa) rats. These hormonal regulations may participate in the body weight reduction induced by SR141716 and suggest a role of metabolic regulation in the antiobesity effect of SR141716.


Previous studies have demonstrated a functional interaction between cannabinoid and opioid systems in the development and expression of morphine tolerance and dependence. In these experiments, we examined the effect of a low oral dose of delta 9-tetrahydrocannabinol (Delta(9)-THC) on the development of oral morphine tolerance and the expression of naloxone-precipitated morphine withdrawal signs of jumping and diarrhea in ICR mice. Chronic treatment with high dose oral morphine produced a 3.12-fold antinociceptive tolerance. Tolerance to morphine was prevented in groups receiving a daily co-treatment with a non-analgetic dose (20 mg/kg, p.o.) of Delta(9)-THC, except when challenged with a very high dose of morphine. The chronic co-administration of low dose Delta(9)-THC also reduced naloxone-precipitated (1 mg/kg s.c.) platform jumping by 50% but did not reduce diarrhea. In separate experiments, mice treated chronically with high dose morphine p.o. were not cross-tolerant to Delta(9)-THC; in fact, these morphine-tolerant mice were more sensitive to the acute antinociceptive effects of Delta(9)-THC. Delta(9)-THC (20 mg/kg p.o.) also reduced naloxone-precipitated jumping but not diarrhea when administered acutely to morphine-tolerant mice. These results represent the first evidence that oral morphine tolerance and dependence can be circumvented by co-administration of a non-analgetic dose of Delta(9)-THC p.o. In summary, co-treatment with a combination of morphine and Delta(9)-THC may prove clinically beneficial in that long-term morphine efficacy is maintained.


The analgesic effects of opioids, such as morphine and codeine, in mice are enhanced by oral administration of the cannabinoid Delta(9)-tetrahydrocannabinol (Delta(9)-THC). However, isobolographic analysis has never been done to confirm a synergy between Delta(9)-THC and morphine or codeine via oral routes of administration. To determine the nature of the interaction between these drugs for pain relief and extend previous experimental results, we performed an isobolographic analysis to evaluate for additivity or synergy in the tail-flick test. Fixed-ratio combinations of Delta(9)-THC with either morphine or codeine were tested for antinociceptive effects. The experimentally derived ED(50) for each combination was compared with the theoretical additive ED(50), using an isobolographic analysis. All of the fixed-ratio combinations tested produced greater antinociception (synergy) than predicted from simple additivity. These findings suggest that the use of a low-dose combination of analgesics is a valid and effective approach for the treatment of pain and necessitates further study.


1 On the basis of previous findings that cannabinoids inhibit the function of human and rat 5-HT(3) receptors in vitro, we investigated whether cannabinoid receptor agonists also modulate the activity of the rat peripheral 5-HT(3) receptors on the terminals of cardiopulmonary afferent C-fibres in vivo. 2 In urethane-anaesthetized rats, pre-treated intravenously (i.v.) with the CB(1) receptor antagonist SR 141716A (3 micro mol kg(-1)) and with the beta(1)/beta(2) adrenoceptor antagonist propranolol (0.3-0.4 micro mol kg(-1)), bolus injection of the serotonin 5-HT(3) receptor agonist phenylbiguanide (3-10 micro g kg(-1), i.v.) or the vanilloid VR1 receptor agonist capsaicin (3-10 micro g kg(-1), i.v.) caused an immediate decrease in heart rate and mean arterial blood pressure (the von Bezold-Jarisch reflex). 3 The phenylbiguanide-induced
bradycardia was dose-dependently attenuated by the cannabinoid receptor agonists CP 55,940 (0.1-1 micro mol kg(-1), i.v.) and WIN 55,212-2 (0.1-3 micro mol kg(-1), i.v.) 20 min after injection, but not by the inactive S(-)-enantiomer of the latter, WIN 55,212-3 (1 micro mol kg(-1), i.v.). The inhibition was reversible within 30 min. The extent of inhibition by the highest doses of cannabinoid receptor agonists amounted to about 50%. Both cannabinoid receptor agonists failed to affect the capsaicin-evoked bradycardia. 4 In conclusion, our results demonstrate that cannabinoid receptor agonists modulate the von Bezold-Jarisch reflex by inhibiting peripheral serotonin 5-HT(3) receptors in rats in vivo. An analogous mechanism of cannabinoid receptor agonists may be assumed to be involved in other serotonin 5-HT(3) receptor-mediated responses. British Journal of Pharmacology (2003) 138, 767-774. doi:10.1038/sj.bjp.0705114


The intestinal secretory actions of the proinflammatory peptide kallidin (lysyl-bradykinin) are mediated partially by enteric neurons. We hypothesized that kallidin produces neurogenic anion secretion through opioid- and cannabinoid-sensitive enteric neural pathways. Changes in short-circuit current (Isc) across sheets of porcine ileal mucosa-submucosa mounted in Ussing chambers were measured in response to kallidin (1 micro M) or drugs added to the contraluminal bathing medium. Kallidin transiently increased Isc, an effect reduced after inhibition of neuronal conduction by 0.1 micro M saxitoxin, cyclooxygenase inhibition by 10 micro M indomethacin, or kinin B2 receptor blockade by 1 micro M HOE-140. Its action was dependent upon extracellular Cl(-) or HCO3(-) ions, but was resistant to 10 mM bumetanide or 0.3 mM DIDS, and appeared to involve luminal alkalization as measured by pH-stat titration. Kallidin-induced Isc elevations were sensitive to saxitoxin in tissues bathed in Cl(-)-, but not HCO 3(-)-deficient media. Tissues pretreated with 0.1 micro M D-Pen(2,5)]enkephalin, a selective delta-opioid agonist, displayed reduced Isc responses to kallidin; this effect was prevented by the delta-opioid antagonist naltrindole. At a contraluminal concentration of 1 micro M, the cannabinoid receptor agonist HU-210 also attenuated responses to kallidin. Proinflammatory kinins appear to stimulate neurogenic anion secretion in porcine ileum by activating enteric neural circuits expressing inhibitory opioid and possibly cannabinoid receptors.


A number of recent studies have demonstrated that a well-known form of short-term plasticity at hippocampal GABAergic synapses, called depolarization-induced suppression of inhibition (DSI), is in fact mediated by the retrograde actions of endocannabinoids released in response to depolarization of the postsynaptic cells. These recent studies suggest that endogenous cannabinoids may play an important role in regulating inhibitory tone in the mammalian CNS. Despite the widespread interest and potential physiological importance of DSI, many questions regarding the physiological relevance of DSI remain. To that end, this study set out to define the specific limiting conditions that could elicit DSI at GABAergic synapses in CA1 hippocampal pyramidal neurons and to determine if DSI could be elicited with pulse trains that mimic hippocampal cell firing patterns that occur in vivo. Whole cell recordings from hippocampal neurons under voltage clamp configuration were made in rat hippocampal slices. Spontaneous and evoked GABAA receptor-mediated inhibitory postsynaptic potentials (sIPSCs and eIPSCs respectively) were recorded prior to and following depolarization of identified CA1 hippocampal pyramidal cells. Depolarizing voltage pulses were shaped to evoke currents in QX-314 treated cells similar to those accompanying single spontaneous voltage-clamped action potentials recorded from the soma. Attempts were made to elicit DSI with trains of these pulses that mimicked hippocampal cell firing patterns in vivo, for instance when animals traverse place fields or are performing a short-term memory task. DSI could not be elicited by such pulse trains or by a number of other combinations of behaviorally specific firing parameters. The minimum duration of depolarization necessary to elicit DSI in hippocampal neurons determined by paired-pulse manipulation was 50-75 ms at a critical interval of 20-30 ms between pulse pairs. Under the
conditions tested, the normal firing patterns of hippocampal neurons that occur in vivo do not appear to elicit DSI.


A series of 1',1'-dimethylalkyl-Delta(8)-tetrahydrocannabinol analogues with C-3 side chains of 2-12 carbon atoms has been synthesized and their in vitro and in vivo pharmacology has been evaluated. The lowest member of the series, 1',1'-dimethylethyl-Delta(8)-THC (8, n=0) has good affinity for the CB(1) receptor, but is inactive in vivo. The dimethylpropyl (8, n=1) through dimethyldecyl (8, n=8) all have high affinity for the CB(1) receptor and are full agonists in vivo. 1',1'-Dimethylundecyl-Delta(8)-THC (8, n=9) has significant affinity for the receptor (K(i)=25.8+/−5.8 nM), but has reduced potency in vivo. The dodecyl analogue (8, n=10) has little affinity for the CB(1) receptor and is inactive in vivo. A quantitative structure-activity relationship study of the side chain region of these compounds is consistent with the concept that for optimum affinity and potency the side chain must be of a length which will permit its terminus to loop back in proximity to the phenolic ring of the cannabinoid.


The effects of a range of cannabinoid receptor agonists and antagonists on phytohaemagglutinin-induced secretion of interleukin-2 from human peripheral blood mononuclear cells were investigated. The nonselective cannabinoid receptor agonist WIN55212-2 ((R)-(+)−[2,3-dihydro-5-methyl-3-[4-morpholinylmethyl]pyrrolo[1,2,3-de]1,4 -benzoxazin-6-yl](1-naphthyl) methanone mesylate) and the selective cannabinoid CB(2) receptor agonist JWH 015 ((2-methyl-1-propyl-1H-indol-3-yl)-1-naphthalenylmethanone) inhibited phytohaemagglutinin (10 &mgr;g/ml)-induced release of interleukin-2 in a concentration-dependent manner (IC(1/2max), WIN55212-2=8.8x10(-7) M, 95% confidence limits (C.L.)=2.2x10(-7)-3.5x10(-6) M; JWH 015=1.8x10(-6) M, 95% C.L.=1.2x10(-6)-2.9x10(-6) M, n=5). The nonselective cannabinoid receptor agonists CP55,940 (((+)-3-[2-hydroxy-4-(1,1-dimethyl-heptyl)-phenyl]-4-[3-hydroxypropyl]cyclo-hexan-1-ol), Delta(9)-tetrahydrocannabinol and the selective cannabinoid CB(1) receptor agonist ACEA (arachidonoyl-2-chloroethylamide) had no significant (P>0.05) inhibitory effect on phytohaemagglutinin-induced release of interleukin-2. Dexamethasone significantly (P<0.05) inhibited phytohaemagglutinin-induced release of interleukin-2 in a concentration-dependent manner (IC(1/2max)=1.3x10(-8) M, 95% C.L.=1.4x10(-9)-3.2x10(-8) M). The cannabinoid CB(1) receptor antagonist SR141716A (N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H- pyrazole-3-carboxamide hydrochloride) (10(-6) M) did not antagonise the inhibitory effect of WIN55212-2 whereas the cannabinoid CB(2) receptor antagonist SR144528 (N-(1-S)-endo-1,3,3-trimethyl bicyclo(2,2,1)heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-pyridyl) pyrazole-3-carboxamide) antagonised the inhibitory effect of WIN55212-2 (pA(2)=6.3+/−0.1, n=5). In addition, CP55,940 (10(-6) M) and Delta(9)-tetrahydrocannabinol (10(-6) M) also antagonised the inhibitory effects of WIN55212-2 (pA(2)=6.1+/−0.1, n=5 and pA(2)=6.9+/−0.2, n=5). In summary, WIN55,212-2 and JWH 015 inhibited interleukin-2 release from human peripheral blood mononuclear cells via the cannabinoid CB(2) receptor. In contrast, CP55,940 and Delta(9)-tetrahydrocannabinol behaved as partial agonists/antagonists in these cells.


The neutral arachidonic acid derivatives N-arachidonylethanolamide (anandamide or AEA) and 2-arachidonylglycerol (2-AG) have been identified as endogenous ligands for the cannabinoid receptors. Quantitation of these endocannabinoids from various tissues has been shown to be essential in the elucidation of cannabinoid-mediated processes in vivo. Here, we describe a novel method for the detection and quantitation of AEA and 2-AG from mammalian tissue. We exploit the ability of silver cation to bind to the polyunsaturated arachidonate backbone of both molecules to form the charged species [M+Ag(+)]. These complexes are amenable to
liquid chromatography-electrospray ionization-tandem mass spectrometry analysis, resulting in the simple and specific quantitation of AEA and 2-AG. The limits of detection of 2-AG and AEA are 13 and 14fmol, respectively, on-column. This method provides an alternative to existing methods, which employ derivation and/or selected ion monitoring (when mass spectrometric detection is used), and may facilitate the understanding of the physiological roles of this new class of compounds.


We have recently reported that the administration of AM404, an inhibitor of the endocannabinoid re-uptake process, which also has affinity for the vanilloid VR1 receptors, is able to reduce hyperkinesia, and causes recovery from neurochemical deficits, in a rat model of Huntington's disease (HD) generated by bilateral intrastrital injections of 3-nitropropionic acid (3NP). In the present study, we wanted to explore the mechanism(s) by which AM404 produces its antihyperkinetic effect in 3NP-lesioned rats by employing several experimental approaches. First, we tried to block the effects of AM404 with selective antagonists for the CB1 or VR1 receptors, i.e. SR141716A and capsazepine, respectively. We found that the reduction caused by AM404 of the increased ambulation exhibited by 3NP-lesioned rats in the open-field test was reversed when the animals had been pre-treated with capsazepine but not with SR141716A, thus suggesting a major role of VR1 receptors in the antihyperkinetic effects of AM404. However, despite the lack of behavioral effects of the CB1 receptor antagonist, the pretreatment with this compound abolished the recovery of neurochemical [gamma-aminobutyric acid (GABA) and dopamine] deficits in the caudate-putamen caused by AM404, as also did capsazepine. In a second group of studies, we wanted to explore the potential antihyperkinetic effects of various compounds which, compared to AM404, exhibit more selectivity for either the endovanilloid or the endocannabinoid systems. First, we tested VDM11 or AM374, two selective inhibitors or the endocannabinoid re-uptake or hydrolysis, respectively. Both compounds were mostly unable to reduce hyperkinesia in 3NP-lesioned rats, although VDM11 produced a certain motor depression, and AM374 exhibited a trend to stimulate ambulation, in control rats. We also tested the effects of selective direct agonists for VR1 (capsaicin) or CB1 (CP55,940) receptors. Capsaicin exhibited a strong antihyperkinetic activity and, moreover, was able to attenuate the reductions in dopamine and GABA transmission provoked by the 3NP lesion, whereas CP55,940 had also antihyperkinetic activity but was unable to cause recovery of either dopamine or GABA deficits in the basal ganglia. In summary, our data indicate a major role for VR1 receptors, as compared to CB1 receptors, in the antihyperkinetic effects and the recovery of neurochemical deficits caused in 3NP-lesioned rats by compounds that activate both CB1 and VR1 receptors, either directly or via manipulation of the levels of endogenous agonists.


Immunologic activation of mast cells through the cross-linking of high affinity IgE receptors results in the release of inflammatory mediators which are important in the pathogenesis of allergic reactions. Early studies investigating the effects of palmitoylethanolamide on animal models of inflammation and on rat mast cells led to the hypothesis that endogenous cannabinoids might act as local autacoids which suppressed inflammation by reducing the activation of mast cells. However, more recent studies produced contradicting results. In order to evaluate if cannabinoid receptors are present in mast cells, we studied the effects of endocannabinoids (anandamide and palmitoylethanolamide) and synthetic cannabinomimetics (CP 55,940, WIN 55,212-2 and HU-210) on histamine release from rat peritoneal mast cells. When incubated with mast cells alone, only anandamide could induce significant level of histamine release at concentrations higher than 10(-6) M. When mast cells were activated with anti-IgE, the histamine release induced was not affected by anandamide, palmitoylethanolamide and CP 55,940. In contrast, both WIN 55,212-2 and HU-210 enhanced anti-IgE-induced histamine release at 10(-5) M and preincubation did not increase the potency. The histamine releasing action of anandamide and the enhancing effects of WIN 55,212-2 and HU-210 on anti-IgE-
induced histamine release were not reduced by the cannabinoid receptor antagonists, AM 281 and AM 630. In conclusion, the present study does not support the hypothesis that cannabinoids suppress mast cell activation. Instead, some of the cannabinoid receptor-directed ligands tested enhanced mast cell activation. However, the high concentrations required and the failure of cannabinoid receptor antagonists to reverse such effects also question the existence of functional cannabinoid receptors in mast cells.


It has been suggested that the cannabinoid CB1 G-protein-coupled receptor is internalized following agonist binding and activation of the second messenger pathways. It is proposed that phosphorylation enhances the down-regulation of the CB1 receptor, thus contributing to tolerance. Alterations in phosphorylation of proteins in the signal transduction cascade following CB1 receptor activation could also alter tolerance to cannabinoids. We addressed our hypothesis by evaluating the role of several kinases in antinociceptive tolerance to Delta(9)-THC. We evaluated PKA using KT5720, a PKA inhibitor; PKC using bisindolylmaleimide I, HCl (bis), a PKC inhibitor; PKG using KT5823, a PKG inhibitor; beta-ARK using low molecular weight heparin (LMWH), a beta-ARK inhibitor; PI3-K using LY294002, a PI3-K inhibitor and PP1, a src family tyrosine kinase inhibitor. The cAMP analog employed was dibutyryl-cAMP and the cGMP analog employed was dibutyryl-cGMP. Our data indicate that selective kinases may be involved in cannabinoid tolerance. Mice and rats were rendered tolerant to Delta(9)-tetrahydrocannabinol (THC). The PKG inhibitor, KT5823, the beta-ARK inhibitor, LMWH, the PI3-K inhibitor, LY294002 and inhibition of PKC by bis had no effect on tolerance. Bis, at a higher dose, attenuated the antinociceptive effect of THC in non-tolerant mice. PP1, the src family tyrosine kinase inhibitor, and KT5720, the PKA inhibitor, reversed THC-induced tolerance. In addition, inhibition of PKA reversed a decrease in dynorphin release shown to accompany THC-tolerance in rats. These data support a role for PKA and tyrosine kinase in phosphorylation events in Delta(9)-THC-tolerant mice.


To test the hypothesis that activation of the vanilloid receptor (VR1) contributes to the anandamide-induced depressor effect in spontaneously hypertensive rats (SHR), we used a selective VR1 antagonist capsazepine (CAPZ) and a selective cannabinoid type 1 receptor antagonist SR141716A in conjunction with a VR1 agonist capsaicin in both SHR and Wistar-Kyoto rats (WKY). Mean arterial pressure was increased in SHR compared with WKY (P<0.05). Intravenous administration of capsaicin caused a greater depressor response in SHR compared with WKY (P<0.05), which was blocked by approximately 60% by CAPZ (P<0.05) in SHR only. Methanandamide caused a similar greater depressor response (P<0.05), which was blocked by approximately 50% and 60% by CAPZ and SR141716A, respectively, in SHR (P<0.05) but not in WKY. Radioimmunooassay showed that methanandamide increased plasma calcitonin gene-related peptide (CGRP) levels from baseline in both SHR and WKY (P<0.05), with no difference between 2 strains. Western blot showed that protein expression for the calcitonin receptor-like receptor-but not receptor activity modifying protein 1, VR1, and cannabinoid type 1 receptors-was increased in mesenteric resistance arteries in SHR compared with WKY (P<0.05). These data indicate that in addition to activation of cannabinoid type 1, anandamide may serve as an endogenous compound to stimulate VR1, leading to a decrease in blood pressure via CGRP release from sensory nerve terminals. Increased mesenteric CGRP receptor expression in SHR may account for increased sensitivity of blood pressure to anandamide and may serve as a compensatory response to buffer the increase in blood pressure in SHR.


Anandamide (N-arachidonoylethanolamine, AEA) is an endogenous lipid that binds to cannabinoid receptors in the central nervous system and in peripheral cells. Quantitative analysis of AEA is generally based on the normalization to the fresh weight of the samples. Here, we show
that the normalization procedure of AEA content is such a critical factor, that it might introduce per se significant discrepancies in the quantification of AEA even in the same sample. We suggest that a rapid, accurate and most reliable reference to quantify AEA and congeners from different sources is the protein content, a common parameter to cells and tissues.


Endocannabinoids seem to play a role in the modulation of alertness. Therefore, we measured cannabinoid receptor 1 (CB1R) protein by Western blot and messenger RNA (mRNA) by reverse transcription-polymerase chain reaction in the pons of rats across the 24-h period. We performed evaluations every 4 h beginning at 09:00 h. Rats were under a controlled light/dark cycle 12:12 (lights on at 08:00 h). Our data suggest that the expression of CB1R gene depends on diurnal variations, with maximum expression at 13:00 h for protein and 21:00 h for mRNA, and minimum expression at 01:00 and 09:00 h, respectively. We also analyzed CB1R protein and mRNA levels in the pons of rats deprived of total sleep for 24 h and in rats with a 24-h period of sleep deprivation plus a 2-h period of sleep rebound. Unlike sleep deprivation, sleep rebound significantly increased CB1R protein while decreasing mRNA. Despite the fact that we used gentle manipulation to deprive the animals of sleep, there may be a potential influence of stress on this effect, too. However, these facts suggest that CB1R gene expression is modulated by the light/dark cycle and by sleep.


The present studies were conducted to test the hypothesis that systemically inactive doses of cannabinoids suppress inflammation-evoked neuronal activity in vivo via a peripheral mechanism. We examined peripheral cannabinoid modulation of spinal Fos protein expression, a marker of neuronal activity, in a rat model of inflammation. Rats received unilateral intraplantar injections of carrageenan (3%). In behavioral studies, carrageenan induced allodynia and mechanical hyperalgesia in response to stimulation with von Frey monofilaments. The cannabinoid agonist WIN55,212-2 (30 &mgr;g intraplantarly), administered concurrently with carrageenan, attenuated carrageenan-evoked allodynia and hyperalgesia relative to control conditions. In immunocytochemical studies, WIN55,212-2 suppressed the development of carrageenan-evoked Fos protein expression in the lumbar dorsal horn of the spinal cord relative to vehicle treatment. The same dose administered systemically or to the noninflamed contralateral paw failed to alter either carrageenan-evoked allodynia and hyperalgesia or carrageenan-evoked Fos protein expression, consistent with a peripheral site of action. The suppressive effects of WIN55,212-2 (30 &mgr;g intraplantarly) on carrageenan-evoked Fos protein expression and pain behavior were blocked by local administration of either the CB(2) antagonist SR144528 (30 &mgr;g intraplantarly) or the CB(1) antagonist SR141716A (100 &mgr;g intraplantarly). WIN55,212-3, the enantiomer of the active compound, also failed to suppress carrageenan-evoked Fos protein expression. These data provide direct evidence that a peripheral cannabinoid mechanism suppresses the development of inflammation-evoked neuronal activity at the level of the spinal dorsal horn and implicate a role for CB(2) and CB(1) in peripheral cannabinoid modulation of inflammatory nociception.


Three experiments examined the influence of pre-exposure to the cannabinoid receptor agonist CP 55,940 ((-)-cis-3-(2-hydroxy-4-(1,1-dimethylheptyl)phenyl)-trans-4-(3-hydroxyprop yl)cyclohexanol) on the sensitization of morphine-induced locomotor hyperactivity and self-administration in Lewis rats. In Experiment 1, rats received daily injections of vehicle or CP 55,940 (0.1 mg/kg for 7 days then 0.2 mg/kg for a further 7 days). Four weeks later, the locomotor response to morphine (10 mg/kg s.c.) was tested once per day over a 3-h period for 14 consecutive days. Rats given morphine showed hypoactivity during the first hour following
morphine but hyperactivity during the second and third hours. A progressive increase in hyperactivity to morphine was seen over the 14 days of administration, which was significantly greater in rats pre-treated with CP 55,940. In Experiment 2, rats were given morphine (10 mg/kg) once a day for 14 days in combination with either vehicle, CP 55,940 (0.1 mg/kg) or the cannabinoid CB(1) receptor antagonist SR 141716 (N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride) (3 mg/kg). Both CP 55,940 and SR 141716 initially inhibited the hyperactive response to morphine, but these effects gradually wore off and by the end of 14 days, hyperactivity was similar in all morphine-treated groups. When tested 3 weeks later for their response to morphine (10 mg/kg) given alone, rats previously given the morphine/CP 55,940 combination, but not the SR 141716/morphine combination, showed a greater locomotor stimulation than those previously exposed to morphine only. In Experiment 3, rats were pre-exposed to CP 55,940 or vehicle for 14 days and were subsequently trained to self-administer morphine intravenously (1 mg/kg per lever press) for 14 days. Rats pre-exposed to CP 55,940 self-administered a significantly greater number of morphine infusions than vehicle pre-exposed rats. However, both active and inactive (‘dummy’) lever presses were increased by cannabinoid pre-treatment. Overall, these results suggest that cannabinoid pre-exposure can lead to an exaggeration of morphine-induced hyperactivity and may alter the reinforcing effects of morphine in Lewis rats. The implications for ‘gateway’ theories of cannabinoid effects in humans are discussed.


The cannabinoid analog abnormal cannabidiol [abn-cbd; (-)-4-(3-3,4-trans-p-menthadien-1,8-yl)-olivetol] does not bind to CB(1) or CB(2) receptors, yet it acts as a full agonist in relaxing rat isolated mesenteric artery segments. Vasorelaxation by abn-cbd is endothelium-dependent, pertussis toxin-sensitive, and is inhibited by the BK(Ca) channel inhibitor charybdotoxin, but not by the nitric-oxide synthase inhibitor N(omega)-nitro-L-arginine methyl ester or by the vanilloid VR1 receptor antagonist capsazepine. The cannabidiol analog O-1918 does not bind to CB(1) or CB(2) receptors and does not cause vasorelaxation at concentrations up to 30 microM, but it does cause concentration-dependent (1-30 microM) inhibition of the vasorelaxant effects of abn-cbd and anandamide. In anesthetized mice, O-1918 dose-dependently inhibits the hypotensive effect of abn-cbd but not the hypotensive effect of the CB(1) receptor agonist (-)-11-OH-Delta(9)-tetrahydrocannabinol dimethylheptyl. In human umbilical vein endothelial cells, abn-cbd induces phosphorylation of p42/44 mitogen-activated protein kinase and protein kinase B/Akt, which is inhibited by O-1918, by pertussis toxin or by phosphatidylinositol 3 (PI3) kinase inhibitors. These findings indicate that abn-cbd is a selective agonist and that O-1918 is a selective, silent antagonist of an endothelial "anandamide receptor", which is distinct from CB(1) or CB(2) receptors and is coupled through G(i)/G(o) to the PI3 kinase/Akt signaling pathway.


This study examined behavioural signs that occur during tolerance development to cannabinoid treatment and hormonal and gene expression alterations induced by spontaneous cannabinoid withdrawal in mice. Tolerance to CP-55,940 treatment developed for hypothermia, ambulatory and exploratory locomotor activity. Cessation of cannabinoid treatment resulted in a behaviour withdrawal syndrome characterized by a pronounced increase in ambulatory activity and rearings. Corticosterone plasma concentrations dramatically increased 24 and 72 h after cessation of cannabinoid treatment. Similarly, an increase (40%) in cannabinoid [35S]GTPgammaS binding autoradiography was detected on days 1 and 3 of abstinence. Spontaneous cannabinoid withdrawal produced time-related significant alterations in gene transcription: (i) decreased (20%) tyrosine hydroxylase (TH) mRNA levels in the ventral tegmental area and increased (50%) in substantia nigra; (ii) increased proenkephalin (PENK) gene expression more than 100% in caudate-putamen, nucleus accumbens, olfactory tubercle and piriform cortex; (iii) increased (20-40%) pro-opiomelanocortin (POMC) gene expression in the arcuate nucleus of the hypothalamus. These results suggest that spontaneous cannabinoid withdrawal occur after cessation of CP-55,940 treatment. This 'syndrome' includes behavioural,
hormonal and gene transcription alterations that seems to be part of the regulation of neuronal plasticity induced by spontaneous cannabinoid withdrawal.


**RATIONALE.** The selective CB(1) receptor antagonist, SR 141716, has been demonstrated to reduce food consumption in a range of animal species. **OBJECTIVE.** To assess the effect of chronic administration of SR 141716 on body weight and ingestive behaviour of lean and obese (fa/fa) Zucker rats. **METHODS.** Lean and obese Zucker rats were orally dosed with SR 141716 (3, 10, 30 mg/kg PO), sibutramine (5 mg/kg PO) or vehicle for one week. Pair-fed controls provided insight as to whether the effect of SR 141716 on body weight was attributable to drug-induced hypophagia. Subsequently, the effect of chronic oral administration of SR 141716 (1, 3, 10 mg/kg) was assessed for 28 days. At the end of this period, all animals were given vehicle for 14 days. The incidence of wet-dog shakes, yawning, scratching, and grooming behaviours, was assessed after acute administration and at weekly intervals thereafter for 4 weeks. **RESULTS.** SR 141716 dose-dependently decreased food intake and body weight gain in both lean and obese animals. The inhibition of food intake and body weight gain was greater in obese Zuckers than in lean Zucker controls. Changes in the body weights of pair-fed controls closely paralleled those of their drug-treated counterparts. Chronic 28-day treatment led to a maintained reduction of body weight gain. Withdrawal of SR 141716 on day 28 resulted in rebound hyperphagia and a significant weight gain. On acute administration, SR 141716 dose-dependently induced motor behaviours that showed tolerance upon repeated administration. **CONCLUSION.** These data indicate that chronic oral treatment with SR 141716 significantly reduces the food intake and body weight gain of obese and lean Zucker rats, an effect that is greater in obese animals and reversible upon drug withdrawal.


Opioids and cannabinoids are among the most widely consumed drugs of abuse in humans and the phenomena of cross-tolerance or mutual potentiation have been demonstrated between the two drugs. Several authors have suggested that both drugs share common links in their molecular mechanisms of action, although this has been a matter of controversy. Furthermore, no data exist on the possible adaptive changes in the contents of arachidonoylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), the two major endogenougs ligands for cannabinoid receptors, in morphine-tolerant rats. In the present work, we investigated the alterations in cannabinoid receptor functionality and endocannabinoid levels in rats chronically treated with morphine (5 mg/kg, s.c., twice a day for 5 days). Autoradiographic-binding studies using ([3]H)CP-55 940 revealed a slight but significant reduction in cannabinoid receptor level in the cerebellum and hippocampus of morphine-tolerant rats, while CP-55 940-stimulated ([35]S)GTPgammaS binding showed a strong decrease (40%) in receptor/G protein coupling in the limbic area of these animals. Moreover, in the same brain regions we measured, by isotope-dilution gas chromatography/mass spectrometry, the contents of AEA and 2-AG. Chronic morphine exposure produced a strong reduction in 2-AG contents without changes in AEA levels in several brain regions (ie striatum, cortex, hippocampus, limbic area, and hypothalamus). These findings clearly demonstrate that prolonged activation of opioid receptors could alter the cannabinoid system, in terms of both receptor functionality and endocannabinoid levels, and suggest the involvement of this system, alone or in combination with other mediators, in the phenomenon of morphine tolerance. Neuropsychopharmacology advance online publication, 12 March 2003; doi:10.1038/sj.npp.1300117

Male Lewis rats (two groups of 10) received intracerebroventricular injections of either AM 630 (vehicle, 2.5, 5, 10 and 20 &mgr;g) or AM 281 (vehicle, 5, 10, 20 and 40 &mgr;g) following overnight food deprivation. The CB2 antagonist AM 630 failed to block deprivation-induced intake at 0.5, 1, 2, 4 and 6 h. The CB1 antagonist AM 281 significantly blocked intake following 20 &mgr;g (1 h) and 40 &mgr;g (1, 2, 4 and 6 h). Results are discussed with respect to cannabinoid receptor systems' involvement in ingestion and the differential pharmacological profiles of AM 630 and AM 281.

CLINICAL SCIENCE


Delta(9)-Tetrahydrocannabinol (the active ingredient of marijuana), as well as endogenous and synthetic cannabinoids, exert many biological functions by activating two types of cannabinoid receptors, CB(1) and CB(2) receptors. CB(1) receptors have been detected on enteric nerves, and pharmacological effects of their activation include gastroprotection, reduction of gastric and intestinal motility and reduction of intestinal secretion. The digestive tract also contains endogenous cannabinoids (i.e., the endocannabinoids anandamide and 2-arachidonylglycerol) and mechanisms for endocannabinoid inactivation (i.e., endocannabinoids uptake and enzymatic degradation). Cannabinoid receptors, endocannabinoids and the proteins involved in endocannabinoids inactivation are collectively referred as the 'endogenous cannabinoid system'. A pharmacological modulation of the endogenous cannabinoid system could provide new therapeutics for the treatment of a number of gastrointestinal diseases, including nausea and vomiting, gastric ulcers, irritable bowel syndrome, Crohn's disease, secretory diarrhoea, paralytic ileus and gastroesophageal reflux disease. Some cannabinoids are already in use clinically, for example, nabilone and Delta(9)-tetrahydrocannabinol are used as antiemetics.


Introduction. - The responsibility of cannabis in juvenile thromboangiitis has been suggested for few years. We describe four new cases. Exegesis. - Young men presented with distal arteriopathy of the lower limbs in 3 cases, and of the left upper limb in the remaining patient. Symptoms occurred progressively, distal pulses had disappeared, and distal necrosis was constant. Three patients suffered from Raynaud phenomenon, none of them presented with venous thrombosis. Radiologic evaluation revealed distal abnormalities in all cases, and proximal arterial thrombosis in one case. The four patients were cannabis smokers for at least four years. With cannabis interruption and symptomatic treatment, lesions improved for three patients. For one of them, recurrence of arteriopathy occurred when he resumed to smoke cannabis. For the fourth one who never stopped cannabis, an amputation was necessary. Conclusion. - Search for cannabis use is important because interruption may improve prognosis.


The ability of Cannabis sativa (marijuana) to increase hunger has been noticed for centuries, although intensive research on its molecular mode of action started only after the characterization of its main psychoactive component Delta(9)-tetrahydrocannabinol in the late 1960s. Despite the public concern related to the abuse of marijuana and its derivatives, scientific studies have pointed to the therapeutic potentials of cannabinoid compounds and have highlighted their ability to stimulate appetite, especially for sweet and palatable food. Later, the discovery of specific receptors and their endogenous ligands (endocannabinoids) suggested the existence of an endogenous cannabinoid system, providing a physiological basis for biological effects induced by marijuana and other cannabinoids. Epidemiological reports describing the
appetite-stimulating properties of cannabinoids and the recent insights into the molecular mechanisms underlying cannabinoid action have proposed a central role of the cannabinoid system in obesity. The aim of this review is to provide an extensive overview on the role of this neuromodulatory system in feeding behavior by summarizing the most relevant data obtained from human and animal studies and by elucidating the interactions of the cannabinoid system with the most important neuronal networks and metabolic pathways involved in the control of food intake. Finally, a critical evaluation of future potential therapeutical applications of cannabinoid antagonists in the therapy of obesity and eating disorders will be discussed.


The major psychoactive constituent of Cannabis sativa, Delta(9)-tetrahydrocannabinol (Delta(9)-THC), and endogenous cannabinoid ligands, such as anandamide, signal through G-protein-coupled cannabinoid receptors localised to regions of the brain associated with important neurological processes. Signalling is mostly inhibitory and suggests a role for cannabinoids as therapeutic agents in CNS disease where inhibition of neurotransmitter release would be beneficial. Anecdotal evidence suggests that patients with disorders such as multiple sclerosis smoke cannabis to relieve disease-related symptoms. Cannabinoids can alleviate tremor and spasticity in animal models of multiple sclerosis, and clinical trials of the use of these compounds for these symptoms are in progress. The cannabinoid nabilone is currently licensed for use as an antiemetic in chemotherapy-induced emesis. Evidence suggests that cannabinoids may prove useful in Parkinson’s disease by inhibiting the excitotoxic neurotransmitter glutamate and counteracting oxidative damage to dopaminergic neurons. The inhibitory effect of cannabinoids on reactive oxygen species, glutamate and tumour necrosis factor suggests that they may be potent neuroprotective agents. Dexamabinol (HU-211), a synthetic cannabinoid, is currently being assessed in clinical trials for traumatic brain injury and stroke. Animal models of mechanical, thermal and noxious pain suggest that cannabinoids may be effective analgesics. Indeed, in clinical trials of postoperative and cancer pain and pain associated with spinal cord injury, cannabinoids have proven more effective than placebo but may be less effective than existing therapies. Dronabinol, a commercially available form of Delta(9)-THC, has been used successfully for increasing appetite in patients with HIV wasting disease, and cannabinoid receptor antagonists may reduce obesity. Acute adverse effects following cannabis usage include sedation and anxiety. These effects are usually transient and may be less severe than those that occur with existing therapeutic agents. The use of nonpsychoactive cannabinoids such as cannabidiol and dexamabinol may allow the dissociation of unwanted psychoactive effects from potential therapeutic benefits. The existence of other cannabinoid receptors may provide novel therapeutic targets that are independent of CB(1) receptors (at which most currently available cannabinoids act) and the development of compounds that are not associated with CB(1) receptor-mediated adverse effects. Further understanding of the most appropriate route of delivery and the pharmacokinetics of agents that act via the endocannabinoid system may also reduce adverse effects and increase the efficacy of cannabinoid treatment. This review highlights recent advances in understanding of the endocannabinoid system and indicates CNS disorders that may benefit from the therapeutic effects of cannabinoid treatment. Where applicable, reference is made to ongoing clinical trials of cannabinoids to alleviate symptoms of these disorders.


Delta(9)-Tetrahydrocannabinol (THC) is the main source of the pharmacological effects caused by the consumption of cannabis, both the marijuana-like action and the medicinal benefits of the plant. However, its acid metabolite THC-COOH, the non-psychotropic cannabidiol (CBD), several cannabinoid analogues and newly discovered modulators of the endogenous cannabinoid system are also promising candidates for clinical research and therapeutic uses. Cannabinoids exert many effects through activation of G-protein-coupled cannabinoid receptors in the brain and peripheral tissues. Additionally, there is evidence for non-receptor-dependent mechanisms. Natural cannabis products and single cannabinoids are usually inhaled or taken orally; the rectal
route, sublingual administration, transdermal delivery, eye drops and aerosols have only been used in a few studies and are of little relevance in practice today. The pharmacokinetics of THC vary as a function of its route of administration. Pulmonary assimilation of inhaled THC causes a maximum plasma concentration within minutes, psychotropic effects start within seconds to a few minutes, reach a maximum after 15-30 minutes, and taper off within 2-3 hours. Following oral ingestion, psychotropic effects set in with a delay of 30-90 minutes, reach their maximum after 2-3 hours and last for about 4-12 hours, depending on dose and specific effect. At doses exceeding the psychotropic threshold, ingestion of cannabis usually causes enhanced well-being and relaxation with an intensification of ordinary sensory experiences. The most important acute adverse effects caused by overdosing are anxiety and panic attacks, and with regard to somatic effects increased heart rate and changes in blood pressure. Regular use of cannabis may lead to dependency and to a mild withdrawal syndrome. The existence and the intensity of possible long-term adverse effects on psyche and cognition, immune system, fertility and pregnancy remain controversial. They are reported to be low in humans and do not preclude legitimate therapeutic use of cannabis-based drugs. Properties of cannabis that might be of therapeutic use include analgesia, muscle relaxation, immunosuppression, sedation, improvement of mood, stimulation of appetite, antiemesis, lowering of intraocular pressure, bronchodilation, neuroprotection and induction of apoptosis in cancer cells.


OBJECTIVES: To determine whether plant-derived cannabis medicinal extracts (CME) can alleviate neurogenic symptoms unresponsive to standard treatment, and to quantify adverse effects. DESIGN: A consecutive series of double-blind, randomized, placebo-controlled single-patient cross-over trials with two-week treatment periods. SETTING: Patients attended as outpatients, but took the CME at home. SUBJECTS: Twenty-four patients with multiple sclerosis (18), spinal cord injury (4), brachial plexus damage (1), and limb amputation due to neurofibromatosis (1). INTERVENTION: Whole-plant extracts of delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), 1:1 CBD:THC, or matched placebo were self-administered by sublingual spray at doses determined by titration against symptom relief or unwanted effects within the range of 2.5-120 mg/24 hours. Measures used: Patients recorded symptom, well-being and intoxication scores on a daily basis using visual analogue scales. At the end of each two-week period an observer rated severity and frequency of symptoms on numerical rating scales, administered standard measures of disability (Barthel Index), mood and cognition, and recorded adverse events. RESULTS: Pain relief associated with both THC and CBD was significantly superior to placebo. Impaired bladder control, muscle spasms and spasticity were improved by CME in some patients with these symptoms. Three patients had transient hypotension and intoxication with rapid initial dosing of THC-containing CME. CONCLUSIONS: Cannabis medicinal extracts can improve neurogenic symptoms unresponsive to standard treatments. Unwanted effects are predictable and generally well tolerated. Larger scale studies are warranted to confirm these findings.


Cannabis occurs naturally in the dried flowering or fruiting tops of the Cannabis sativa plant. Cannabis is most often consumed by smoking marihuana. Cannabinoids are the active compounds extracted from cannabis. Recently, there has been renewed interest in cannabinoids for medicinal purposes. The two proven indications for the use of the synthetic cannabinoid (dronabinol) are chemotherapy-induced nausea and vomiting and AIDS-related anorexia. Other possible effects that may prove beneficial in the oncology population include analgesia, antitumor effect, mood elevation, muscle relaxation, and relief of insomnia. Two types of cannabinoid receptors, CB1 and CB2, have been detected. CB1 receptors are expressed mainly in the central
and peripheral nervous system. CB2 receptors are found in certain nonneuronal tissues, particularly in the immune cells. Recent discovery of both the cannabinoid receptors and endocannabinoids has opened a new era in research on the pharmaceutical applications of cannabinoids. The use of cannabinoids should be continued in the areas indicated, and further studies are needed to evaluate other potential uses in clinical oncology.


There has been a surge in interest in medicinal cannabis in Canada. We conducted a questionnaire survey to determine the current prevalence of medicinal cannabis use among patients with chronic non-cancer pain, to estimate the dose size and frequency of cannabis use, and to describe the main symptoms for which relief was being sought. Over a 6-week period in mid-2001, 209 chronic non-cancer pain patients were recruited in an anonymous cross-sectional survey. Seventy-two (35%) subjects reported ever having used cannabis. Thirty-two (15%) subjects reported having used cannabis for pain relief (pain users), and 20 (10%) subjects were currently using cannabis for pain relief. Thirty-eight subjects denied using cannabis for pain relief (recreational users). Compared to never users, pain users were significantly younger (P=0.001) and were more likely to be tobacco users (P=0.0001). The largest group of patients using cannabis had pain caused by trauma and/or surgery (51%), and the site of pain was predominantly neck/upper body and myofascial (68% and 65%, respectively). The median duration of pain was similar in both pain users and recreational users (8 vs. 7 years; P=0.7). There was a wide range of amounts and frequency of cannabis use. Of the 32 subjects who used cannabis for pain, 17 (53%) used four puffs or less at each dosing interval, eight (25%) smoked a whole cannabis cigarette (joint) and four (12%) smoked more than one joint. Seven (22%) of these subjects used cannabis more than once daily, five (16%) used it daily, eight (25%) used it weekly and nine (28%) used it rarely. Pain, sleep and mood were most frequently reported as improving with cannabis use, and ‘high’ and dry mouth were the most commonly reported side effects. We conclude that cannabis use is prevalent among the chronic non-cancer pain population, for a wide range of symptoms, with considerable variability in the amounts used. Discussions between patients and health care providers concerning cannabis use may facilitate education and follow up, and would allow side effects and potential interactions with other medications to be monitored. Clinical trials of cannabis for chronic non-cancer pain are warranted.

BEHAVIOURAL SCIENCE


LITTLE IS KNOWN ABOUT THE RISK OF INJURY among adolescents who drive after the use of alcohol or cannabis or ride in cars driven by drunk drivers. We examined data from self-administered interviews with 1846 students in grades 7 to 13 who participated in the 2001 Ontario Student Drug Use Survey about their experiences related to alcohol, cannabis and driving during the 12 months preceding the survey. In all, 31.9% of the students reported being a passenger in a car driven by a drunk driver; of the students in grades 10 to 13 who had a driver's licence, 15.1% reported driving within an hour after consuming 2 or more drinks, and 19.7% reported driving within an hour after using cannabis. Our study shows that a sizeable proportion of adolescents are exposed to alcohol- and drug-related driving risks.


The high prevalence of psychoactive substance abuse or dependence among schizophrenic patients has now been well established. Mueser et al. stressed the need to assess the abuse of specific classes of substances and analyse the data accordingly. The objective of this study was to compare the socio-demographic correlates and the clinical features in a group of schizophrenic patients with a lifetime cannabis abuse or dependence according to the DSM III-R with a group of schizophrenic patients who had never presented any abuse or dependence.
Subjects and methods - The study included 124 subjects with diagnoses of schizophrenia or schizoaffective disorders according to the DSM III-R. Inclusion criteria for participation in the study were age 18 years or older and willingness to provide consent to participate in the study. The inpatients were evaluated when their condition was stabilised. Assessment tools were the psychoactive substance use disorder section of the Composite International Diagnostic Interview (CIDI), the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning Scale (GAF). Subjects with cannabis abuse or dependence during their lifetime were compared with subjects without abuse or dependence, using c(2) test for categorical variables and analyses of covariance (ANCOVA) for quantitative variables. Results - Forty-nine subjects (42.6%) presented lifetime abuse or dependence on one or more substances. Since 19 patients with alcohol, stimulant, sedative or opiate abuse or dependence were excluded, the study finally included 96 subjects including a first group of schizophrenic patients with cannabis abuse (n=6) or dependence (n=24) and a second group without any psychoactive substance abuse (n=66). Thirteen (11.3%) patients presented cannabis abuse or dependence within the 6 months prior to the assessment. The mean SD age of onset of cannabis abuse or dependence was 19.6 3.0 years. Cannabis abuse/dependence preceded the first psychiatric treatment in 70% of the subjects (n=21). 83.3% of the schizophrenic patients with cannabis abuse or dependence were male (n=25) compared to 62.1% in the group without substance abuse (n=41) (c(2)=4.32, df=1, p=0.04). Schizophrenic patients with cannabis abuse were significantly younger (mean age: 28.9 6.3 vs 37.0 12.7, ANCOVA, F=7.2, df=1,96 p=0.009). There was no significant difference between the two groups for marital status, (c(2)=5.34, df=2, p=0.07), level of education, (c(2)=0.93, df=2, p=0.62) professional status, (c(2)=8.7, df=5, p=0.11), on PANSS total score (ANCOVA, F=0.42, df=1,93, p=0.52), GAF score (ANCOVA, F=0.06, df=1,92, p=0.80), mean number of hospitalizations (ANCOVA, F=3.25, df=1,85, p=0.08), mean age of first psychiatric contact (ANCOVA, F=0.74, df=1,93, p=0.39), and neuroleptic dosages (ANCOVA, F=0.03, df=1,90, p=0.87). In contrast, the total duration of hospitalization was significantly longer for the group with cannabis abuse. Patients with cannabis abuse were more likely to have an history of suicide attempts than subjects without substance abuse (c(2)=11.52, df=1, p=0.0007). Discussion - The prevalence rates for substance abuse and the socio-demographic characteristics of the population of our study are consistent with findings of previous studies. Male gender and age were significantly related to history of cannabis abuse or dependence. Cannabis abuse frequently preceded the onset of psychiatric treatment. However, both schizophrenia and substance abuse tend to develop gradually, with no clear demarcation for the onset of schizophrenia. The absence of any link between the scores for the subscales of the PANSS and cannabis abuse, both in our study and in some retrospective previous studies, is not suggestive of cannabis abuse as a self-medication of positive or negative symptoms of schizophrenia. Self-medication could concern other symptoms, such as cognitive deficits. In addition, the hypothesis of self-medication has especially been suggested in cocaine abuse or dependence. Some limitations to this study can be discussed. First, although the recruitment was systematic and done in a public mental health service, the patients of our study are not necessarily representative of all schizophrenic patients. Secondly, as in any retrospective study, the prevalence of lifetime substance abuse may have been under-estimated. Urinary toxicology tests may have been able to improve the sensitivity of the diagnosis of recent substance abuse, but structured interviews are more appropriate for the diagnosis of lifetime substance abuse in schizophrenic patients than urinary toxicology tests. Conclusion - The socio-demographic characteristics of cannabis abuse or dependence in schizophrenia are similar to those found in general population. Cannabis using schizophrenic patients were more likely to be younger and male than non users. The duration of hospitalization was significantly longer for the group with cannabis abuse. Prevalence of suicide attempts in schizophrenia is closely correlated to cannabis abuse.


BACKGROUND: Cannabis use is widespread in our community. Dependence on cannabis may be associated with significant mental and physical harms. OBJECTIVE: This article aims to give an overview of the adverse effects of cannabis use and guidelines for management of cannabis dependence. DISCUSSION: General practitioners can manage cannabis
dependence from a harm minimisation framework using motivational interviewing and other counselling measures. Occasionally, pharmacologic approaches may be used with the caveat that they should be brief and carefully monitored.


BACKGROUND: Individuals who initiate cannabis use at an early age, when the brain is still developing, might be more vulnerable to lasting neuropsychological deficits than individuals who begin use later in life. METHODS: We analyzed neuropsychological test results from 122 long-term heavy cannabis users and 87 comparison subjects with minimal cannabis exposure, all of whom had undergone a 28-day period of abstinence from cannabis, monitored by daily or every-other-day observed urine samples. We compared early-onset cannabis users with late-onset users and with controls, using linear regression controlling for age, sex, ethnicity, and attributes of family of origin. RESULTS: The 69 early-onset users (who began smoking before age 17) differed significantly from both the 53 late-onset users (who began smoking at age 17 or later) and from the 87 controls on several measures, most notably verbal IQ (VIQ). Few differences were found between late-onset users and controls on the test battery. However, when we adjusted for VIQ, virtually all differences between early-onset users and controls on test measures ceased to be significant. CONCLUSIONS: Early-onset cannabis users exhibit poorer cognitive performance than late-onset users or control subjects, especially in VIQ, but the cause of this difference cannot be determined from our data. The difference may reflect (1) innate differences between groups in cognitive ability, antedating first cannabis use; (2) an actual neurotoxic effect of cannabis on the developing brain; or (3) poorer learning of conventional cognitive skills by young cannabis users who have eschewed academics and diverged from the mainstream culture.