INTRODUCTION
Here is the latest summary of research abstracts.

BASIC SCIENCE

The cannabinoid analog abnormal cannabidiol (abn-cbd) causes endothelium-dependent vasodilation in rat isolated mesenteric arteries through a G protein-coupled receptor distinct from CB1 or CB2. We examined the actions of abn-cbd on the electrophysiology of human umbilical vein endothelial cells (HUVEC), using the whole-cell version of the patch clamp technique. Voltage-steps produced non-inactivating outward currents, which were abolished by iberiotoxin or intracellular BAPTA. The presence of a BKCa channel in HUVEC was documented by RT-PCR. Abn-cbd concentration-dependently potentiated the outward current produced by a single voltage step. This potentiation was abolished by the cannabidiol analog O-1918 or by pertussis toxin, but was unaffected by CB1 or CB2 antagonists. HU-210, a CB1/CB2 receptor agonist, had no effect on the outward current. Clamping [Ca2+]i did not prevent abn-cbd-induced increases in outward current. cGMP potentiated the outward current and abn-cbd increased the cellular levels of cGMP. The increase in outward current produced by abn-cbd was blocked by KT-5823, an inhibitor of protein kinase G or ODQ, an inhibitor of soluble guanylate cyclase. We conclude that a Ca2+-activated K+ current in HUVEC is potentiated by activation of a Gi/Go-coupled receptor distinct from CB1 or CB2, which signals through cGMP and protein kinase G to increase channel availability, or the channels sensitivity to voltage and/or Ca2+. As iberiotoxin also inhibited abn-cbd-induced relaxation of intact, but not of endothelium-denuded, rat mesenteric artery segments, modulation of endothelial BKCa channels may underlie the mesenteric vasodilator action of abn-cbd.


RATIONALE. Despite the increasing use of cannabis among adolescents, there is scarce information about the long-term effects of cannabinoid receptor agonists in appropriate animal models. OBJECTIVES. We aimed to investigate the behavioural features of adult male and female Wistar rats that had been exposed to a chronic treatment with the cannabinoid receptor agonist CP 55,940 (CP) during the juvenile period. METHODS. CP (0.4 mg/kg i.p.) or its corresponding vehicle was administered once daily, from day 35 to day 45. In adulthood, the animals were tested in the holeboard, the open field and the elevated plus-maze, under different stress (illumination) conditions. After a resting period, the serum corticosterone levels (radioimmunoassay) of the animals were measured. The effects of CP on food intake and somatic growth were monitored throughout the experimental period. RESULTS. The CP treatment induced significant sex-dependent effects on holeboard activity, as well as a decrease in the level of emotionality/anxiety in the open field and in the plus-maze. The animals receiving CP also showed diminished food intake and body weights during the treatment period, but both parameters recovered normal values during the period after treatment. No significant effect of the
CP treatment on corticosterone levels was found. CONCLUSIONS. The results demonstrate that chronic administration of CP during the peri-adolescent period resulted in marked behavioural effects in adulthood. The nature of these effects depended on the sex of the animals and on the specific behavioural test. The possible neurobiological substrates underlying the effects of CP are discussed.


Three further derivatives of 5,7,2',4'-tetrahydroxy-6-methyl isoflavanone have been isolated from the root extract of Desmodium canum and assigned the structures 2,3-dihydro-5,7-dihydroxy-6-methyl-3-{1a,2,3a,8b,8c-hexahydro-6-hydroxy-1,1,3a-trimethyl-1H-4-oxabenzo[f]cyclobut[c,d]inden-7-yl]-4H-1-benzopyran-4-one (1) 2,3-dihydro-5,7-dihydroxy-6-methyl-3-(6a,7,8,10a-tetrahydro-3-hydroxy-6,9-trimethyl-6H-dibenzo[b,d]pyran-2-yl)-4H-1-benzopyran-4-one (2) 2,3-dihydro-5,7-dihydroxy-6-methyl-3-(3-hydroxy-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-2-yl) 4H-1-benzopyran-4-one (3). The three compounds and the previously isolated chromene 4 all derive from the geranylated precursor 5 by a series of cannabinoid-like oxidative rearrangements.


Many types of neurons can release endocannabinoids that act as retrograde signals to inhibit neurotransmitter release from presynaptic terminals. Little is known, however, about the properties or role of such inhibition under physiological conditions. Here we report that brief bursts of presynaptic activity evoked endocannabinoid release, which strongly inhibited parallel fiber-to-Purkinje cell synapses in rat cerebellar slices. This retrograde inhibition was triggered by activation of either postsynaptic metabotropic or ionotropic glutamate receptors and was restricted to synapses activated with high-frequency bursts. Thus, endocannabinoids allow neurons to inhibit specific synaptic inputs in response to a burst, thereby dynamically fine-tuning the properties of synaptic integration.


Chronic treatment with cannabinoid agonists leads to tolerance. One possible mechanism for this is receptor internalization, but tolerance has also been reported with compounds that only cause internalization to a low degree. Furthermore, cannabinoid antagonist administration precipitates a characteristic withdrawal syndrome in tolerant subjects, accompanied by neuronal activation and enhanced release of corticotropin-releasing hormone (CRH) in the central amygdala. The underlying molecular mechanisms are unknown. We examined the role of cannabinoid tolerance and withdrawal for the expression of the cannabinoid 1 (CB1) receptor and of CRH in rats. Tolerance was first established functionally. An acute dose (100 microg/kg) of the CB1 agonist HU-210 suppressed locomotor activity, and had an anxiogenic-like effect on the elevated plus-maze. Both effects were absent following daily treatment with the same agonist or a lower (40 microg/kg) dose for 14 days. Next, withdrawal was reliably precipitated by a single dose (3 mg/kg) of the CB1 antagonist SR141716A in rats treated subchronically with 14-day HU-210. Using in situ hybridization, a robust suppression of CB1 mRNA expression was found in the caudate-putamen, indicating a downregulation of CB1 expression levels as one mechanism for tolerance to the locomotor suppressant effects of HU-210. The CRH transcript was upregulated in the central amygdala in precipitated withdrawal compared to nonwithdrawn tolerant subjects, suggesting that increased gene expression contributes to the previously reported CRH release in withdrawal. Most importantly, this increase occurred from a suppressed level in tolerant subjects, and behavioral signs of withdrawal, presumably mediated by CRH, were seen at the CRH expression that had only returned to normal nontolerant levels. This suggests the possibility of an allostatic shift, as previously proposed on theoretical grounds. The expression of CRH-R1, CRH-R2alpha, NPY, and its Y1 receptor mRNA was analyzed in search of neural substrates for the allostatic shift observed, but
did not seem to contribute to the dysregulated state. Neuropsychopharmacology advance online publication, 10 September 2003; doi:10.1038/sj.npp.1300296


The medicinal properties of exogenous cannabinoids have been recognized for centuries and can largely be attributed to the activation in the nervous system of a single G-protein-coupled receptor, CB1. However, the beneficial properties of cannabinoids, which include relief of pain and spasticity, are counterbalanced by adverse effects such as cognitive and motor dysfunction. The recent discoveries of anandamide, a natural lipid ligand for CB1, and an enzyme, fatty acid amide hydrolase (FAAH), that terminates anandamide signaling have inspired pharmacological strategies to augment endogenous cannabinoid (endocannabinoid) activity with FAAH inhibitors, which might exhibit superior selectivity in their elicited behavioral effects compared with direct CB1 agonists.


1 We investigated the effect of the cannabinoid CB1 receptor antagonist, SR 141716, on indomethacin-induced small intestine inflammation and Escherichia coli lipopolysaccharide (LPS)-induced plasma TNF-alpha (TNF) release in comparison to the cannabinoid CB2 receptor antagonist, SR 144528, in rodents. 2 In rats, indomethacin induced significant ulcer formation in the small intestine; this was accompanied by an increase in tissue TNF levels and myeloperoxidase (MPO) activity. SR 14176 prevented the ulcers and the rise in TNF levels (ID50 3.3, 0.4 mg kg-1, respectively) and MPO activity. SR 144528 prevented intestinal ulcers only. 3 The effect of SR 141716 against indomethacin-induced ulcers and increase of plasma TNF levels after LPS was also studied in wild-type and CB1 receptor knockout mice. Indomethacin induced intestinal ulcers in mice, but not tissue TNF production and MPO activity. SR 141716 reduced the ulcers to a similar extent in wild-type and CB1 receptor knockout mice. In rats and wild-type mice, but not in CB1 receptor knockout mice, SR 141716 inhibited the LPS-induced increase in plasma TNF levels. 4 These findings provide evidence that the indomethacin model of intestinal lesions differs in rat and mouse and support the existence of several mechanisms for the antilulcer activity of SR141716, the most important involving the inhibition of TNF production. The potent anti-inflammatory activity of SR141716 in rodents indicated its potential therapeutic interest in chronic immune-inflammatory diseases. British Journal of Pharmacology (2003) 140, 115-122. doi:10.1038/sj.bjp.0705412


The present studies used a psychophysical approach to examine the effect of cannabinoids on temporal processing. Rats trained to discriminate 2- and 8-s (Experiment 1, n=72) and 4- and 16-s (Experiment 2, n=60) intervals were tested with intermediate durations. Psychophysical functions for time, relating the probability of judging a duration as "long" as a function of the actual stimulus durations, were characterized by measures of central tendency (point of subjective equality, PSE) and variability (Weber fraction, WF). The potent cannabinoid agonist, WIN55,212-2 (1-3mg/kg), produced a dose-related decrease in sensitivity to time (i.e. increase in WF) without systematically affecting PSE (Experiments 1 and 2). The central cannabinoid CB1 antagonist, SR141716A (1-3mg/kg), did not alter either the WF or PSE (Experiments 1 and 2). Coadministration of SR141716A with WIN55,212-2 blocked the effect of the agonist on WF (Experiment 2), suggesting that the WF effect is mediated by actions at cannabinoid CB1 receptors. Computational modeling with an information processing theory of timing suggests that the reduction in sensitivity to time can be attributed to a disorder of attention.

The effect of systemic administration of the cannabinoid antagonist SR 141716A (N-(piperidin-1-yl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide) on penile erection and yawning induced by apomorphine was investigated in rats. SR 141716A (2 mg/kg, i.p.) administered 40 min before apomorphine (40 and 80 microg/kg, s.c.) increased the number of penile erection and yawning responses. The administration of cannabinoid agonist Delta(9)-tetrahydrocannabinol (1.25 mg/kg, i.p.) 15 min before apomorphine (40 and 80 microg/kg, s.c.) did not affect penile erection, however it decreased yawning. The present results provide additional evidence that cannabinoid agonists interfere with dopaminergic systems and that SR 141716A together with a dopaminergic agonist could be useful to potentiate dopaminergic activity.


Large doses (10-40 mg/kg) of the selective cannabinoid CB(1) receptor antagonist, SR 141716A, produce the head-twitch response (HTR) and scratching in rodents and vomiting in the least shrew (Cryptotis parva). Agents that increase brain serotonin (5-HT) levels induce the HTR in rodents, whereas enhancements in either brain 5-HT or dopamine concentrations can lead to production of emesis in vomiting species. The present study was undertaken to demonstrate whether large doses of SR 141716A can (1) induce the HTR and scratching in the least shrew and (2) cause concurrent biochemical changes in brain 5-HT and dopamine concentrations. SR 141716A (0, 1, 5, 10, 20 and 40 mg/kg ip) administration induced the HTR, scratching and vomiting. The HTR effect was bell shaped with a maximum frequency occurring at the 20 mg/kg SR 141716A dose, whereas the scratching and vomiting behaviors displayed dose-dependent effects. The selective 5-HT(2A/C) receptor antagonist, SR 46349B (0, 0.1, 0.25, 1, 3 and 6 mg/kg ip), differentially attenuated all SR 141716A (20 mg/kg)-induced behaviors because the HTR was relatively more potent and completely blocked. In the shrew forebrain, SR 141716A (20 and 40 mg/kg ip) caused dose- and time-dependent increases in the levels of 5-HT and dopamine and the concentrations of their major metabolites [5-hydroxyindole acetic acid (5-HIAA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] and the turnover of both monoamines. Although the effects of SR 141716A on brainstem concentrations of both monoamines and their metabolites were not always consistent, the CB(1) antagonist did increase the turnover of both 5-HT and dopamine. The present findings suggest that the mechanism and the neurochemical substrate for SR 141716A-induced HTR and scratching behaviors is enhancement of 5-HT release, whereas increased release of 5-HT and dopamine probably contributes to the production of emesis.


SUMMARY: The present study estimated the apparent intrinsic activity of the cannabinoid CB1 receptor ligands CP 55,940, Delta9-tetrahydrocannabinol (Delta9-THC) and SR 141716A in a highly sensitive in vivo assay. Rats were trained to discriminate the cannabinoid CB1 receptor agonist CP 55,940 (either 0.03 or 0.014 mg/kg, i.p., t=30 min) from vehicle, in a two-lever food-reinforced procedure, and were subsequently tested with the three compounds. Although reduction of the training dose did not affect the maximum level of generalization or antagonism (>80% generalization for CP 55,940 and Delta9-THC; 0% generalization and >80% antagonism for SR 141716A), the potency of the compounds was differentially affected. Thus, the generalization curves obtained with CP 55,940 and Delta9-THC were shifted three- and sixfold to the left; whereas no potency difference was obtained for the antagonism of CP 55,940 by SR 141716A. The data are consistent with the hypothesis that the level of intrinsic activity of CP 55,940 is higher than that of Delta9-THC, and that SR 141716A may have a very low level of intrinsic activity. It is concluded that variation of the training dose increases the sensitivity of the in vivo intrinsic activity estimation of cannabinoid CB1 receptor ligands.

The effects of cannabinoids (CB) that have been reported in various leukocyte populations were mainly immunosuppressive or immunomodulatory. Almost nothing is known, however, about direct interactions of cannabinoids with human polymorphonuclear cells (PMN), although m-RNA for the cannabinoid receptor-2 (CB(2)) was found in human PMN. In order to investigate a potential influence of cannabinoids on human PMN, the migration and phagocytosis of PMN were studied in the presence of Delta(9)-Tetrahydrocannabinol (Delta(9)-THC) at final concentrations between 10(-10) and 10(-5) M. No effect was detectable on these essential PMN functions; and besides, no CB(2)-receptor expression could be detected using the Western blotting technique. Thus, circulating human PMN from healthy individuals remain unaffected by Delta(9)-THC due to the absence of functional CB(2)-receptor expression.


Analgeseic effects of cannabimimetic compounds have been known to be related to their central effects. Cannabinoid receptors also exist in the periphery but their role in pain perception has been remained to be clarified. Therefore, we assessed topical antinociceptive effects of WIN 55, 212-2, a mixed CB(1) and CB(2) receptors agonist, in mice using tail-flick test. Immersion of the tail of mouse into the WIN 55, 212-2 solution produced dose-dependent antinociception. This antinociceptive activity was limited to the portion of the tail exposed to WIN 55, 212-2. The antinociceptive response was dependent on duration of exposure to WIN 55, 212-2 solution. The topical antinociceptive effects of WIN 55, 212-2 were dose dependently blocked by topical pretreatment of CB(1) receptor-selective antagonist, AM 251. Thus, topical antinociceptive action of WIN 55, 212-2 involve CB(1) receptors. Intrathecal (i.th.) administration of WIN 55, 212-2 produced a dose-dependent antinociceptive effect. Interestingly, ineffective i.th. doses of WIN 55, 212-2 produced a marked antinociceptive when combined with topical application of WIN 55, 212-2 and topical antinociceptive effect was potentiated. The dose-response curve of i.th. WIN 55, 212-2 was shifted to the left 15-fold by topical WIN 55, 212-2. This finding suggests that there is an antinociceptive synergy between peripheral and spinal sites of cannabinoid action and it also implicates that local activation of cannabinoid system may regulate pain initiation in cutaneous tissue. Our findings support that cannabinoid system participates in buffering the emerging pain signals at the peripheral sites in addition to their spinal and supraspinal sites of action. In addition, an antinociceptive synergy between topical and spinal cannabinoid actions exists. These results also indicate that topically administered cannabinoid agonists may reduce pain without the dysphoric side effects and abuse potential of centrally acting cannabimimetic drugs.


The mechanism of action of immune suppression by cannabinoids involves suppression of interleukin-2 (IL-2) production in phorbol ester plus calcium ionophore (PMA/lo)-stimulated lymphocytes. This decrease in IL-2 was due to inhibition of activator protein-1 (AP-1) and nuclear factor of activated T cells (NF-AT) transcription factors, both of which depend on proteins that are regulated by the extracellular signal-regulated kinase subgroup of the mitogen-activated protein kinases (ERK MAPK). Thus, the objective of the present study was to characterize the effects of cannabinoid compounds on ERK MAPK under conditions where IL-2 expression was suppressed. Using the MEK inhibitor PD098059 in order to assess the role of ERK MAPK in PMA/lo-stimulated splenocytes (SPLC), it was determined that IL-2 production and expression of c-fos and c-jun nuclear protein expression depended on activation of ERK MAPK. In response to PMA/lo, expression of nuclear phosphorylated ERK MAPK was rapidly induced, peaked at approximately 15 min, and was sustained for up to 240 min. Pretreatment with cannabiol (CBN) inhibited expression of phosphorylated ERK MAPK at several time points up to 240 min post cellular activation. Furthermore, WIN-55212-2, a synthetic cannabinoid, inhibited expression of phosphorylated ERK MAPK at 240 min post cellular activation. CBN did not induce activation of
ERK MAPK in the absence of PMA/Io. Collectively, these studies suggest that cannabinoid-induced inhibition of IL-2 in PMA/Io-stimulated splenocytes might be due, in part, to inhibition of ERK MAPK activation.


The analgesic potential of cannabinoids may be hampered by their ability to produce aversive emotion when administered systemically. We investigated the hypothesis that the midbrain periaqueductal grey (PAG) is a common substrate mediating the anti-nociceptive and potential aversive effects of cannabinoids. The rat formalin test was used to model nociceptive behaviour. Intra-PAG microinjection of the excitatory amino acid D,L-homocysteic acid (DLH) was used to induce an aversive, panic-like reaction characteristic of the defensive "fight or flight" response. Administration of the cannabinoid receptor agonist HU210 (5 microg/rat) into the dorsal PAG significantly reduced the second phase of formalin-evoked nociceptive behaviour, an effect which was blocked by co-administration of the CB(1) receptor antagonist SR141716A (50 microg/rat). This anti-nociceptive effect was accompanied by an HU210-induced attenuation of the formalin-evoked increase in Fos protein expression in the caudal lateral PAG. Intra-dorsal PAG administration of HU210 (0.1, 1 or 5 microg/rat) significantly reduced the aversive DLH-induced explosive locomotor response. The anti-nociceptive effect of HU210 is likely to result from activation of the descending inhibitory pain pathway. Mechanisms mediating the anti-aversive effects of cannabinoids in the PAG remain to be elucidated. These data implicate a role for the PAG in both cannabinoid-mediated anti-nociceptive and anti-aversive responses.


It has previously been shown that the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG) inhibit the proliferation of C6 glioma cells in a manner that can be prevented by a combination of capsazepine (Caps) and cannabinoid (CB) receptor antagonists. It is not clear whether the effect of 2-AG is due to the compound itself, due to the rearrangement to form 1-arachidonoylglycerol (1-AG) or due to a metabolite. Here, it was found that the effects of 2-AG can be mimicked with 1-AG, both in terms of its potency and sensitivity to antagonism by Caps and CB receptor antagonists. In order to determine whether the effect of Caps could be ascribed to actions upon vanilloid receptors, the effect of a more selective vanilloid receptor antagonist, SB366791 was investigated. This compound inhibited capsaicin-induced Ca(2+) influx into rVR1-HEK293 cells with a pK(B) value of 6.8+/-.0.3. The combination of SB366791 and CB receptor antagonists reduced the antiproliferative effect of 1-AG, confirming a vanilloid receptor component in its action. 1-AG, however, showed no direct effect on Ca(2+) influx into rVR1-HEK293 cells indicative of an indirect effect upon vanilloid receptors. Identification of the mechanism involved was hampered by a large inter-experimental variation in the sensitivity of the cells to the antiproliferative effects of 1-AG. A variation was also seen with anandamide, which was not a solubility issue, since its water soluble phosphate ester showed the same variability. In contrast, the sensitivity to methanandamide, which was not sensitive to antagonism by the combination of Caps and CB receptor antagonists, but has similar physicochemical properties to anandamide, did not vary between experiments. This variation greatly reduces the utility of these cells as a model system for the study of the antiproliferative effects of anandamide. Nevertheless, it was possible to conclude that the antiproliferative effects of anandamide were not solely mediated by either its hydrolysis to produce arachidonic acid or its CB receptor-mediated activation of phospholipase A(2) since palmitoyl trifluoromethyl ketone did not prevent the response to anandamide. The same result was seen with the fatty acid amide hydrolase inhibitor palmitoyl ethylamide. Increasing intracellular arachidonic acid by administration of arachidonic acid methyl ester did not affect cell proliferation, and the modest antiproliferative effect of umbelliferyl arachidonate was not prevented by a combination of Caps and CB receptor antagonists.

Focal cerebral ischemia (FCI) induces rapid neuronal death in the ischemic core, which gradually expands toward the penumbra, partly as the result of a neuroinflammatory response. It is known that propagation of neuroinflammation involves microglial cells, the resident macrophages of the brain, which are highly motile when activated by specific signals. However, the signals that increase microglial cell motility in response to FCI remain mostly elusive. Here, we tested the hypothesis that endocannabinoids mediate neuroinflammation propagation by increasing microglial cell motility. We found that, in mouse cerebral cortex, FCI greatly increases palmitoylethanolamide (PEA), only moderately increases anandamide [arachidonylethanolamide (AEA)], and does not affect 2-arachidonoylglycerol levels. We also found that PEA potentiates AEA-induced microglial cell migration, without affecting other steps of microglial activation, such as proliferation, particle engulfment, and nitric oxide production. This potentiation of microglial cell migration by PEA involves reduction in cAMP levels. In line with this, we provide evidence that PEA acts through Gi/o-coupled receptors. Interestingly, these receptors engaged by PEA are pharmacologically distinct from CB1 and CB2 cannabinoid receptors, as well as from the WIN and abn-CBD (abnormal-cannabidiol) receptors, two recently identified cannabinoid receptors. Our results show that PEA and AEA increase after FCI and synergistically enhance microglial cell motility. Because such a response could participate in the propagation of the FCI-induced neuroinflammation within the CNS, and because PEA is likely to act through its own receptor, a better understanding of the receptor engaged by PEA may help guide the search for improved therapies against neuroinflammation.


Oleylethanolamide (OEA) is a naturally occurring lipid that regulates satiety and body weight. Although structurally related to the endogenous cannabinoid anandamide, OEA does not bind to cannabinoid receptors and its molecular targets have not been defined. Here we show that OEA binds with high affinity to the peroxisome-proliferator-activated receptor-alpha (PPAR-alpha), a nuclear receptor that regulates several aspects of lipid metabolism. Administration of OEA produces satiety and reduces body weight gain in wild-type mice, but not in mice deficient in PPAR-alpha. Two distinct PPAR-alpha agonists have similar effects that are also contingent on PPAR-alpha expression, whereas potent and selective agonists for PPAR-gamma and PPAR-beta/delta are ineffective. In the small intestine of wild-type but not PPAR-alpha-null mice, OEA regulates the expression of several PPAR-alpha target genes: it initiates the transcription of proteins involved in lipid metabolism and represses inducible nitric oxide synthase, an enzyme that may contribute to feeding stimulation. Our results, which show that OEA induces satiety by activating PPAR-alpha, identify an unexpected role for this nuclear receptor in regulating behaviour, and raise possibilities for the treatment of eating disorders.


Increased COX-2 expression and elevated PGE2 have been associated with a poor prognosis in lung cancer. Cannabinoids have been known to exert some of their biological effects via modulation of prostaglandin production. We evaluated the impact of methanandamide on COX-2 expression, PGE2 production, and tumor growth in murine lung cancer. Methanandamide administration (5 mg/kg, four times/wk i.p.) resulted in an increased rate of tumor growth (P<0.01 compared with diluent treated controls). The CB1 and CB2 receptor antagonists, SR141716 and SR144528, did not block the methanandamide-mediated increase in tumor growth. In vivo, methanandamide treatment increased the production of PGE2 at the tumor site as well as in splenocytes. Consistent with these results, methanandamide increased PGE2 and COX-2 levels in murine lung cancer cells in vitro via a cannabinoid receptor-independent mechanism. The COX-2-specific inhibitor, SC58236, abrogated methanandamide induction of PGE2 production in vitro and blocked methanandamide-enhanced tumor growth in vivo. Furthermore, the p38/MAPK inhibitor, SB203582, and the p42/44 inhibitor, PD98059, blocked methanandamide-mediated induction of PGE2 and COX-2. These results suggest that methanandamide augments tumor
growth by a cannabinoid receptor-independent pathway that is associated with the up-regulation of COX-2.


Dronabinol, a synthetic agonist at cannabinoid receptors, was reported to decrease the pruritus of cholestasis, in an uncontrolled observation. We hypothesized that the reported antipruritic effect of dronabinol might have resulted from an increased threshold to experience nociception (i.e. pruritus) by the drug. To test this hypothesis, we studied the effect of WIN 55, 212-2, a cannabinoid agonist, on the threshold to experience nociception, using a tail-flick assay in rats with cholestasis secondary to bile duct resection and in sham-resected controls. The administration of WIN 55, 212-2 was associated with a significant increase in the mean tail-flick latency in both groups as compared to baseline. Pruritus is a nociceptive stimulus; accordingly, drugs that increase the threshold to nociception in human beings may be a novel approach to the treatment of this symptom in patients with liver disease.


The effects of neurotoxic destruction of catecholaminergic projections to the spinal cord on cannabinoid antinociception were examined in models of acute and tonic nociception. High performance liquid chromatography was used to quantify monoamine levels in sham-operated and lesioned rats. Intrathecal administration of the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA) induced a selective depletion of norepinephrine (by approximately 85% of control) in rat lumbar spinal cord without altering levels of dopamine or serotonin. By contrast, brain levels of monoamines did not differ in sham-operated and lesioned rats. Pain behavior was similar in sham-operated and lesioned rats receiving vehicle in models of both acute and tonic nociception. The cannabinoid agonist WIN55,212-2 (5 or 10 mg/kg, i.p.) produced antinociception in the tail-flick test in sham-operated rats. The antinociceptive effect of WIN55,212-2 was attenuated relative to control conditions in rats depleted of spinal norepinephrine. WIN55,212-2 suppressed tonic pain behavior in the formalin test in sham-operated rats during phase 2 (15-60 min post formalin) of nociceptive responding. By contrast, in lesioned rats, WIN55,212-2 suppressed pain behavior during phase 1 (0-9.9 min) and phase 2A (10-39.9 min), but not during phase 2B (40-60 min). The cannabinoid agonist suppressed formalin-evoked Fos protein expression, a marker of neuronal activity, in the lumbar dorsal horn of sham-operated rats, but no suppression was observed in lesioned rats. The number of formalin-evoked Fos-like immunoreactive (FLI) cells was greater in lamina I and II of lesioned rats relative to sham-operated rats. These data indicate that the suppressive effect of the cannabinoid on formalin-evoked Fos protein expression in the superficial dorsal horn was attenuated following destruction of descending noradrenergic pathways. Our data are consistent with the hypothesis that cannabinoids produce antinociception, in part, by modulating descending noradrenergic systems and support a differential involvement of noradrenergic projections to the spinal cord in cannabinoid modulation of acute versus tonic nociception.


Knowledge of the cannabinoid system and its components has expanded greatly over the past decade. There is increasing evidence for its role in the regulation of food intake and appetite. Cannabinoid system activity in the hypothalamus is thought to contribute to the homeostatic regulation of energy balance, under the control of the hormone leptin. A second component of cannabinoid-mediated food intake appears to involve reward pathways and the hedonic aspect of eating. With the cannabinoid system contributing to both regulatory pathways, it presents an attractive therapeutic target for the treatment of both obesity and eating disorders.

Anandamide (AEA) is an endogenous cannabinoid ligand acting predominantly on the cannabinoid 1 (CB(1)) receptor, but it is also an agonist on the capsaicin VR(1)/TRPV(1) receptor. In the present study we examined the effects of AEA and the naturally occurring cannabinoid 2 (CB(2)) receptor agonist palmitylethanolamide (PEA) on basal and resiniferatoxin (RTX)-induced release of calcitonin gene-related peptide (CGRP) and somatostatin in vivo. Since these sensory neuropeptides play important role in the development of neuropathic hyperalgesia, the effect of AEA and PEA was also examined on mechanonociceptive threshold changes after partial ligation of the sciatic nerve. Neither AEA nor PEA affected basal plasma peptide concentrations, but both of them inhibited RTX-induced release. The inhibitory effect of AEA was prevented by the CB(1) receptor antagonist SR141716A. AEA abolished and PEA significantly decreased neuropathic mechanical hyperalgesia 7 days after unilateral sciatic nerve ligation, which was antagonized by SR141716A and the CB(2) receptor antagonist SR144528, respectively. Both SR141716A and SR144528 increased hyperalgesia, indicating that endogenous cannabinoids acting on CB(1) and peripheral CB(2)-like receptors play substantial role in neuropathic conditions to diminish hyperalgesia. AEA and PEA exert inhibitory effect on mechanonociceptive hyperalgesia and sensory neuropeptide release in vivo suggesting their potential therapeutic use to treat chronic neuropathic pain.


Mantle cell lymphoma (MCL) is a moderately aggressive B-cell lymphoma that responds poorly to currently used therapeutic protocols. In order to identify tumour characteristics that improve the understanding of biology of MCL, analysis of oligonucleotide microarrays were used to define specific gene expression profiles. Biopsy samples of MCL cases were compared to reactive lymphoid tissue. Among genes differentially expressed in MCL were genes that are involved in the regulation of proliferation, cell signalling, adhesion and homing. Furthermore, some genes with previously unknown function, such as C11orf32, C2orf10, TBC1D9 and ABCA6 were found to be differentially expressed in MCL compared to reactive lymphoid tissue. Of special interest was the high expression of the cannabinoid receptor 1 (CB1) gene in all MCL cases analysed. These results were further confirmed at the cellular and protein level by immunocytochemical staining and immunoblotting of MCL cells. Furthermore, there was a reduced expression of a regulator of G protein signalling, RGS13 in all MCLs, with a complete absence in the majority of cases while present in control lymphoid tissue. These results were further confirmed by PCR. Sequencing of the RGS13 gene revealed changes suggesting polymorphisms, indicating that downregulation of the expression of RGS13 is not related to mutations, but may serve as a new specific marker for MCL. Moreover, comparison between individual cases of MCL, revealed that the CCND1 gene appears to be differently expressed in MCL cases with high vs low proliferative activity.Leukemia (2003) 17, 1880-1890. doi:10.1038/sj.leu.2403057


Background & Aims: Cholera toxin (CT) is the most recognizable enterotoxin causing secretory diarrhea, a major cause of infant morbidity and mortality throughout the world. In this study, we investigated the role of the endogenous cannabinoid system (i.e., the cannabinoid receptors and their endogenous ligands) in CT-induced fluid accumulation in the mouse small intestine. Methods: Fluid accumulation was evaluated by enteropooling; endocannabinoid levels were measured by isotope-dilution gas chromatography mass spectrometry; CB(1) receptors were localized by immunohistochemistry and their messenger RNA (mRNA) levels were quantified by reverse-transcription polymerase chain reaction (PCR). Results: Oral administration of CT to mice resulted in an increase in fluid accumulation in the small intestine and in increased levels of the endogenous cannabinoid, anandamide, and increased expression of the
The cannabinoid receptor agonist CP55,940 and the selective cannabinoid CB(1) receptor agonist arachidonoyl-chloro-ethanolamide inhibited CT-induced fluid accumulation, and this effect was counteracted by the CB(1) receptor antagonist SR141716A, but not by the CB(2) receptor antagonist SR144528. SR141716A, per se, but not the vanilloid VR1 receptor antagonist capsazepine, enhanced fluid accumulation induced by CT, whereas the selective inhibitor of anandamide cellular uptake, VDM11, prevented CT-induced fluid accumulation. Conclusions: These results indicate that CT, along with enhanced intestinal secretion, causes overstimulation of endocannabinoid signaling with an antisecretory role in the small intestine.


This study examined the effects of the cannabinoid CB(1) receptor agonist (R)-methanandamide and the CB(1) receptor antagonist SR-141716 on open-field behaviors in rats. Animals were examined after administration of (R)-methanandamide (dose range 10 to 30 mg/kg) plus vehicle, and the two drugs in combination; the dose range of SR-141716 was 0.3 to 5.6 mg/kg. Injections were given intraperitoneally 20 min prior to initial testing. Additional exposures to the open-field arena occurred for the groups treated with 30 mg/kg (R)-methanandamide at 60 and 120 min post administration. There was a dose-related suppression of ambulation (horizontal activity) and rearing (vertical activity) after (R)-methanandamide administration. Coadministration of SR-141716 did not counteract the suppression induced by 10 and 18 mg/kg (R)-methanandamide but rather tended to augment it, especially with regard to ambulation using SR-141716 doses of 1 mg/kg and up. The latency to leave the starting area in the center of the field was significantly elevated by 30 mg/kg (R)-methanandamide. This effect was completely blocked by SR-141716. With increasing doses of SR-141716, there was an increase in grooming and scratching. Generally, the strongest effects occurred 20 min post administration with the exception of grooming, which reached maximum at 60 min post. Differences in the number of circlings, vocalizations, urination, and defecation generally did not differ clearly among treatments. These results coupled with previous open-field data examining combinations of Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and SR-141716 [Pharmacol. Biochem. Behav. 73 (2002) 911] underscore pharmacological differences between (R)-methanandamide and Delta(9)-THC revealed by their interactions with SR-141716.

Klein, T. W., C. Newton, et al. (2003). "The cannabinoid system and immune modulation." *J Leukoc Biol.* Studies on the effects of marijuana smoking have evolved into the discovery and description of the endocannabinoid system. To date, this system is composed of two receptors, CB1 and CB2, and endogenous ligands including anandamide, 2-arachidonoylglycerol, and others. CB1 receptors and ligands are found in the brain as well as immune and other peripheral tissues. Conversely, CB2 receptors and ligands are found primarily in the periphery, especially in immune cells. Cannabinoid receptors are G protein-coupled receptors, and they have been linked to signaling pathways and gene activities in common with this receptor family. In addition, cannabinoids have been shown to modulate a variety of immune cell functions in humans and animals and more recently, have been shown to modulate T helper cell development, chemotaxis, and tumor development. Many of these drug effects occur through cannabinoid receptor signaling mechanisms and the modulation of cytokines and other gene products. It appears the immunocannabinoid system is involved in regulating the brain-immune axis and might be exploited in future therapies for chronic diseases and immune deficiency.


Background & Aims: The endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG) inhibit cancer cell proliferation by acting at cannabinoid receptors (CBRs). We studied (1) the levels of endocannabinoids, cannabinoid CB(1) and CB(2) receptors, and fatty acid amide hydrolase (FAAH, which catalyzes endocannabinoid hydrolysis) in colorectal carcinomas (CRC),
adenomatous polyps, and neighboring healthy mucosa; and (2) the effects of endocannabinoids, and of inhibitors of their inactivation, on human CRC cell proliferation. Methods: Tissues were obtained from 21 patients by biopsy during colonoscopy. Endocannabinoids were measured by liquid chromatography-mass spectrometry (LC-MS). CB(1), CB(2), and FAAH expression were analyzed by RT-PCR and Western immunoblotting. CRC cell lines (CaCo-2 and DLD-1) were used to test antiproliferative effects. Results: All tissues and cells analyzed contain anandamide, 2-AG, CBrs, and FAAH. The levels of the endocannabinoids are 3- and 2-fold higher in adenomas and CRCs than normal mucosa. Anandamide, 2-AG, and the CBR agonist HU-210 potently inhibit CaCo-2 cell proliferation. This effect is blocked by the CB(1) antagonist SR141716A, but not by the CB(2) antagonist SR144528, and is mimicked by CB(1)-selective, but not CB(2)-selective, agonists. In DLD-1 cells, both CB(1) and CB(2) receptors mediate inhibition of proliferation. Inhibitors of endocannabinoid inactivation enhance CaCo-2 cell endocannabinoid levels and block cell proliferation, this effect being antagonized by SR141716A. CaCo-2 cell differentiation into noninvasive cells results in increased FAAH expression, lower endocannabinoid levels, and no responsiveness to cannabinoids. Conclusions: Endocannabinoid levels are enhanced in transformed colon mucosa cells possibly to counteract proliferation via CBrs. Inhibitors of endocannabinoid inactivation may prove useful anticancer agents.


Exogenous cannabinoids are effective in attenuating neuropathic pain behaviors induced by peripheral nerve injury, but the mechanisms of their effectiveness remain unclear. Here we examined the expression of spinal cannabinoid-1-receptors (CB1Rs) following chronic constriction sciatic nerve injury (CCI) and its relation to the effects of a CBR agonist (Win 55,212-2) on neuropathic pain in rats. CCI induced a time-dependent upregulation of spinal CB1Rs primarily within the ipsilateral superficial spinal cord dorsal horn as revealed by both Western blot and immunohistochemistry. This CCI-induced CB1R upregulation was at least in part mediated through tyrosine kinase receptors (Trk), because intrathecal treatment with the Trk inhibitor K252a (1 microg) for postoperative days 1-6 significantly reduced the CB1R upregulation in CCI rats. At the intracellular level, the mitogen-activated protein kinase (ERK-MAPK) inhibitor PD98059 (1 microg) prevented, while the protein kinase C inhibitor chelerythrine (10 microg) partially reduced, the CCI-induced CB1R upregulation when each agent was administered intrathecally for postoperative days 1-6. Importantly, the CCI-induced upregulation of spinal CB1Rs enhanced the effects of Win 55,212-2 on both thermal hyperalgesia and mechanical allodynia, since inhibition of the CB1R upregulation by PD98059 resulted in a significant reduction of the effects of Win 55,212-2 in CCI rats. These results indicate that upregulation of spinal CB1Rs following peripheral nerve injury may contribute to the therapeutic effects of exogenous cannabinoids on neuropathic pain.


Macrophage-derived endocannabinoids have been implicated in endotoxin (lipopolysaccharide [LPS])-induced hypotension, but the endocannabinoid involved and the mechanism of its regulation by LPS are unknown. In RAW264.7 mouse macrophages, LPS (10 ng/ml) increases anandamide (AEA) levels >10-fold via CD14-, NF- B- and p44/42-dependent, platelet-activating factor (PAF)-independent activation of the AEA biosynthetic enzymes, N-acetyltransferase (NAT) and phospholipase D (PLD). LPS also induces the AEA degrading enzyme fatty acid amidohydrolase (FAAH), and inhibition of FAAH activity potentiates, whereas actinomycin D or cycloheximide blocks the LPS-induced increase in AEA levels and NAT and PLD activities. In contrast, cellular levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) are unaffected by LPS but increased by PAF. LPS similarly induces AEA, but not 2-AG, in mouse peritoneal macrophages where basal AEA levels are higher and the LPS-stimulated increase in AEA is potentiated in cells from FAAH-/- compared to FAAH++/+ mice. Intravenous administration of 107 LPS-treated mouse macrophages to anesthetized rats elicits hypotension, which is much greater in response to FAAH-/- than FAAH++/+ cells, and is susceptible to inhibition by SR141716,
a cannabinoid CB1 receptor antagonist. We conclude that AEA and 2-AG synthesis are differentially regulated in macrophages, and AEA rather than 2-AG is a major contributor to LPS-induced hypotension.


The effect on rat catalepsy induced by Delta(9)-tetrahydrocannabinol (Delta(9)-THC) in association with haloperidol (HP) or clozapine (CLOZ) administration was investigated. Delta(9)-THC dose-dependently increased HP (0.05-1 mg kg(-1), s.c.)-induced rat catalepsy, while no catalepsy was observed after CLOZ (1-20 mg kg(-1), s.c.) or Delta(9)-THC+CLOZ administration. The CB1 antagonist SR141716A (0.5-5 mg kg(-1), i.p.) reversed the increase mediated by Delta(9)-THC on HP-induced catalepsy. The D2 agonist quinpirole completely reversed the catalepsy induced by both HP and HP+Delta(9)-THC; however, higher doses of quinpirole were needed in the presence of Delta(9)-THC. The M1 antagonist scopolamine and alpha2 antagonist yohimbine were able to reduce the catalepsy induced by HP and HP+Delta(9)-THC in a similar manner. CLOZ and the 5-HT2A/2C antagonists ritanserin, RS102221 and SB242084 were more effective in antagonizing HP than HP+Delta(9)-THC-induced catalepsy. HP and CLOZ failed to inhibit in vitro [(3)H]CP-55,940 binding, while Delta(9)-THC and SR141716A did not show an appreciable affinity for the D2 receptor. It was suggested that the different effects on rat catalepsy induced by Delta(9)-THC following HP or CLOZ administration may depend on the receptor-binding profiles of the two antipsychotics. The preferential use of CLOZ rather than HP in the treatment of psychotic symptoms in cannabis abusers was discussed.


Type 1 cannabinoid receptors, selectively located on axon terminals of GABAergic interneurons in the hippocampus, are known to be involved in endocannabinoid-mediated retrograde synaptic signalling. The question arises whether type 1 cannabinoid receptors appear on these axons during early post-natal life, when GABAergic transmission is still depolarizing, and whether there are any developmental changes in the cellular or subcellular expression pattern. Here we demonstrate, using single and double immunocytochemical methods at the light and electron microscopic levels, that type 1 cannabinoid receptors are expressed only on the membrane of axon terminals and pre-terminal axons but not on the soma-dendritic membrane at all examined timepoints between post-natal days 0 and 20, similar to the adult distribution. All type 1 cannabinoid receptor-positive boutons formed symmetric synapses. Granular labelling in the somata was already strong at post-natal day 0 and corresponded to multivesicular bodies, lysosomes, Golgi apparatus and rough endoplasmic reticulum. The type 1 cannabinoid receptor-positive axons were shown to originate largely from cholecystokinin-immunoreactive basket and bistratified neurons throughout the hippocampus (90% of all type 1 cannabinoid receptor-containing cells) and dentate gyrus (70% of all type 1 cannabinoid receptor-containing cells). The remaining cells have not been identified but probably belong to the somatostatin- and/or neuropeptide Y-containing subsets, as cholecystokinin-negative, type 1 cannabinoid receptor-positive axons have been observed in strata moleculare and lacunosum-moleculare of the dentate gyrus and CA1-3, respectively, where these neurons are known to arborize. No cell types were found that expressed type 1 cannabinoid receptors transiently at some developmental stage. We conclude that the cellular and subcellular pattern of type 1 cannabinoid receptor expression during early post-natal life is similar to the adult pattern and type 1 cannabinoid receptors are expressed on the cholecystokinin-containing axons as soon as synapse formation begins. This suggests that retrograde synaptic signalling by endocannabinoids is required for the normal operation of GABAergic neurotransmission even before it becomes hyperpolarizing.


The effects of cannabinoid receptor agonists on the non-adrenergic non-cholinergic (NANC) inhibitory responses to electrical field stimulation in guinea-pig trachea were assessed. R-(+)-[2,3-dihydro-5-methyl-3-[(morpholilinyl) methyl]pyrrolo [1,2,3-de]-1,4-benzoxazin-6-yl]-1-
naphthalenyl)methanone mesylate (WIN 55,212-2; 10(-5) M) significantly enhanced the frequency-dependent response to electrical stimulation. The same concentration of R-(N)-(2-hydroxy-1-methylethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide (R(+)-methanandamide) and 1-propyl-2-methyl-3-(1-naphthyl)indole (JWH-015) did not affect significantly the electrically induced inhibitory NANC responses. The effect of WIN 55,212-2 was not modified by the cannabinoid CB(1) and CB(2) receptor-selective antagonists, N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716A; 10(-5) M) and N-(1S)-endo-1,3,3-trimethyl bicyclo [2.2.1] heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-car boxamide (SR 144528; 10(-5) M), respectively. Moreover, the nitric oxide synthase inhibitor, L-N(G)-nitro-arginine methyl ester (L-NAME; 10(-4) M), but not the peptidase, alpha-chymotrypsin (2 U/ml), blocked the effect of WIN 55,212-2. Postsynaptically, WIN 55,212-2 did not produce any change of tracheal smooth muscle tone, either basal or histamine-induced, and did not interfere with the relaxant activity of the nitric oxide donor, sodium nitroprusside (10(-8)-10(-4) M). In conclusion, our results suggest that (a) cannabinoid CB(1) and CB(2) receptor stimulation does not alter the inhibitory NANC transmission in guinea-pig trachea, and (b) WIN 55,212-2 potentiates the NO-mediated component of the NANC relaxant response to electrical stimulation through a cannabinoid receptor-independent mechanism.

Padley, J. R., Q. Li, et al. (2003). "Cannabinoid receptor activation in the rostral ventrolateral medulla oblongata evokes cardiorespiratory effects in anaesthetised rats." Br J Pharmacol. 1 The nature of the cardiorespiratory effects mediated by cannabinoids in the hindbrain is poorly understood. In the present study we investigated whether cannabinoid receptor activation in the rostral ventrolateral medulla oblongata (RVLM) affects cardiovascular and/or respiratory function.2 Initially, we looked for evidence of CB1 receptor gene expression in rostral and caudal sections of the rat ventrolateral medulla (VLM) using reverse transcription-polymerase chain reaction. Second, the potent cannabinoid receptor agonists WIN55,212-2 (0.05, 0.5 or 5 pmol per 50 nl) and HU-210 (0.5 pmol per 50 nl) or the CB1 receptor antagonist/inverse agonist AM281 (1 pmol per 100 nl) were microinjected into the RVLM of urethane-anaesthetised, immobilised and mechanically ventilated male Sprague-Dawley rats (n=22). Changes in splanchnic nerve activity (sSNA), phrenic nerve activity (PNA), mean arterial pressure (MAP) and heart rate (HR) in response to cannabinoid administration were recorded.3 The CB1 receptor gene was expressed throughout the VLM. Unilateral microinjection of WIN55,212-2 into the RVLM evoked short-latency, dose-dependent increases in sSNA (0.5 pmol; 175+/−8%, n=5) and MAP (0.5 pmol; 26+/−3%, n=8) and abolished PNA (0.5 pmol; duration of apnoea: 5.4+/−0.4 s, n=8), with little change in HR (P<0.005). HU-210, structurally related to Delta(9)-tetrahydrocannabinol (THC), evoked similar effects when microinjected into the RVLM (n=4). Surprisingly, prior microinjection of AM281 produced agonist-like effects, as well as significantly attenuated the response to subsequent injection of WIN55,212-2 (0.5 pmol, n=4).4 The present study reveals CB1 receptor gene expression in the rat VLM and demonstrates sympathoexcitation, hypertension and respiratory inhibition in response to RVLM-administered cannabinoids. These findings suggest a novel link between CB1 receptors in this region of the hindbrain and the central cardiorespiratory effects of cannabinoids. The extent to which these central effects contribute to the cardiovascular and respiratory outcomes of cannabis use remains to be investigated.

Patel, H. J., M. A. Birrell, et al. (2003). "Inhibition of guinea-pig and human sensory nerve activity and the cough reflex in guinea-pigs by cannabinoid (CB2) receptor activation." Br J Pharmacol. 1 There is considerable interest in novel therapies for cough, since currently used agents such as codeine have limited beneficial value due to the associated side effects. Sensory nerves in the airways mediate the cough reflex via activation of C-fibres and RARs. Evidence suggests that cannabinoids may inhibit sensory nerve-mediated responses.2 We have investigated the inhibitory actions of cannabinoids on sensory nerve depolarisation mediated by capsaicin, hypertonic saline and PGE2 on isolated guinea-pig and human vagus nerve preparations, and the cough reflex in conscious guinea-pigs.3 The non-selective cannabinoid (CB) receptor agonist, CP 55940, and the selective CB2 agonist, JWH 133 inhibited sensory nerve depolarisations of the guinea-pig vagus nerve induced by hypertonic saline, capsaicin and PGE2. These responses were abolished by the CB2 receptor antagonist SR144528, and unaffected by the CB1 antagonist
SR141716A. Similarly, JWH 133 inhibited capsaicin-evoked nerve depolarisations in the human vagus nerve, and was prevented by SR144528.4 Using a guinea-pig in vivo model of cough, JWH 133 (10 mg kg\(^{-1}\), i.p., 20 min) significantly reduced citric acid-induced cough in conscious guinea pigs compared to those treated with the vehicle control.5 These data show that activation of the CB2 receptor subtype inhibits sensory nerve activation of guinea-pig and human vagus nerve, and the cough reflex in guinea-pigs, suggesting that the development of CB2 agonists, devoid of CB1-mediated central effects, will provide a new and safe antitussive treatment for chronic cough.


Stimulation of cannabinoid CB1 receptors by 2-methyl-arachidonyl-2'-fluoro-ethylamide (Met-F-AEA) inhibits the growth of a rat thyroid cancer cell-derived tumor in athymic mice by inhibiting the activity of the oncogene product p21ras. Here we report that Met-F-AEA also blocks the growth of tumors previously induced in nude mice by the s.c. injection of the same rat thyroid carcinoma cells. Met-F-AEA significantly inhibited, in tumors as well as transformed cells, the expression of the vascular endothelial growth factor, an angiogenetic factor known to be up-regulated by p21ras, as well as of one of its receptors, flt-1/VEGFR-1. The levels of the cyclin-dependent kinase inhibitor p27(kip1), which is down-regulated by p21ras, were instead increased by Met-F-AEA. All these effects were antagonized by the selective CB1 receptor antagonist SR141716A. Met-F-AEA inhibited in vitro the growth of a metastasis-derived thyroid cancer cell line more potently than a primary cancer cell line. Therefore, the hypothesis that CB1 receptor stimulation interferes not only with angiogenesis but also with metastatic processes was tested in a widely used model of metastatic infiltration in vivo, the Lewis lung carcinoma (3LL) in C57Bl/6 mice. Three weeks from the paw injection of 3LL cells, Met-F-AEA reduced significantly the number of metastatic nodes, in a way antagonized by SR141716A. Our findings indicate that CB1 receptor agonists might be used therapeutically to retard tumor growth in vivo by inhibiting at once tumor growth, angiogenesis, and metastasis.


We studied whether cannabinoid CB1 receptor gene disruption (to yield CB1(-/-) mice) affects the electrically evoked tritium overflow from vas deferens and atrial pieces preincubated with [(3)H]-noradrenaline (NA) (noradrenaline release) and from cerebral cortex slices preincubated with [(3)H]-choline (acetylcholine release). NA release was higher by 37% in vas deferens from CB1(-/-) mice than in vas deferens from CB1(+/+) mice. The cannabinoid receptor agonist WIN 55,212-2 inhibited, and the CB1 receptor inverse agonist/antagonist SR 141716, increased NA release in vas deferens from CB1(+/+) mice without affecting it in vas deferens from CB1(-/-) mice. Atrial NA release did not differ between CB1(+/+) and CB1(-/-) mice nor did WIN 55,212-2 affect NA release in either strain. Cortical acetylcholine (Ach) release did not differ between CB1(+/+) and CB1(-/-) mice. WIN 55,212-2 inhibited, but SR 141716 did not affect, Ach release in the cortex from CB1(+/+) mice. Both drugs did not alter Ach release in the cortex from CB1(-/-) mice. Tritium content did not differ between CB1(+/+) and CB1(-/-) mice in any preparation. In conclusion, the increase in NA release associated with CB1 receptor deficiency in the vas deferens, which cannot be ascribed to an alteration of tritium content of the preparations, suggests an endogenous tone at the CB1 receptors of CB1(+/+) mice in this tissue. Furthermore, the effect of WIN 55,212-2 on NA release in the vas deferens and on cortical Ach release involves CB1 receptors, whereas the involvement of non-CB1-non-CB2 receptors can be excluded.


Arachidonylsulfonlf fluoride (3), reported here for the first time, is similar in potency to its known methyl arachidonylfluorophosphonate (2) analogue as an inhibitor of mouse brain fatty
acid amide hydrolase activity (IC(50) 0.1 nM) and cannabinoid CB1 agonist [3H]CP 55,940 binding (IC(50) 304-530 nM). Interestingly, 3 is much more selective than 2 as an inhibitor for fatty acid amide hydrolase relative to acetylcholinesterase, butyrylcholinesterase and neuropathy target esterase. N-(2-Hydroxyethyl)arachidonylsulfonamide (4) is at least 2500-fold less potent than N-(2-hydroxyethyl)arachidonamide (anandamide) (1) at the CB1 agonist site.


Potent cannabinoid CB1 receptor ligands include anandamide [N-(2-hydroxyethyl)arachidonamide], Delta(9)-tetrahydrocannabinol and [(3)H]CP 55,940 at the agonist site and selected organophosphorus esters (including some pesticides) and organosulfur compounds at a proposed closely-coupled "nucleophilic" site. This study considers the toxicological and structural features of alkylfluorophosphonates, benzodioxaphosphorin oxides, alkanesulfonyl fluorides and analogs acting at the nucleophilic site. Binding at the agonist site, using [(3)H]CP 55,940 in assays with mouse brain membranes, is inhibited by O-isopropyl dodecylfluorophosphate (compound 2), dodecanesulfonyl fluoride (compound 14) and dodecylbenzodioxaphosphorin oxide with IC50 values of 2-11 nM. Compounds 2 and 14 are also effective in vivo, with 84% inhibition of mouse brain CB1 binding 4 h after intraperitoneal dosage at 30 mg/kg. Compound 14-inhibited CB1 in mouse brain requires about 3-4 days for recovery of 50% activity, suggesting covalent derivatization. Delayed toxicity (mortality in 0.3-5 days) from compounds 2, 14 and octanesulfonyl fluoride (18) is more closely associated with in vivo inhibition of brain neuropathy target esterase - lysophospholipase (NTE-LysoPLA) than with that of CB1 or acetylcholinesterase. NTE-LysoPLA inhibited by sulfonyl fluorides 14 and 18 cannot "age," a proposed requirement for NTE phosphorylated by organophosphorus delayed neurotoxicants. Several octane- and dodecanesulfonamides with N-(2-hydroxyethyl) and other substituents based on anandamide give depressed mobility and recumbent posture in mice, but the effects do not correlate with potency for CB1 inhibition in vitro. Specific toxicological responses are not clearly associated with organophosphorus- or organosulfur-induced inhibition of the proposed CB1 nucleophilic site in mouse brain. On the other hand, the most potent CB1 inhibitors examined here are also NTE-LysoPLA inhibitors and cause delayed toxicity in mice.


Cannabinoid receptor agonists significantly inhibit nociceptive responses in a large number of animal models. The present study examined whether mice displaying different basal levels of anxiety in the plus-maze test of anxiety might differ in terms of responsiveness to the antinociceptive effects of Delta(9)-tetrahydrocannabinol (Delta(9)-THC). Further, the involvement of the cannabinoid and/or opioid receptors in Delta(9)-THC-induced antinociception was investigated by using SR 141716A and naloxone, respectively, cannabinoid and opioid receptor antagonists. Delta(9)-THC-induced antinociception was evaluated in the formalin test that involves a biphasic response with an early and a late phase of high paw-licking activity. This characteristic biphasic response was observed in all control animals selected as "anxious" and "nonanxious." Delta(9)-THC (0.5-5 mg/kg ip) caused a dose-dependent antinociceptive effect in both groups of mice during the early and late phases. This response was fully reversed by SR 141716A (1 mg/kg ip) and partially reversed by naloxone (2 mg/kg ip). These findings suggest that mice selected for differences in anxiety-related behavior show similar responses to the antinociceptive action of Delta(9)-THC and that this action involves predominantly cannabinoid mechanisms.


Several lines of evidence suggest that cannabinoid compounds are anticonvulsant. However, the anticonvulsant potential of cannabinoids and, moreover, the role of the endogenous cannabinoid system in regulating seizure activity has not been tested in an in vivo model of epilepsy that is characterized by spontaneous, recurrent seizures. Here, using the rat pilocarpine model of epilepsy, we show that the marijuana extract Delta(9)-THC (10 mg/kg) as well as the cannabimimetic, R(+)-WIN55,212 (5 mg/kg), completely abolished spontaneous epileptic seizures. Conversely, application of the CB1 receptor antagonist, SR141716A, significantly increased both seizure duration and frequency. In some animals, CB1 receptor antagonism resulted in seizure durations that were protracted to a level consistent with the clinical condition status epilepticus (SE). Furthermore, we determined that during an acute pilocarpine induced seizure, levels of the endogenous CB1 ligand 2-AG increased significantly within the hippocampal brain region. These data indicate not only anticonvulsant activity of exogenously applied cannabinoids, but also suggest that endogenous cannabinoid tone modulates seizure termination and duration through activation of the CB1 receptor. Furthermore, Western blot and immunohistochemical analyses revealed that CB1 receptor protein expression was significantly increased throughout the CA regions of epileptic hippocampi. By demonstrating a role for the endogenous cannabinoid system in regulating seizure activity, these studies define a role for the endogenous cannabinoid system in modulating neuroexcitation and suggest that plasticity of the CB1 receptor occurs with epilepsy.


Astrocytes play an important role in neuroprotective responses. Recent studies indicate that endothelin-1, a neuropeptide upregulated during brain injury, increases levels of the endocannabinoid anandamide, a lipid with neuroprotective properties, in astrocytes in primary cultures. However, whether this neuropeptide also alters levels of 2-arachidonoyl glycerol (2-AG), the most abundant endocannabinoid in the CNS, in astrocytes remains unknown. In addition, 2-AG levels in astrocytes have never been measured. In this report we use chemical ionization gas chromatography/mass spectrometry to quantify picomole amounts of 2-AG in primary cultures of mouse astrocytes. We also demonstrate that endothelin-1 increases 2-AG production by 5-fold in these cells, a response that requires extracellular calcium and endothelin-1(A) receptor engagement. Immunocytochemistry showed that although cultured mouse neurons and microglia express cannabinoid receptors, cultured astrocytes do not. The data suggest that endothelin-1 modulates 2-AG production in astrocytes and that this endocannabinoid may participate in paracrine signaling toward neurons and microglia.


Opioids and cannabinoids produce antinociception through both spinal and supraspinal action. Both opioids and cannabinoids also have important peripheral action. Many previous studies indicate that systemically administered cannabinoids enhance antinociceptive properties of opioids. Experiments were conducted to test the hypothesis that topical cannabinoids would enhance the topical antinociceptive effects of morphine. Antinociception was measured in the radiant tail-flick test after immersion of the tail of mice into a solution of dimethyl sulfoxide (DMSO) containing WIN 55, 212-2, a cannabinoid agonist and morphine, an opioid agonist. Morphine and WIN 55, 212-2 produce time dependent topical analgesic effects limited to the portion of the tail exposed to drugs. WIN 55, 212-2 had a potency lower than that of morphine. The topical antinociceptive effects of WIN 55, 212-2 were blocked by systemic pretreatment of cannabinoid CB1 receptor selective antagonist, AM 251. This suggests that topical antinociceptive effects of WIN 55, 212-2 involve CB1 receptors. Combination of topical WIN 55, 212-2 with topical morphine yielded significantly greater analgesic effects than that of topical morphine alone. The ability of the CB1 receptor antagonist AM 251 to antagonize the enhancement of antinociception of morphine by WIN 55, 212-2 indicates that WIN 55, 212-2 acts through a CB1 receptor to enhance the potency of topical morphine. Additionally, spinally
administered ineffective doses of WIN 55, 212-2 potentiated the antinociceptive effects of topical morphine. These results demonstrate an antinociceptive interaction between topical opioids with topical, and spinal cannabinoids. These observations are significant in using of topical combination of cannabinoid and morphine in the management of pain.


BACKGROUND: Although spinal cannabinoid receptor agonist (WIN 55,212-2) has been shown to encounter various models of pain, the role of two subtypes of cannabinoid receptor for the antinociceptive effect of cannabinoids has not been investigated at the spinal level. Spinal alpha 2 receptor agonist (clonidine) and cholinesterase inhibitor (neostigmine) are also active in the modulation of nociception. The authors examined the properties of drug interaction after coadministration of WIN 55,212-2-clonidine, and intrathecal WIN 55,212-2-neostigmine, and further clarified the role of cannabinoid 1 and 2 receptors in cannabinoid-induced antinociception at the spinal level. METHODS: Catheters were inserted into the intrathecal space of male Sprague-Dawley rats, and 50 microl of 5% formalin solution was injected into the hind paw to evoke the pain. Isobolographic analysis was used for evaluation of pharmacologic interaction. RESULTS: Intrathecal 55,212-2, clonidine, and neostigmine dose-dependently suppressed the flinching observed during phase 1 and 2 in the formalin test. Isobolographic analysis revealed a synergistic interaction after intrathecal delivery of WIN 55,212-2-clonidine or WIN 55,212-2-neostigmine mixture in both phases. The antinociceptive effect of WIN 55,212-2 was antagonized by cannabinoid 1 receptor antagonist (AM 251) but not by cannabinoid 2 receptor antagonist (AM 630). No antinociceptive effect was seen after intrathecal administration of cannabinoid 2 receptor agonist (JWH 133). CONCLUSIONS: Intrathecal 55,212-2, clonidine, and neostigmine attenuate the facilitated state and acute pain. WIN 55,212-2 interacts synergistically with either clonidine or neostigmine. The antinociception of WIN 55,212-2 is mediated through the cannabinoid 1 receptor, but not the cannabinoid 2 receptor, at the spinal level.

CLINICAL SCIENCE


GW Pharmaceuticals is undertaking a major research programme in the UK to develop and market distinct cannabis-based prescription medicines [THC:CBD, High THC, High CBD] in a range of medical conditions. The cannabis for this programme is grown in a secret location in the UK. It is expected that the product will be marketed in the US in late 2003. GW's cannabis-based products include selected phytocannabinoids from cannabis plants, including D9 tetrahydrocannabinol (THC) and cannabidiol (CBD). The company is investigating their use in three delivery systems, including sublingual spray, sublingual tablet and inhaled (but not smoked) dosage forms. The technology is protected by patent applications. Four different formulations are currently being investigated, including High THC, THC:CBD (narrow ratio), THC:CBD (broad ratio) and High CBD. GW is also developing a specialist security technology that will be incorporated in all its drug delivery systems. This technology allows for the recording and remote monitoring of patient usage to prevent any potential abuse of its cannabis-based medicines. GW plans to enter into agreements with other companies following phase III development, to secure the best commercialisation terms for its cannabis-based medicines. In June 2003, GW announced that exclusive commercialisation rights for the drug in the UK had been licensed to Bayer AG. The drug will be marketed under the Sativex(R) brand name. This agreement also provides Bayer with an option to expand their license to include the European Union and certain world markets. GW was granted a clinical trial exemption certificate by the Medicines Control Agency to conduct clinical studies with cannabis-based medicines in the UK. The exemption includes investigations in the relief of pain of neurological origin and defects of neurological function in the following indications: multiple sclerosis (MS), spinal cord injury, peripheral nerve
injury, central nervous system damage, neuroinvasive cancer, dystonias, cerebral vascular accident and spina bifida, as well as for the relief of pain and inflammation in rheumatoid arthritis and also pain relief in brachial plexus injury. The UK Government stated that it would be willing to amend the Misuse of Drugs Act 1971 to permit the introduction of a cannabis-based medicine. GW stated in its 2002 Annual Report that it was currently conducting five phase III trials of its cannabis derivatives, including a double-blind, placebo-controlled trial with a sublingual spray containing High THC in more than 100 patients with cancer pain in the UK. Also included is a phase III trial of THC:CBD (narrow ratio) being conducted in patients with severe pain due to brachial plexus injury, as are two more phase III trials of THC:CBD (narrow ratio) targeting spasticity and bladder dysfunction in multiple sclerosis patients. Another phase III trial of THC:CBD (narrow ratio) in patients with spinal cord injury is also being conducted. Results from the trials are expected during 2003. Three additional trials are also in the early stages of planning. These trials include a phase I trial of THC:CBD (broad ratio) in patients with inflammatory bowel disease, a phase I trial of High CBD in patients with psychotic disorders such as schizophrenia, and a preclinical trial of High CBD in various CNS disorders (including epilepsy, stroke and head injury). GW Pharmaceuticals submitted an application for approval of cannabis-based medicines to UK regulatory authorities in March 2003. Originally GW hoped to market cannabis-based prescription medicines by 2004, but is now planning for a launch in the UK towards the end of 2003. Several trials for GW's cannabis derivatives have also been completed, including four randomised, double-blind, placebo-controlled phase III clinical trials conducted in the UK. The trials were initiated by GW in April 2002, to investigate the use of a sublingual spray containing THC:CBD (narrow ratio) in the following medical conditions: pain in spinal cord injury, pain and sleep in MS and spinal cord injury, neuropathic pain in MS and general neuropathic pain (presented as allodynia). Results from these trials show that THC:CBD (narrow ratio) caused statistically significant reductions in neuropathic pain in patients with MS and other conditions. In addition, improvements in other MS symptoms were observed as well. Phase II studies of THC:CBD (narrow ratio) have also been completed in patients with MS, spinal cord injury, neuropathic pain and a small number of patients with peripheral neuropathy secondary to diabetes mellitus or AIDS. A phase II trial of THC:CBD (broad ratio) has also been completed in a small number of patients with rheumatoid arthritis, as has a trial of High CBD in patients with neurogenic symptoms. A phase II trial has also been evaluated with High THC in small numbers of patients for the treatment of perioperative pain. The phase II trials provided positive results and confirmed an excellent safety profile for cannabis-based medicines. GW Pharmaceuticals received an IND approval to commence phase II clinical trials in Canada in patients with chronic pain, multiple sclerosis and spinal cord injury in 2002. Following meetings with the US FDA, Drug Enforcement Agency (DEA), the Office for National Drug Control Policy, and National Institute for Drug Abuse, GW was granted an import license from the DEA and has imported its first cannabis extracts into the US. Preclinical research with these extracts in the US is ongoing.


BACKGROUND: Cannabinoid use could potentially alter HIV RNA levels by two mechanisms: immune modulation or cannabinoid-protease inhibitor interactions (because both share cytochrome P-450 metabolic pathways). OBJECTIVE: To determine the short-term effects of smoked marijuana on the viral load in HIV-infected patients. DESIGN: Randomized, placebo-controlled, 21-day intervention trial. SETTING: The inpatient General Clinical Research Center at the San Francisco General Hospital, San Francisco, California. PARTICIPANTS: 67 patients with HIV-1 infection. INTERVENTION: Participants were randomly assigned to a 3.95%-tetrahydrocannabinol marijuana cigarette, a 2.5-mg dronabinol (delta-9-tetrahydrocannabinol) capsule, or a placebo capsule three times daily before meals. MEASUREMENTS: HIV RNA levels, CD4+ and CD8+ cell subsets, and pharmacokinetic analyses of the protease inhibitors. RESULTS: 62 study participants were eligible for the primary end point (marijuana group, 20 patients; dronabinol group, 22 patients; and placebo group, 20 patients). Baseline HIV RNA level was less than 50 copies/mL for 36 participants (58%), and the median CD4+ cell count was 340 x 109 cells/L. When adjusted for baseline variables, the estimated average effect versus placebo
on change in log10 viral load from baseline to day 21 was -0.07 (95% CI, -0.30 to 0.13) for marijuana and -0.04 (CI, -0.20 to 0.14) for dronabinol. The adjusted average changes in viral load in marijuana and dronabinol relative to placebo were -15% (CI, -50% to 34%) and -8% (CI, -37% to 37%), respectively. Neither CD4+ nor CD8+ cell counts appeared to be adversely affected by the cannabinoids. CONCLUSIONS: Smoked and oral cannabinoids did not seem to be unsafe in people with HIV infection with respect to HIV RNA levels, CD4+ and CD8+ cell counts, or protease inhibitor levels over a 21-day treatment.


From folk medicine and anecdotal reports it is known that Cannabis may reduce pain. In animal studies it has been shown that delta-9-tetrahydrocannabinol (THC) has antinociceptive effects or potentiates the antinociceptive effect of morphine. The aim of this study was to measure the analgesic effect of THC, morphine, and a THC-morphine combination (THC-morphine) in humans using experimental pain models. THC (20 mg), morphine (30 mg), THC-morphine (20 mg THC+30 mg morphine), or placebo were given orally and as single doses. Twelve healthy volunteers were included in the randomized, placebo-controlled, double-blinded, crossover study. The experimental pain tests (order randomized) were heat, cold, pressure, single and repeated transcutaneous electrical stimulation. Additionally, reaction time, side-effects (visual analog scales), and vital functions were monitored. For the pharmacokinetic profiling, blood samples were collected. THC did not significantly reduce pain. In the cold and heat tests it even produced hyperalgesia, which was completely neutralized by THC-morphine. A slight additive analgesic effect could be observed for THC-morphine in the electrical stimulation test. No analgesic effect resulted in the pressure and heat test, neither with THC nor THC-morphine. Psychotropic and somatic side-effects (sleepiness, euphoria, anxiety, confusion, nausea, dizziness, etc.) were common, but usually mild.


AIM: To test the hypothesis that schizophrenia might be associated with alterations of the endogenous cannabinoid system in human blood. RESULTS: Blood from 20 healthy volunteers and 12 patients with schizophrenia, 5 of which both before and after a successful antipsychotic treatment, was analysed for: 1) the amounts of the endocannabinoid anandamide; 2) the levels of cannabinoid CB1 and CB2 receptor mRNAs, and 3) the levels of the mRNA encoding the enzyme fatty acid amide hydrolase (FAAH), responsible for anandamide degradation. The amounts of anandamide were significantly higher in the blood of patients with acute schizophrenia than in healthy volunteers (7.79 PlusMinus; 0.50 vs. 2.58 PlusMinus; 0.28 pmol/ml). Clinical remission was accompanied by a significant decrease of the levels of anandamide (3.88 PlusMinus; 0.72 pmol/ml) and of the mRNA transcripts for CB2 receptors and FAAH. CONCLUSION: These findings indicate that endocannabinoid signalling might be altered during the acute phase of schizophrenia not only in the central nervous system but also in the blood. These changes might be related to the several immunological alterations described in schizophrenia.


SETTING: New cases of pulmonary tuberculosis (TB) were noted in a cluster of young Caucasian males, an unusual ethnic group for this disease in Queensland, Australia. It was noted
that marijuana water pipe ('bong') smoking was common amongst cases and contacts. OBJECTIVE: To report this cluster of TB and to investigate whether shared use of a marijuana water pipe was associated with transmission of TB. DESIGN: All contacts were identified and screened according to standard protocols. Cases were asked to list contacts with whom they had shared a marijuana water pipe. RESULTS: Five cases of open pulmonary TB were identified clinically and on sputum culture, and all isolates of Mycobacterium tuberculosis were identical on typing. Of 149 contacts identified, 114 (77%) completed screening, and 57 (50%) had significant tuberculin skin test (TST) reactions on follow-up. Of 45 contacts who had shared a marijuana water pipe with a case, 29 (64%) had a significant TST reaction. CONCLUSION: Sharing a marijuana water pipe with a case of pulmonary TB was associated with transmission of TB (OR 2.22, 95% CI 0.96-5.17), although the most important risk factor for acquiring TB infection in this cluster was close household contact with a case (OR 4.91, 95% CI 1.13-20.70).


From folk medicine and anecdotal reports it is known that Cannabis may reduce pain. In animal studies it has been shown that delta-9-tetrahydrocannabinol (THC) has antinociceptive effects or potentiates the antinociceptive effect of morphine. The aim of this study was to measure the analgesic effect of THC, morphine, and a THC-morphine combination (THC-morphine) in humans using experimental pain models. THC (20 mg), morphine (30 mg), THC-morphine (20 mg THC+30 mg morphine), or placebo were given orally and as single doses. Twelve healthy volunteers were included in the randomized, placebo-controlled, double-blinded, crossover study. The experimental pain tests (order randomized) were heat, cold, pressure, single and repeated transcutaneous electrical stimulation. Additionally, reaction time, side-effects (visual analog scales), and vital functions were monitored. For the pharmacokinetic profiling, blood samples were collected. THC did not significantly reduce pain. In the cold and heat tests it even produced hyperalgesia, which was completely neutralized by THC-morphine. A slight additive analgesic effect could be observed for THC-morphine in the electrical stimulation test. No analgesic effect resulted in the pressure and heat test, neither with THC nor THC-morphine. Psychotropic and somatic side-effects (sleepiness, euphoria, anxiety, confusion, nausea, dizziness, etc.) were common, but usually mild.


BACKGROUND: Multiple sclerosis (MS) is one of the most common neurological diseases affecting young adults. The prevalence of MS in Alberta has been described as among the highest reported in the world, estimated at 217 per 100,000. Numerous anecdotal reports, and a few small empirical investigations have suggested that cannabis use may relieve the symptom experience of those with MS. The present study was undertaken to describe cannabis use by this patient group. Information on peoples’ beliefs, practices and experiences related to use were investigated. METHODS: A questionnaire was mailed to a sample of 780 adults with MS in southern Alberta, Canada. RESULTS: Completed questionnaires were returned by 420/673 eligible subjects (response rate 62%). Mean sample age was 48 years and 75% were women. Respondents ranged from mildly to severely impaired. The majority of respondents (96%) was aware cannabis was potentially therapeutically useful for MS and most (72%) supported legalization for medicinal purposes. Forty-three percent had tried cannabis at some point in their lives, 16% for medicinal purposes. Symptoms reported to be ameliorated included anxiety/depression, spasticity and chronic pain. Reasons given for not trying cannabis were the fact that it is an illegal substance, concern about side effects and lack of knowledge on how to obtain it. CONCLUSIONS: Subjective improvements in symptom experience were reported by the majority of people with MS who currently use cannabis. Further evaluation of this substance is warranted.

The binocular depth inversion illusion (BDII) has been shown to be a sensitive measure of impaired visual information processing under conditions including cannabinoid-intoxicated states, alcohol withdrawal, sleep deprivation, and in patients with positive symptoms of schizophrenia. This study assessed whether the BDII could detect subtle cognitive impairment due to regular cannabis use by comparing 10 regular cannabis users and 10 healthy controls from the same community sources, matched for age, sex, and premorbid IQ. Subjects were also compared on measures of executive functioning, memory, and personality. Regular cannabis users were found to have significantly higher BDII scores for inverted images. This was not due to a problem in the primary processing of visual information, as there was no significant difference between the groups for depth perception of normal images. There was no relationship between BDII scores for inverted images and time since last dose, suggesting that the measured impairment of BDII more closely reflected chronic than acute effects of regular cannabis use. There were no significant differences between the groups for other neuropsychological measures of memory or executive function. A positive relationship was found between EPQ-R-psychoticism and cannabis, tobacco, and alcohol use. Cannabis users also used significantly larger amounts of alcohol. However, no relationship was found between BDII scores and drug use other than cannabis or psychoticism. Compared to the other neuropsychological tests used, the BDII appears to be a more sensitive tool for the detection of subtle impairments in visual information processing related to chronic cannabis use.


**BEHAVIOURAL SCIENCE**


The objective of this study was to get an insight into the prevalence of medicinal and illegal drugs among car drivers in a Danish rural area. The police randomly stopped about 1000 car drivers and asked them to deliver a saliva sample and gave them a questionnaire to fill in at home. Laboratory analyses by specific methods of samples, which a screening found positive, confirmed that 2% were positive for benzodiazepines or illegal drugs (amphetamine, cannabis, cocaine or opiates): 1.3% were positive for illegal drugs and 0.7% for benzodiazepines. Questionnaire statements from some of the drivers confirm that occasionally some of these drive despite a suspicion to be under the influence of an illegal drug (2.8%), an illegal drug including alcohol (4%), a hazardous medicinal drug including alcohol (8.5%), or alcohol alone above the legal limit (24.5%). These results are considered reliable for the survey area and may not reflect national conditions. The overall results indicate that in this study driving under the influence of illegal drugs or alcohol seems to be associated especially to men, aged 22-44 years. Driving under the influence of hazardous medicinal drugs seems to be associated to middle-aged/elderly drivers, both men and women.


Withdrawal symptoms following cessation of heavy cannabis (marijuana) use have been reported, yet their time course and clinical importance have not been established. A 50-day outpatient study assessed 18 marijuana users during a 5-day smoking-as-usual phase followed by a 45-day abstinence phase. Parallel assessment of 12 ex-users was obtained. A withdrawal pattern was observed for aggression, anger, anxiety, decreased appetite, decreased body weight, irritability, restlessness, shakiness, sleep problems, and stomach pain. Onset typically occurred between Days 1-3, peak effects between Days 2-6, and most effects lasted 4-14 days. The magnitude and time course of these effects appeared comparable to tobacco and other withdrawal syndromes. These effects likely contribute to the development of dependence and difficulty stopping use. Criteria for cannabis withdrawal are proposed.

Dafters, R. I., R. Hoshi, et al. (2003). "Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users." *Psychopharmacology (Berl).*
RATIONALE. Establishing whether cognitive changes follow long-term use of MDMA ("ecstasy") in humans has been difficult because of possible confounds with other drug use, particularly cannabis. Convincing evidence may be only obtained using experimental designs that account for such confounds. OBJECTIVE. In the present study, cognitive/behavioural measures were used to investigate whether long-term MDMA use or long-term cannabis use is responsible for the changes sometimes observed in recreational MDMA users. METHOD. Tests of attention and memory were administered to subjects who used both MDMA and cannabis, cannabis only, or neither drug. RESULTS. The main finding was that cannabis users, whether or not they also used MDMA, showed significantly impaired memory function on word free-recall and on immediate and delayed story recall compared to non-users. CONCLUSIONS. The findings highlight the importance of controlling for other drug use (particularly cannabis) when investigating persistent effects of MDMA in humans.


An economic evaluation of five outpatient adolescent treatment approaches (12 total site-by-conditions) was conducted. The economic cost of each of the 12 site-specific treatment conditions was determined by the Drug Abuse Treatment Cost Analysis Program (DATCAP). Economic benefits of treatment were estimated by first monetizing a series of treatment outcomes and then analyzing the magnitude of these monetized outcomes from baseline through the 12-month follow-up. The average economic costs ranged from $90 to $313 per week and from $839 to $3,279 per episode. Relative to the quarter before intake, the average quarterly cost to society for the next 12 months (including treatment costs) significantly declined in 4 of the 12 site-by-treatment conditions, remained unchanged in 6 conditions, and increased in 2 treatment conditions (both in the same site). These results suggest that some types of substance-abuse intervention for adolescents can reduce social costs immediately after treatment.

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