INTRODUCTION
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BASIC SCIENCE
Alberich Jorda, M., N. Rayman, et al. (2004). "The peripheral cannabinoid receptor Cb2, frequently expressed on AML blasts, either induces a neutrophilic differentiation block or confers abnormal migration properties in a ligand-dependent manner." Blood.

Cb2, the gene encoding the peripheral cannabinoid receptor, is located in a common virus integration site and is overexpressed in retrovirally-induced murine myeloid leukemias. Here we show that this G protein-coupled receptor (GPCR) is also aberrantly expressed in a high percentage of human acute myeloid leukemias. We investigated the mechanism of transformation by Cb2 and demonstrate that aberrant expression of this receptor on hematopoietic precursor cells results in distinct effects depending on the ligand used. Cb2-expressing myeloid precursors migrate upon stimulation by the endocannabinoid 2-arachidonoylglycerol and are blocked in neutrophilic differentiation upon exposure to another ligand, CP55,940. Both effects depend on the activation of Galphai proteins and require the MEK/ERK pathway. Downregulation of cAMP levels upon Galphai activation is important for migration induction, but is irrelevant for the maturation arrest. Moreover, the highly conserved G protein interacting DRY-motif, present in the second intracellular loop of GPCRs, is critical for migration, but unimportant for the differentiation block. This suggests that the Cb2-mediated differentiation block requires interaction of Galphai proteins with other currently unknown motifs. This indicates a unique mechanism by which a transforming GPCR, in a ligand-dependent manner, causes two distinct oncogenic effects, i.e. altered migration and block of neutrophilic development.


We clarified the modulating action of the endocannabinoid system, and its possible mediation by the arachidonic acid cascade, on the reinstatement of methamphetamine (METH)-seeking behavior, using the intravenous self-administration paradigm in rats. Following 12 days of self-administration of METH, the replacement of METH with saline resulted in a gradual decrease in lever press responses (extinction). Under extinction conditions, METH-priming or re-exposure to cues previously paired with METH infusion markedly increased the responses (reinstatement of drug-seeking). The cannabinoid CB1 receptor antagonist, SR141716A, blocked this behavior. Although the cannabinoid agonist, Delta(8)-tetrahydrocannabinol (THC), had no effects by itself, coadministration of the agonist and METH at small doses reinstated the drug-seeking behavior. THC attenuated the effects of the reinstatement-inducing dose of METH, but enhanced the effect of cues. Either given repeatedly during the extinction or singly, 24 h before the first METH-priming or cues challenge, THC suppressed the reinstatement. In another set of experiments, we found that diclofenac, a cyclooxygenase inhibitor, also attenuated the reinstatement induced by exposure to cues or drug-priming. These results suggest that the endocannabinoid system, through possible mediation by the arachidonic acid cascade, serves as a modulator of the reinstating effects of METH-priming and cues. Extending the current view on the treatment of
drug dependence, these results indicate that endocannabinoid-activating substances as well as cyclooxygenase inhibitors may be promising as antirelapse agents. Neuropsychopharmacology advance online publication, 7 April 2004; doi:10.1038/sj.npp.1300454


We have investigated the effect of 0.001 mg/kg Delta(8)-tetrahydrocannabinol (THC) on food consumption, cognitive function, and neurotransmitters in mice. Sabra mice were treated with vehicle, THC, or THC+CB1 antagonist (SR141716A). The mice were fed for 2.5 h a day for 9 or 50 days. In the 9-day schedule, THC-treated mice showed a 16% increase in food intake compared with controls (P<.001). This effect was reversed by the antagonist (P<.01). In the long-term schedule a 22% increase in intake (P<.05) was recorded. During the course of the 9- and 50-day experimental protocol, all mice lost about 20% and 10% of their original weight, respectively, to reach approximately the same weights, which were not significantly different between the different treatment groups. In addition, THC caused an increase in activity (P<.05). Cognitive function showed a tendency to improve (P<.06) in the THC-treated mice, which was reversed by the antagonist for Days 4 and 5 of the maze (P<.01, and P<.05, respectively). Significant decreases in dopamine and serotonin (5-HT) levels were found both in the hypothalamus (P<.01) and the hippocampus (P<.01, P<.05), respectively, while norepinephrine (NE) levels showed tendency to increase in both the hypothalamus and hippocampus. Delta(8)-THC increased food intake significantly more (P<.05) than did Delta(9)-THC, while performance and activity were similar. Thus, Delta(8)-THC (0.001 mg/kg) caused increased food consumption and tendency to improve cognitive function, without cannabimimetic side effects. Hence, a low dose of THC might be a potential therapeutic agent in the treatment of weight disorders.


Endocannabinoids and CB1 receptors (CB1) have been implicated in endotoxin (lipopolysaccharide [LPS])-induced hypotension; LPS stimulates the synthesis of anandamide in macrophages, and the CB1 antagonist SR141716 inhibits the hypotension induced by treatment of rats with LPS or LPS-treated macrophages. Recent evidence indicates the existence of cannabinoid receptors distinct from CB1 or CB2 which are inhibited by SR141716 but not by other CB1 antagonists such as AM251. In pentobarbital-anesthetized rats, i.v. injection of 10 mg/kg LPS elicits hypotension associated with profound decreases in cardiac contractility, moderate tachycardia and an increase in lower body vascular resistance. Pretreatment with 3 mg/kg SR141716 prevented the hypotension and decrease in cardiac contractility, slightly attenuated the increase in peripheral resistance and had no effect on the tachycardia caused by LPS, whereas pretreatment with 3 mg/kg AM251 did not affect any of these responses. SR141716 also elicited an acute reversal of the hypotension and decreased contractility when administered after the response to LPS had fully developed. The LPS-induced hypotension and its inhibition by SR141716 were similar in pentobarbital-anesthetized wild-type, CB1(-/-) and CB1 (-/-)/CB2(-/-) mice. We conclude that SR141716 inhibits the acute hemodynamic effects of LPS by interacting with a cardiac receptor distinct from CB1 or CB2, which mediates negative inotropy and may be activated by anandamide or a related endocannabinoid released during endotoxemia.


We investigated levels and compositions of N-acyl ethanolamines (NAEs) and their precursors, N-acyl phosphatidylethanolamines (N-acyl PEs), in a rat stroke model applying striatal microdialysis for glutamate assay. Rats (n = 18) were treated with either intravenous saline (control), NMDA receptor antagonist MK801 (1 mg/kg), or CB1 receptor antagonist SR141716A (1 mg/kg) 30 min after permanent middle cerebral artery occlusion (MCAO). MK801 significantly attenuated the release of glutamate in the infarcted striatum (79 +/- 22 micromol/L)
as compared with controls (322 +/- 104 micromol/L). The administration of CB1 antagonist SR141716A had no statistically significant effect on glutamate release (340 +/- 89 micromol/L), but reduced infarct volume at 5 h after MCAO significantly by approximately 40%, whereas MK801 treatment resulted in a non-significant (18%) reduction of infarct volume. In controls, striatal and cortical NAE concentrations were about 30-fold higher in the infarcted than in the non-infarcted hemisphere, whereas ipsilateral N-acyl phosphatidylethanolamine (N-acyl PE) levels exceeded contralateral levels by only a factor of two to three. Treatment with MK801 or SR141716A, or glutamate release in the infarcted tissue, had no significant effect on these levels. NAE accumulation during acute stroke may be due to increased synthesis as well as decreased degradation, possibly by inhibition of fatty acid amide hydrolase (FAAH).


Compelling evidence indicates that endocannabinoids are implicated in drug addiction. In the present study, we have addressed the interaction between cocaine and endocannabinoid system by means of neurochemical and neurophysiological experiments in rat brain slices. Using gas chromatography-electron impact mass spectrometry, we have found that cocaine increased the levels of the endocannabinoid anandamide in the striatum, a brain area primarily involved in the compulsive drug-seeking and drug-taking behaviors typical of addiction. This effect was attenuated by pharmacological inhibition of D2-like receptors but not D1-like receptors, and it was mimicked by D2-like but not D1-like receptor stimulation. The cocaine-induced increase in anandamide concentrations was attributable to both stimulation of its synthesis and inhibition of its degradation, as suggested by the ability of cocaine and quinpirole, a D2-like receptor agonist, to enhance the activity of NAPE-phospholipase D and to inhibit fatty acid amide hydrolase. By means of electrophysiological recordings from single striatal neurons, we have then observed that the ability of cocaine to inhibit, via D2-like receptors, GABA transmission was partially prevented following blockade of cannabinoid receptors, suggesting that endocannabinoids may act as downstream effectors in the action of cocaine in the striatum. Understanding the molecular and physiological effects of drugs of abuse in the brain is essential for the development of effective strategies against addiction. Neuropsychopharmacology advance online publication, 21 April 2004; doi:10.1038/sj.npp.1300458


Objective. Delta(9)-Tetrahydrocannabinol, the active agent of Cannabis sativa, exhibits well-documented antitumor properties, but little is known about the possible effects mediated by endogenous cannabinoids on human tumors. In the present study, we analyzed the effect of arachidonyl ethanolamide (AEA) on cervical carcinoma (CxCa) cell lines. Methods. To assess the sensitivity of CxCa cells to AEA, we selected three cell lines that were exposed to increasing doses of AEA with or without antagonists to receptors to AEA. DNA fragmentation and caspase-7 activity were used as apoptosis markers. The expression of receptors to AEA were analyzed in CxCa cell lines as well as CxCa biopsies. Results. The major finding was that AEA induced apoptosis of CxCa cell lines via aberrantly expressed vanilloid receptor-1, whereas AEA binding to the classical CB1 and CB2 cannabinoid receptors mediated a protective effect. Furthermore, unexpectedly, a strong expression of the three forms of AEA receptors was observed in ex vivo CxCa biopsies. Conclusion. Overall, these data suggest that the specific targeting of VR1 by endogenous cannabinoids or synthetic molecules offers attractive opportunities for the development of novel potent anticancer drugs.


Several studies have demonstrated reciprocal, as well as synergistic interactions between cannabinoid and opioid systems. The aim of this study was to explore the time-related effects of repeated administration of Delta9-tetrahydrocannabinol on mu-opioid receptor
autoradiography in various brain regions of the rat. To this aim, the effects of Delta9-tetrahydrocannabinol (Delta9-THC, 5 mg/kg/day; i.p.) were examined after 1, 3, 7 and 14 days of repeated administration on regions containing mu-opioid receptors: (i) forebrain [caudate-putamen, nucleus accumbens (core and shell) and piriform cortex]; (ii) amygdala (medial pars and cortical posteromedial pars), hypothalamus (ventromedial and dorsomedial nuclei, zona incerta), hippocampal regions (CA1, CA2, CA3, dentate gyrus), hindbrain (substantia nigra and ventral tegmental area); and (iii) thalamus, including 12 thalamic nuclei. In most of these regions, repeated cannabinoid administration increases mu-opioid receptor density; however, the onset, degree of magnitude reached and time-related effects produced by administration with Delta9-tetrahydrocannabinol are dependent upon the brain region examined. It appears that the major increase in mu-opioid receptor density occurs 1 and 3 days after Delta9-THC administration. In some regions, this increase is maintained and, for most of the brain areas examined, this effect is no longer significant by 14 days of administration, suggesting tolerance to cannabinoid treatment. Taken together, the results of this study suggest that cannabinoids produce a time-related differential responsiveness in mu-opioid receptor density in several brain areas that may be relevant to an understanding of the alterations associated with cannabinoid exposure.


Delta-9-tetrahydrocannabinol (delta-9-THC) prevents cisplatin-induced emesis via cannabinoid CB(1) receptors. Whether central and/or peripheral cannabinoid CB(1) receptors account for the antiemetic action(s) of delta-9-THC remains to be investigated. The 5-hydroxytryptamine (5-HT=serotonin) precursor, 5-hydroxytryptophan (5-HTP), is an indirect 5-HT agonist and simultaneously produces the head-twitch response (a centrally mediated serotonin 5-HT(2A) receptor-induced behavior) and emesis (a serotonin 5-HT(3) receptor-induced response, mediated by both peripheral and central mechanisms) in the least shrew (Cryptotis parva). The peripheral amino acid decarboxylase inhibitor, carbidopa, prevents the conversion of 5-HTP to 5-HT in the periphery and elevates 5-HTP levels in the central nervous system (CNS). When administered i.p. alone, a 50 mg/kg dose of 5-HTP failed to induce either behaviour while its 100 mg/kg dose produced robust frequencies of both head-twitch response and emesis. Pretreatment with carbidopa (0, 10, 20 and 40 mg/kg) potentiated the ability of both doses of 5-HTP to produce the head-twitch response in a dose-dependent but bell-shaped manner, with maximal potentiation occurring at 20 mg/kg carbidopa. Carbidopa dose-dependently reduced the frequency of 5-HTP (100 mg/kg)-induced emesis, whereas the 10 mg/kg dose potentiated, and the 20 and 40 mg/kg doses suppressed the frequency of vomits produced by the 50 mg/kg dose of 5-HTP. The peripheral and/or central antiemetic action(s) of delta-9-THC (0, 1, 2.5, 5, 10 and 20 mg/kg) against 5-HTP (100 mg/kg)-induced head-twitch response and emesis were investigated in different groups of carbidopa (0, 10 and 20 mg/kg) pretreated shrews. Irrespective of carbidopa treatment, delta-9-THC attenuated the frequency of 5-HTP-induced head-twitch response in a dose-dependent manner with similar ID(50) values. Although delta-9-THC also reduced the frequency of 5-HTP-induced emesis with similar ID(50)s, at the 5 mg/kg delta-9-THC dose however, 5-HTP induced significantly less vomits in the 10 and 20 mg/kg carbidopa-treated groups relative to its 0 mg/kg control group. Moreover, increasing doses of carbidopa significantly shifted the inhibitory dose-response effect of delta-9-THC in protecting shrews from 5-HTP-induced emesis to the left. Relatively, a large dose of delta-9-THC (20 mg/kg) was required to significantly reduce the number of vomits produced by direct acting serotonergic 5-HT(3) receptor agonists, serotonin and 2-methylserotonin. Low doses of delta-9-THC (0.1-1 mg/kg) nearly completely prevented 2-methylserotonin-induced, centrally mediated, head-twitch and ear-scratch responses. The results indicate that delta-9-THC probably acts pre- and postsynaptically to attenuate emesis produced by indirect and direct acting 5-HT(3) receptor agonists via both central and peripheral mechanisms. In addition, delta-9-THC prevents 5-HTP-induced head-twitch and emesis via cannabinoid CB(1) receptors since the CB(1) receptor antagonist, SR 141716A [N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide], countered the inhibitory actions of an effective dose of delta-9-THC against both behaviours.

The administration of the endocannabinoid anandamide to rats produces hypokinesia in parallel to a decrease in the activity of nigrostriatal dopaminergic neurons. It was earlier hypothesized that this effect was mediated through the activation of CB(1) receptors, although these receptors have not been found in dopaminergic neurons, but in striatal projection neurons connected with them. However, two recent discoveries: (i) that anandamide is also able to activate vanilloid VR(1) receptors, and (ii) that VR(1) receptors are located on nigrostriatal dopaminergic neurons, allow to re-evaluate this hypothesis and suggest that the activation of vanilloid-like receptors rather than CB(1) receptors might be responsible of anandamide-induced hypokinesia and decreased nigrostriatal dopaminergic activity. To validate this new hypothesis, we carried out two different experiments. First, we explored whether the inhibitory effects of anandamide on motor activity and dopaminergic transmission were reversed by capsazepine, an antagonist for vanilloid-like receptors. Our data demonstrated that anandamide reduced ambulation, stereotypies and exploration, measured in the open-field test, whereas it increased the time spent in inactivity. All these effects were completely reversed by capsazepine, which had no effect by itself. Anandamide also caused a significant decrease in nigrostriatal dopaminergic activity, reflected by a reduction in DOPAC contents in the caudate-putamen, which was also reversed by capsazepine. As a second objective, we explored whether anandamide is able to directly influence nigrostriatal dopaminergic function by examining its effects on in vitro dopamine (DA) release using perfused striatal fragments. Our data confirmed that anandamide significantly decreased K(+)–stimulated dopamine release from nigrostriatal terminals and that this effect was vanilloid-like receptor-mediated since it was prevented by capsazepine. This in vitro inhibitory effect was not seen with a classic cannabinoid agonist that does not bind vanilloid-like receptors. In summary, anandamide behaves as a hypokinetic substance, thus producing motor depression in the open-field test, presumably related to a decrease in nigrostriatal dopaminergic activity. These effects were completely reversed by the vanilloid-like receptor antagonist capsazepine, thus indicating a role of these receptors, which are located on dopaminergic neurons, in mediating hypokinetic effects of anandamide. In vitro studies, using perfused striatal fragments, support this vanilloid-like receptor-mediated direct action, which would not be available for classic cannabinoid agonists.


Both cannabinoid CB1 receptor agonists, such as delta-tetrahydrocannabinol (delta-THC), CP 55,940 and WIN 55,212-2, and the antagonist/inverse agonist SR141716A, dose-dependently suppress operant behavior. The present study investigated to what extent combined i.p. application of SR141716A with these cannabinoids resulted in mutually antagonistic effects, in additive effects, or in no interactive effects on operant responding in rats trained in a fixed-ratio 10, food-reinforced 10-min procedure. Pretreatment with SR141716A either had no effect on (at 0.3-1mg/kg), or partially blocked (at 3 mg/kg), the inhibitory effects on responding induced by delta-THC (3-5 mg/kg) and CP 55,940 (0.03-0.2 mg/kg). Interestingly, while 3 mg/kg SR141716A induced moderate inhibitory effects on operant responding, its combination with either agonist resulted in the same level of inhibitory activity on responding as that obtained by SR141716A when tested alone. Pretreatment with a low dose of CP 55,940 (0.01 mg/kg) or WIN 55,212-2 (0.3 mg/kg) did not affect response inhibition induced by SR141716A. Combination of SR141716A (0.5 and 1mg/kg) with delta-THC (3 mg/kg) resulted in the same level of response inhibition, independently of whether SR141716A was given 5 min before or 15 min after delta-THC. Although alternative explanations are conceivable, the data may indicate that SR141716A is a partial agonist at those cannabinoid receptors mediating the response-rate suppressive effects of cannabinoids.

This study compared the potency and efficacy of the cannabinoids delta-tetrahydrocannabinol (delta-THC), HU-210, WIN 55,212-2 and CP 55,940 in suppressing food-reinforced operant behavior, increasing reaction latency in a hot-plate test and inducing hypothermia, and tested whether these behavioral effects induced by CP 55,940 showed differential sensitivity to the cannabinoid CB1 receptor antagonist SR141716A, and to tolerance development. After acute i.p. administration to rats, operant behavior was more potently affected than reaction latency and body temperature, but the order of potency of the different drugs was similar across the tests: HU-210<CP 55,940<WIN 55,212-2=delta-THC. SR141716A blocked the hypothermic and analgesic effects more potently/efficiently than the response-rate suppressive effect of CP 55,940. After repeated administration of CP 55,940, the extent and speed of tolerance development was most pronounced in the hypothermia test, and least pronounced in the operant test. It is concluded that the more the behavioral effect induced by a cannabinoid receptor agonist is situated at the left-hand side of the dose-spectrum, the more the effect is resistant to blockade by a cannabinoid receptor antagonist and to the development of tolerance. The possible consequence of this observation for the therapeutic use of cannabinoids is discussed.


Depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE) are two related forms of short-term synaptic plasticity of GABAergic and glutamatergic transmission, respectively. They are induced by calcium concentration increases in postsynaptic cells and are mediated by the release of a retrograde messenger, which reversibly inhibits afferent synapses via presynaptic mechanisms. We review here: The evidence accumulated during the 1990s that has led to the conclusion that DSI/DSE rely on retrograde signaling. The more recent research that has led to the identification of endocannabinoids as the retrograde messengers responsible for DSI/DSE. The possible mechanisms by which presynaptic type 1 cannabinoid receptors reduce synaptic efficacy during DSI/DSE. The possible modes of induction of DSI/DSE by physiological activity patterns, and the partially conflicting evaluations of the calcium concentration increases required for cannabinoid synthesis. Finally, the relation between DSI/DSE and other forms of long- and short-term synaptic inhibition, which were more recently associated with the production of endocannabinoids by postsynaptic cells. We conclude that recent studies on DSI/DSE have uncovered a specific and original mode of action for endocannabinoids in the brain, and that they have opened new avenues to understand the role of retrograde signaling in central synapses.

enhancement of anandamide bioavailability. The startle response was enhanced only following a lower AM404 dose (2.5 mg/kg), indicating that AM404 induced hyperreactivity at a dose that did not affect PPI, further reinforcing a selective disruption of PPI.


Cannabinoid receptors have been studied extensively in view of their potential functional role in several physiological and pathological processes. For this reason, the search for new potent, selective ligands for subtype CB receptors, CB(1) and CB(2), is still of great importance, in order to investigate their role in various physiological functions. The present study describes the synthesis and the biological properties of a series of 1,8-naphthyridine derivatives, characterised by the presence of some important structural requirements exhibited by other classes of cannabinoid ligands, such as an aliphatic or aromatic carboxamide group in position 3, and an alkyl or arylalkyl substituent in position 1. These compounds were assayed for binding both to the brain and to peripheral cannabinoid receptors (CB(1) and CB(2)). The results obtained indicate that the naphthyridine derivatives examined possess a greater affinity for the CB(2) receptor than for the CB(1) receptor. In particular, derivatives 6a and 7a possess an appreciable affinity for the CB(2) receptor, with K(i) values of 5.5 and 8.0 nM respectively; also compounds 4a, 5a and 8a exhibit a good CB(2) affinity, with K(i) values in the range of 10-44 nM. Furthermore, compounds 3g-i and 18 revealed a good CB(2) selectivity, with a CB(1)/CB(2) ratio >20.


There is considerable interest in developing new therapies that are based on compounds that modulate the endocannabinoid system to treat several disease states (e.g., pain, neurodegeneration and cancer). However, recent evidence from studies in experimental animals has suggested that three clinically used drugs, the anaesthetic agent propofol and the non-steroidal anti-inflammatory drugs indomethacin and flurbiprofen (when given spinally), activate cannabinoid receptors as an important part of their actions. In this article, the findings of these studies are summarized and possible spectra of actions of these drugs is discussed.


Whether chronic cannabinoid consumption produces a dependent state comparable to that occurring with other drugs (e.g., the appearance of withdrawal signs when consumption is interrupted), and whether chronic cannabinoid consumption increases the risk of consuming other drugs of greater addictive power, are probably the two questions relating to cannabinoid addiction that provoke the most controversy. The present study was designed to further explore these two questions in laboratory animals. Firstly, we examined the effects of an acute challenge with SR141716 (an antagonist for the cannabinoid CB(1) receptor) in Delta(9)-tetrahydrocannabinol (Delta(9)-THC)-tolerant rats. This antagonist has been reported to precipitate a cannabinoid withdrawal syndrome. Thus, the administration of SR141716 to Delta(9)-THC-tolerant rats reduced inactivity in the open-field test and enhanced responses as tremor, turning and retropulsion-these responses that were only slightly enhanced in control rats. The administration of SR141716 increased the plasma prolactin and the corticosterone concentration in controls, but these increases were much lesser in Delta(9)-THC-tolerant rats. In addition, CRF-mRNA levels in the paraventricular hypothalamic nucleus, while reduced in SR141716-treated controls, were significantly increased in Delta(9)-THC-tolerant rats. The analysis of endocannabinoids also revealed that the administration of SR141716, which was mostly inactive in control rats, was able to reverse the changes in anandamide or 2-arachidonoylglycerol concentrations found in Delta(9)-THC-tolerant rats, in the striatum, limbic forebrain, diencephalon, cerebellum and brainstem, but not in the midbrain and hippocampus. As a second objective, we evaluated whether Delta(9)-THC-tolerant rats were more vulnerable to morphine in a self-administration
paradigm. The Delta(9)-THC-tolerant and control rats self-administered morphine to a similar extent, in concordance with the similar values of dopaminergic activity in limbic and motor regions. In summary, our data indicate that Delta(9)-THC-tolerant rats were not more vulnerable to the reinforcing properties of morphine. However, they responded to the blockade of CB(1) receptors by exhibiting slightly but possibly relevant differences in behavioral, endocrine and molecular parameters compared to the response in non-tolerant rats. This is indicative of the existence of a withdrawal syndrome in cannabinoid-tolerant rats that is mild compared with abstinence in opioid-dependent rats.


Abstract Contrasting data were reported regarding the effects of cannabinoids on anxiety and social behaviour in both animals and humans. The cognitive effects of cannabinoids and their interactions with the HPA-axis raise the possibility that cannabinoid effects are context but not behaviour specific. To assess this hypothesis, we submitted CB1 receptor knock-out (CB1-KO) and wild-type (WT) mice to tests, which involved similar behaviours, but the behavioural context was different. The elevated plus-maze test was performed under less and more anxiogenic conditions, i.e. under low and high light, respectively. We also compared the social behaviour of the two genotypes in the resident/intruder and social interaction tests. Both tests represent a social challenge and induce similar behaviours, but involve different contexts. The behaviour of CB1-KO and WT mice was similar under low light, but CB1 gene disruption increased anxiety-like behaviour under the high light condition. CB1 gene disruption promoted aggressive behaviour in the home-cage, whereas it inhibited social behaviour in the unfamiliar cage. Thus, the anxiogenic-like effect was restricted to the more stressful unfamiliar environment. These data suggest that the effects of CB1 gene disruption were context and not behaviour specific. Novelty stress resulted in higher ACTH levels in CB1-KOs than in WT, which suggests that context dependency occurred in conjunction with an altered HPA axis function. The present data at least partly explain contrasting effects of cannabinoids in different contexts as well as in different species and strains that show differential stress responses and coping strategies.


From a historical perspective to the present day, all the evidence suggests that activation of cannabinoid receptors (CBRs) is beneficial for gut discomfort and pain, which are symptoms related to dysmotility and visceral perception. CBRs comprise G-protein coupled receptors that are predominantly in enteric and central neurones (CB1R) and immune cells (CB2R). In the last decade, evidence obtained from the use of selective agonists and inverse agonists/antagonists indicates that manipulation of CB1R can alter (1) sensory processing from the gut, (2) brain integration of brain-gut axis, (3) extrinsic control of the gut and (4) intrinsic control by the enteric nervous system. The extent to which activation of CB1R is most critical at these different levels is related to the region of the GI tract. The upper GI tract is strongly influenced by CB1R activation on central vagal pathways, whereas intestinal peristalsis can be modified by CB1R activation in the absence of extrinsic input. Actions at multiple levels make the CB1R a target for the treatment of functional bowel disorders, such as IBS. Since low-grade inflammation may act as a trigger for occurrence of IBS, CB2R modulation could be beneficial, but there is little supporting evidence for this yet. The challenge is to accomplish CBR activation while minimizing adverse effects and abuse liabilities. Potential therapeutic strategies involve increasing signaling by endocannabinoids (EC). The pathways involved in the biosynthesis, uptake and degradation of EC provide opportunities for modulation of CB1R and some recent evidence with inhibitors of EC uptake and metabolism suggest that these could be exploited for therapeutic gain. British Journal of Pharmacology (2004) 141, 1335-1345. doi:10.1038/sj.bjp.0705783

Abstract Cannabinoid type 1 (CB1) receptors play a central role in the protection against excitotoxicity induced by treatment of mice with kainic acid (KA). As inactivation of CB1 receptor function in mice blocks KA-induced increase of brain-derived neurotrophic factor (BDNF) mRNA levels in hippocampus, the notion was put forward that BDNF might be a mediator, at least in part, of CB1 receptor-dependent neuroprotection [Marsicano et al. (2003) Science, 302, 84-88]. To assess this signalling cascade in more detail, organotypic hippocampal slice cultures were used, as this in vitro system conserves morphological and functional properties of the hippocampus. Here, we show that both genetic ablation of CB1 receptors and pharmacological blockade with the specific CB1 receptor antagonist SR141716A increased the susceptibility of the in vitro cultures to KA-induced excitotoxicity, leading to extensive neuronal death. Next, we found that the application of SR141716A to hippocampal cultures from wild-type mice abolished the KA-induced increase in BDNF protein levels. Therefore, we tried to rescue these organotypic cultures from neuronal death by exogenously applied BDNF. Indeed, BDNF was sufficient to prevent KA-induced neuronal death after blockade of CB1 receptor signalling. In conclusion, our results strongly suggest that BDNF is a key mediator in CB1 receptor-dependent protection against excitotoxicity, and further underline the physiological importance of the endogenous cannabinoid system in neuroprotection.


The cannabinoid 1 receptor antagonist AM 251 is known to block the inhibitory effects of endocannabinoids and synthetic cannabinoid agonists on transmitter release through an action at presynaptic cannabinoid 1 receptors in brain. We examined the ability of AM 251 to inhibit sodium channel-dependent functions and the binding of [(3)H]batrachotoxinin A 20-alpha-benzoate to sodium channels in mouse brain synaptic preparations. Depolarization of synaptoneurosomes by the sodium channel site 2-specific neurotoxin veratridine, which is abolished by tetrodotoxin, was found to be inhibited in a concentration-dependent fashion by AM 251 (IC(50)=8.9 microM). Veratridine-dependent (tetrodotoxin suppressible) release, of L-glutamic acid and GABA from synaptosomes was also reduced by AM 251 (IC(50)s=8.5 microM (L-glutamic acid), 9.2 microM (GABA)). The binding of the radioligand [(3)H]batrachotoxinin A 20-alpha-benzoate to site 2 on sodium channels was displaced by AM 251 (IC(50)=11.2 microM). Scatchard analysis of binding showed that at its IC(50), AM 251 increased (by 2.3 times) the K(D) of radioligand without altering B(max), suggesting a competitive mechanism of inhibition by AM 251. Kinetic experiments indicated that AM 251 inhibits equilibrium binding by allosterically accelerating the dissociation of the [(3)H]-batrachotoxinin A 20-alpha-benzoate:sodium channel complex. Our data suggest that micromolar concentrations of AM 251 are capable of reducing neuronal excitability and inhibiting release of excitatory and inhibitory transmitters through blockade of voltage-sensitive sodium channels in brain.


We have studied the possible interaction between the cannabinoid receptor agonist CP 55,940 (1 and 50 microg/kg) and the 5-HT1A receptor antagonist WAY 100635 (1 mg/kg) in the modulation of plus-maze and holeboard activity in Wistar adult male rats. In the plus-maze, the higher dose of CP 55,940 induced an anxiogenic-like effect, whereas the lower dose induced anxiolytic-like responses. The 5-HT1A antagonist, which was silent in this test, attenuated the anxiogenic, but not the anxiolytic, effect of CP 55,940. In the holeboard, the higher dose of CP 55,940 significantly decreased head-dipping duration, and WAY 100635, which did not affect exploratory head-dipping when administered alone, antagonized this effect. The administration of WAY 100635 significantly increased grooming behaviour, and this effect was inhibited by the two doses of CP 55,940, which did not exert any effect, per se, on this parameter. We provide the first evidence implicating 5-HT1A receptors in anxiety-related behavioural responses to a cannabinoid agonist.

Excessive inflammatory responses can emerge as a potential danger for organisms' health. Physiological balance between pro- and anti-inflammatory processes constitutes an important feature of responses against harmful events. Here, we show that cannabinoid receptors type 1 (CB1) mediate intrinsic protective signals that counteract proinflammatory responses. Both intrarectal infusion of 2,4-dinitrobenzene sulfonic acid (DNBS) and oral administration of dextrane sulfate sodium induced stronger inflammation in CB1-deficient mice (CB1(-/-)) than in wild-type littermates (CB1(+/+)). Treatment of wild-type mice with the specific CB1 antagonist N-(piperidino-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide (SR141716A) mimicked the phenotype of CB1(-/-) mice, showing an acute requirement of CB1 receptors for protection from inflammation. Consistently, treatment with the cannabinoid receptor agonist R(-)-7-hydroxy-Delta(6)-tetra-hydrocannabinol-dimethylheptyl (HU210) or genetic ablation of the endocannabinoid-degrading enzyme fatty acid amidase (FAAH) resulted in protection against DNBS-induced colitis. Electrophysiological recordings from circular smooth muscle cells, performed 8 hours after DNBS treatment, revealed spontaneous oscillatory action potentials in CB1(-/-) but not in CB1(+/+) colons, indicating an early CB1-mediated control of inflammation-induced irritation of smooth muscle cells. DNBS treatment increased the percentage of myenteric neurons expressing CB1 receptors, suggesting an enhancement of cannabinoid signaling during colitis. Our results indicate that the endogenous cannabinoid system represents a promising therapeutic target for the treatment of intestinal disease conditions characterized by excessive inflammatory responses.


The endocannabinoid system consists of two cannabinoid (CB) receptors, seven ligands, and ligand-catabolizing enzymes such as fatty acid amid hydrolase (FAAH) and monoglyceride lipase (MGL). The system's phylogenetic distribution is poorly known. The ligands cannot be molecularly investigated because they are not polypeptides and their specific synthetic enzymes have not been identified, so no sequences are available. Ligand phylogenetics can be inferred, nonetheless, by their presence in a range of extant organisms. Thus a meta-analysis of ligand extraction studies was performed (chemotaxonomy), and compared to a molecular search for homologs of CB receptors, vanilloid receptors (VR1), FAAH, and MGL in the genomes of sequenced organisms (phylogenomics). Putative homologs underwent functional mapping to ascertain the presence of critical amino acid motifs known to impart protein functionality. From an evolutionary perspective it appears that (1) endocannabinoid ligands evolved before CB receptors; (2) the ligands evolved independently multiple times; (3) CB receptors evolved prior to the metazoan-bilaterian divergence (ie, between extant Hydra and leech), but were secondarily lost in the Ecdysozoa; (4) VR1 may predate CB receptors but its affinity for endocannabinoids is a recent acquisition, appearing after the lower vertebrate-mammal divergence; (5) MGL may be as old as the ligands, whereas FAAH evolved recently, after the appearance of vertebrates. FAAH's emergence correlates with VR1's newly-found affinity for anandamide; this overlap in evolutionary time is recapitulated by complementary distribution patterns of FAAH, VR1, and anandamide in the brain. Linking FAAH, VR1, and anandamide implies a coupling among the remaining "older" parts of the endocannabinoid system, MGL, CB receptors, and 2-AG.


The effect of cannabinoid CB1 receptor agonists and antagonists on penile erection was studied in male rats when injected into the paraventricular nucleus of the hypothalamus. The CB1 receptor antagonist SR 141716A [N-(piperidino-1-yl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide ] (0.5-5 microg) induced penile erection in a dose-dependent manner. The minimal effective dose was 1 microg, while the maximal response was found with 5 microg of the compound. In contrast, the CB1 receptor agonists WIN 55,212-2 [4,5-dihydro-2-methyl-4(4-morpholinoethyl)-1-(1-naphthalenyl-carbonyl)-6 H-pyrrolo[3,2,1-i,j]quinolin-6-one] (0.5-5 microg) and CP 55,940 [1alpha,2beta-(R)-5alpha]-5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-
hydroxy -propyl)cyclohexyl]phenol (0.5-5 microg) were ineffective at all the doses tested. Nevertheless, both compounds reduced the enhancing effect of SR 141716A on penile erection when given into the paraventricular nucleus at the above doses before SR 141716A. The pro-erectile effect of SR 141716A was also reduced by the non-competitive NMDA receptor antagonist dizocilpine (MK-801) (0.2 microg) and by the NO synthase inhibitor NG-nitro-l-arginine methylster (L-NAME) (20 microg) but not by the dopamine receptor antagonist cis-flupenthixol (10 microg) or the oxytocin receptor antagonist d(CH(2))(5)Tyr(Me)(2)-Orn(8)-vasotocin (0.1 microg), when given into the paraventricular nucleus. In spite of its inability to prevent the pro-erectile effect of SR 141716A when given in the paraventricular nucleus, d(CH(2))(5)Tyr(Me)(2)-Orn(8)-vasotocin (1 microg) reduced almost completely SR 141716A-induced penile erection when given into the lateral ventricles. The present results show that cannabinoid CB1 receptors present in the paraventricular nucleus may influence erectile function and sexual activity by modulating paraventricular oxytocinergic neurons mediating erectile function.


The endothelium-dependent mesenteric vasorelaxant effect of anandamide has been attributed to stimulation of a G(i)/G(o)-coupled receptor, for which the nonpsychoactive analog abnormal cannabidiol (abn-cbd, (-)-4-(3,3,4-trans-p-menthadien-1,8-y1)olivetol) is a selective agonist and the compound O-1918 ((-)-4-(3,3,4-trans-p-menthadien-(1,8)-yl)-orcinol) is a selective antagonist. In human umbilical vein endothelial cells abn-cbd was reported to increase the phosphorylation of p44/42 mitogen activated protein kinase (MAPK) and protein kinase B/Akt, and these effects could be inhibited by pertussis toxin, by phosphatidylinositol 3-kinase (PI3K) inhibitors or by O-1918 [Mol. Pharmacol. 63 (2003) 699]. In the present experiments, abn-cbd caused a concentration-dependent increase in human umbilical vein endothelial cell migration, as quantified in a transwell chamber. This effect was antagonized by O-1918, by the PI3K inhibitor wortmannin, and by pertussis toxin, but not by the cannabinoid CB(1) receptor antagonist AM251 or the cannabinoid CB(2) receptor antagonist SR144528. The EDG-1 receptor agonist sphingosine-1-phosphate also increased human umbilical vein endothelial cell migration, but this response was unaffected by O-1918. In Chinese hamster ovary cells stably transfected with the gene encoding the EDG-1 receptor, p44/42 MAPK phosphorylation was unaffected by abn-cbd, but strongly induced by sphingosine-1-phosphate. These results indicate that an abn-cbd-sensitive endothelial receptor distinct from cannabinoid CB(1), CB(2) or EDG-1 receptors mediates not only vasorelaxation but also endothelial cell migration.


The acute effects of cannabinoid drugs on the synthesis of noradrenaline, dopamine, and serotonin (5-HT) were assessed, simultaneously, using the accumulation of 3,4-dihydroxyphenylalanine (dopa) and 5-hydroxytryptophan (5-HTP) after decarboxylase inhibition as a measure of the rate of tyrosine and tryptophan hydroxylation in the rat brain in vivo. Treatment (1 h, i.p.) with Delta(9)-tetrahydrocannabinol (THC, 5, 10, and 20 mg/kg) and the cannabinoid receptor agonist WIN 55,212-2 (WIN, 2 and 4 mg/kg) increased dopa/noradrenaline synthesis (40-70%) in various brain regions enriched in this neurotransmitter (e.g., cerebral cortex, hippocampus, hypothalamus). In most brain regions, the content of noradrenaline was reduced by cannabinoid drugs (27-66%). For the effects of WIN (2 and 4 mg/kg), an inverse correlation ( r=-0.61, P=0.036) was obtained between the accumulation of dopa and the content of noradrenaline in the hypothalamus. The stimulatory effect on dopa accumulation induced by THC was antagonized by the selective CB(1) receptor antagonists SR141716A and AM 281 (10 mg/kg). In contrast, THC and WIN decreased the synthesis of dopa/dopamine in the corpus striatum (16-37%) and that of 5-HTP/5-HT (20-35%) in brain regions enriched in 5-HT (e.g., cerebral cortex and hippocampus). These inhibitory effects of THC and WIN were also antagonized by AM 281 and/or SR141716A. THC did not alter the content of 5-HT or dopamine in the brain. The effects may be related to the activation of presynaptic inhibitory cannabinoid CB(1)
receptors located on the neurones themselves (serotonin) and on facilitatory (dopamine) and inhibitory interneurones (noradrenaline).


Cannabinoid-MDMA interactions were examined in male Wistar rats. MDMA (formula: mg/kg over 4 h on each of 2 days) was administered with or without Delta(9)-tetrahydrocannabinol (THC) (formula: mg/kg), the synthetic cannabinoid receptor agonist CP 55,940 (formula: mg/kg or formula: mg/kg over 4 h on each of 2 days) or the cannabinoid receptor antagonist SR 141716 (formula: mg/kg). Co-administered Delta(9)-THC and CP 55,940 but not SR 141716 prevented MDMA-induced hyperthermia, causing a powerful hypothermia. Co-administered Delta(9)-THC, CP 55,940 and SR 141716 all tended to decrease MDMA-induced hyperactivity. Co-administered Delta(9)-THC provided protection against the long-term increases in anxiety seen in the emergence test, but not the social interaction test, 6 weeks after MDMA treatment. Co-administered Delta(9)-THC and CP 55,940, but not SR 141716, partly prevented the long-term 5-HT and 5-HIAA depletion caused by MDMA in various brain regions. SR 141716 administered with CP 55,940 and MDMA prevented the hypothermic response to the CP 55,940/MDMA combination but did not alter the CP 55,940 attenuation of MDMA-induced 5-HT depletion. These results suggest a partial protective effect of co-administered cannabinoid receptor agonists on MDMA-induced 5-HT depletion and long-term anxiety. This action appears to operate independently of cannabinoid CB1 receptors.


This study aimed to examine the behavioural and neurochemical (cannabinoid CB1 receptor gene expression) changes induced by spontaneous cannabinoid withdrawal in mice. Tolerance was assessed by measuring rectal temperature and motor activity in the open-field test after CP-55, 940 administration. Cannabinoid withdrawal symptoms were determined by measuring motor activity and behavioural signs of abstinence. Cessation of CP-55, 940 treatment in tolerant mice induced a spontaneous time-dependent behavioural withdrawal syndrome consisting of marked increases (140%) in motor activity, number of rearings (170%), decreases in grooming (57%), wet dog shakes (73%) and rubbing behaviours (74%) on day 1, progressively reaching values similar to vehicle-treated mice on day 3. Interestingly, this spontaneous cannabinoid withdrawal resulted in CB1 gene expression upregulation (20-30%) in caudate-putamen, ventromedial hypothalamic nucleus, central amygdaloid nucleus and CA1, whereas in the CA3 field of hippocampus, a significant decrease (15-20%) was detected. Taken together, the results of this study suggest that cessation of CP-55, 940 administration in tolerant mice produces a behavioural cannabinoid withdrawal syndrome and a selective and differential responsiveness in CB1 receptor gene expression in several brain regions of the mice. These findings further suggest a time and regional differential role for cannabinoid receptors in short- and long-term neuroadaptations that occur after exposure to cannabis derivatives.


The effects of endogenous and synthetic cannabinoid receptor agonists including 2-arachidonoylglycerol, R-methanandamide, WIN55,212-2, CP55,940 and the psychoactive constituent of marijuana, Delta(9)-THC, on the function of homomeric alpha7 nicotinic ACh receptors expressed in Xenopus oocytes was investigated using the two-electrode voltage-clamp technique. The endogenous cannabinoid receptor ligands 2-arachidonoylglycerol and the metabolically stable analogue of anandamide, R-methanandamide, reversibly inhibited currents evoked with ACh (100 micro M) in a concentration-dependent manner (IC50 values of 168 nM and 183 nM, respectively). In contrast, the synthetic cannabinoid receptor agonists CP55,940, WIN55,212-2, and the phytochemical Delta(9)-THC did not alter alpha7 nicotinic ACh receptor...
function. The inhibition of alpha7-mediated currents by 2-arachidonylglycerol was found to be non-competitive and voltage-independent. Additional experiments using endocannabinoid metabolites suggested that arachidonic acid, but not ethanolamine or glycerol, could also inhibit the alpha7-nACh receptor function. Whereas the effects of arachidonic acid were also noncompetitive and voltage-independent, its potency was much lower than 2-AG and anandamide. Results of studies with chimeric alpha7-nACh-5-HT3 receptors that were comprised of the amino-terminal domain of the alpha7-nACh receptor and the transmembrane and carboxyl-terminal domains of 5-HT3 receptors indicated that the site of interaction of the endocannabinoids with the alpha7-nAChR was not located on the N-terminal region of the receptor. These data indicate that cannabinoid receptor ligands that are produced in-situ potently inhibit alpha7-nACh receptor function, whereas the synthetic cannabinoid ligands, and Delta(9)-THC, are without effect or are relatively ineffective at inhibiting these receptors.


RATIONALE. Previous studies have demonstrated that the activation and blockade of the cannabinoid type 1 receptor (CB1) leads to an enhancement and decrease of the consumption of food and other orally ingested reinforcers, respectively. OBJECTIVE. To gain further knowledge about the role of CB1 in sucrose/saccharin reinforcing efficacy and intake, we tested CB1 knockout (CB1-KO) and littermate wild-type (WT) control mice in several self-administration experimental protocols. METHODS. Operant (fixed or progressive ratio schedule) and non-operant conditioning procedures were used. In addition, a choice analysis based on the "matching law" as well as a microstructural analysis of the intra-session pattern of self-administration was performed. RESULTS. CB1-KO mice consume less sucrose under operant conditions or when using a two-bottle free choice procedure. Moreover, as revealed by additional behavioural analysis, CB1-KO mice exhibit a decreased sensitivity to the rewarding properties of sucrose. In agreement with this finding, the differences between WT and CB1-KO mice faded away when the palatability of sucrose was devaluated by adding quinine, but not when a non-caloric sweetener, saccharin, was available. CONCLUSIONS. These results demonstrate a modulatory role of CB1 in the determination of the rewarding properties of sucrose and probably, as suggested by previous studies, other reinforcers.


The roles of the two cannabinoid receptor subtypes, CB-1 and CB-2, have not been clarified in cannabinoid-mediated analgesia. We investigated the efficacy of the non-selective cannabinoid receptor agonist CP55,940 in the modulation of responses in the rat to both acute pain (tail flick) and neuropathic pain (tactile allodynia following chronic L5/6 spinal nerve ligation). Responses were also assessed in the presence of the CB-1 antagonist SR141716A (SR1) and the CB-2 antagonist SR144528 (SR2). CP55,940 attenuated tactile allodynia (ED(50) 0.04 mg/kg i.t. (95% CI 0.032-0.044 mg/kg), 0.12 mg/kg i.p. (95% CI 0.10-0.15 mg/kg)) and induced thermal antinociception (ED(50) tail flick 0.07 mg/kg i.t. (95% CI 0.05-0.10 mg/kg), 0.17 mg/kg i.p. (95% CI 0.11-0.26 mg/kg)). SR1 0.5 mg/kg i.t. attenuated the antinociceptive effect of CP55,940 in both modalities. However, SR1 1.0 mg/kg i.p. decreased tail flick latency but had no effect on tactile allodynia antinociception. In contrast, SR2 1.0 mg/kg i.p. significantly decreased the effect of i.p. CP55,940 on both tail flick antinociception and tactile allodynia [Formula: see text] The combination of SR1 and SR2 (i.p.) had an additive effect in decreasing the antinociception induced by CP55,940 on tail flick responses [Formula: see text] These results suggest a role for CB-2 receptor-mediated antinociception in both acute and neuropathic pain in addition to centrally located CB-1 mechanisms.


One concern about the widespread use of cannabis is that exposure to its active ingredient, Delta-9-tetrahydrocannabinol (THC), might increase future reinforcing effects of other
abused drugs such as heroin. In this study, we investigated the effects of pre-exposure to THC on subsequent intravenous self-administration of heroin by Sprague-Dawley rats. In one group of rats, we studied (1) acquisition of heroin self-administration behavior using a continuous-reinforcement (fixed-ratio (FR) 1) schedule, (2) heroin dose-response relationships using an FR1/variable-dose schedule, and (3) reinforcing efficacy of heroin using a progressive-ratio schedule. The number of rats pre-exposed to THC that subsequently learned to self-administer 50 microg/kg injections of heroin within 10 daily sessions did not differ from vehicle-pretreated controls. In contrast, rats pre-exposed to THC subsequently self-administered significantly more heroin injections per session and showed significantly shorter post-injection pauses over a range of heroin doses (12.5-100 microg/kg/injection) using the variable-dose schedule. Interestingly, the maximum effort rats would exert to receive an injection of the different doses of heroin under the progressive-ratio schedule was not altered by THC pre-exposure. In a second group of rats, we varied the 'price' of heroin (responses required/dose), by manipulating FR response requirements at different doses of heroin across sessions, to calculate demand and response output curves. Again, consumption was significantly higher in the THC-treated rats at the lowest prices of heroin (FR1/100 microg/kg and FR1/50 microg/kg) but there were no differences in the reinforcing efficacy of heroin between THC- and vehicle-pretreated rats. Altogether, these results demonstrate that pre-exposure to THC alters some pharmacological effects of heroin that determine frequency of heroin taking, but offer no support for the hypothesis that pre-exposure to THC alters heroin’s efficacy as a reinforcer.


The role of cannabinoid CB(1) receptors in the action of anxiolytics was examined. Deletion of CB(1) receptors resulted in increased anxiety-like behaviours in light/dark box, elevated plus maze and social interaction tests. Mutant mice presented basal low corticosterone concentrations and low proopiomelanocortin gene expression in the anterior lobe of the pituitary gland compared to wild-type mice. Ten minutes of restraint stress resulted in a twofold increase in corticosterone concentrations in the plasma of mutant mice, compared to wild-type mice. Bromazepam (50 or 100 microg/kg) markedly increased the time spent in light area in wild-type animals, though both doses were without effect in mutant mice. Administration of buspirone (1 or 2 mg/kg) produced anxiolytic effects in wild-type mice. In contrast, only the highest dose of buspirone had anxiolytic results in mutant mice. Our findings reveal that CB(1) receptors are involved in the regulation of emotional responses, and play a pivotal role in the action mechanism of anxiolytics. They suggest that alterations in the functional activity of the CB(1) receptor may be related to the emergence of anxiety disorders, and may affect treatment with anxiolytics.


The endogenous ligands of cannabinoid receptors, also known as endocannabinoids, have been implicated in many physiological and pathological processes of the central nervous system. Here we show that the levels of the two major endocannabinoids, anandamide and 2-arachidonoyl-glycerol (2-AG), in four areas of the rat brain, change dramatically between the light and dark phases of the day. While anandamide levels in the nucleus accumbens, pre-frontal cortex, striatum and hippocampus were significantly higher in the dark phase, the opposite was observed with 2-AG, whose levels were significantly higher during the light phase in all four regions. We found that the activity of the fatty acid amide hydrolase, which catalyzes the metabolism of anandamide, was significantly lower during the dark phase, thus providing a possible explanation for the increase in anandamide levels. However, the activities of monoacylglycerol lipase and diacylglycerol lipase, two of the possible enzymes catalyzing the degradation and biosynthesis of 2-AG, respectively, changed significantly only in the striatum. These data suggest that the levels of the two major endocannabinoids might be under the control of endogenous factors known to undergo diurnal variations, and underscore the different roles, suggested by previous studies, of anandamide and 2-AG in neurophysiological processes.

The cannabinoid receptor subtype 1 (CB1R) is a member of the Gi(i)-protein-coupled receptor family and cannabinoid signaling is largely dependent on the suppression of adenylyl cyclase-catalyzed cAMP production. In cell lines transfected with the CB1R or in native tissue preparations, treatment with cannabinoid agonists reduces both basal and forskolin-stimulated cAMP synthesis. We measured extracellular cAMP concentrations in the striatum of freely moving rats utilizing microdialysis to determine if changes in cAMP concentrations in response to CB1R agonists can be monitored in vivo. Striatal infusion of the CB1R agonist WIN55,212-2 (100 microM or 1 mM), dose-dependently decreased basal and forskolin-stimulated extracellular cAMP. These effects were reversed by co-infusion of the CB1R antagonist SR141716A (30 microM), which alone had no effect up to the highest concentration tested (300 microM). These data indicate that changes in extracellular cAMP concentrations in response to CB1R stimulation can be monitored in vivo allowing the study of cannabinoid signaling in the whole animal.

**CLINICAL SCIENCE**


Cannabis (marijuana) has been proposed as a treatment for a widening spectrum of medical conditions and has many properties that may be applicable to the management of amyotrophic lateral sclerosis (ALS). This study is the first, anonymous survey of persons with ALS regarding the use of cannabis. There were 131 respondents, 13 of whom reported using cannabis in the last 12 months. Although the small number of people with ALS that reported using cannabis limits the interpretation of the survey findings, the results indicate that cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling. Cannabis was reported ineffective in reducing difficulties with speech and swallowing, and sexual dysfunction. The longest relief was reported for depression (approximately two to three hours).


**BACKGROUND:** The cannabinoid CB(1) receptor agonist Delta(9)-THC has been suggested for treatment of Tourette syndrome (TS). Based on animal studies, the CB(1) antagonist [(123)I]AM281 (N-(Morpholin-4-yl)-1-(2,4-dichlorophenyl)-5-(4-[(123)I]iodophenyl)-4-methy1-1H-pyrazole-3-carboxamide) has been proposed for single photon emission computed tomography (SPECT) in humans. Our aims were to 1) evaluate specific binding of [(123)I]AM281 to CB(1) receptors in TS patients and 2) assess radiation exposure associated with the use of AM281 labeled with (123)I for SPECT and (124)I for positron emission tomography. **METHODS:** We employed [(123)I]AM281 in six TS patients before and after Delta(9)-THC treatment. Dynamic SPECT, plasma measurements (including metabolite analysis with thin layer chromatography), and whole-body imaging were performed. Regions of interest derived from magnetic resonance images were used to extract from SPECT uptake in an area with high CB(1) density (lentiform nuclei) and reference regions. Specific over nonspecific partition coefficients V(3)* were calculated. Whole-body images were carried out for dosimetric analysis. Data obtained with [(123)I]AM281 were used to predict doses from [(124)I]AM281. **RESULTS:** Mean V(3)* ranged from.19 to.31 and did not change significantly after Delta(9)-THC treatment. Nevertheless, in the only patient with a marked clinical response, V(3)* clearly declined. Thin layer chromatography revealed biexponential kinetics of tracer metabolism; about 60% remained nonmetabolized after 3 hours. Effective doses of.011 mSv/MBq for [(123)I]AM281 and.34 for [(124)I]AM281 were computed. **CONCLUSIONS:** This study suggests that specific binding of [(123)I]AM281 to CB(1)
receptors can be detected in patients using SPECT. Radiation exposure with [(123)I]AM281 is low; that with [(124)I]AM281 is higher but acceptable for single investigations.


**BACKGROUND:** Disabling tremor is common in patients with multiple sclerosis (MS). Data from animal model experiments and subjective and small objective studies involving patients suggest that cannabis may be an effective treatment for tremor associated with MS. To our knowledge, there are no published double-blind randomized controlled trials of cannabis as a treatment for tremor in MS patients. **METHODS:** The authors conducted a randomized double-blind placebo-controlled crossover trial to examine the effect of oral cannador (cannabis extract) on 14 patients with MS with upper limb tremors. There were eight women and six men, with a mean age of 45 years and mean Expanded Disability Status Scale score of 6.25. Patients were randomly assigned to receive each treatment and the doses escalated over a 2-week period before each assessment. The primary outcome was change on a tremor index, measured using a validated tremor rating scale. The study was powered to detect a functionally significant 50% improvement in the tremor index. Secondary outcomes included accelerometry, an ataxia scale, spiral drawing, finger tapping, and nine-hole pegboard test performance. **RESULTS:** Analysis of the data showed no significant improvement in any of the objective measures of upper limb tremor with cannabis extract compared to placebo. Finger tapping was faster on placebo compared to cannabis extract (p < 0.02). However, there was a nonsignificant trend for patients to experience more subjective relief from their tremors while on cannabis extract compared to placebo. **CONCLUSIONS:** Cannabis extract does not produce a functionally significant improvement in MS-associated tremor.


Tourette syndrome (TS) is a complex inherited disorder of unknown etiology, characterized by multiple motor and vocal tics. Involvement of the central cannabinoid system is suggested because of therapeutic effects of marijuana (Cannabis sativa L.) consumption and Delta(9)-tetrahydrocannabinol (THC) treatment in TS patients. The central cannabinoid receptor (CNR1) gene encoding the CNR1 was considered as a candidate gene for TS and systematically screened by single-strand conformation polymorphism (SSCP) analysis and sequencing. Compared with the published CNR1 sequence, three single base substitutions were identified: 1326T --> A, 1359G --> A, 1419 + 1G --> C. The change at position 1359 is a common polymorphism (1359 G/A) without allelic association with TS. 1326T --> A was present in only one TS patient and is a silent mutation which does not change codon 442 (valine). 1419 + 1G --> C affects the first nucleotide immediately following the coding sequence. It was first detected in three of 40 TS patients and none of 81 healthy controls. This statistically significant association with TS (p = 0.034) could not be confirmed in two subsequent cohorts of 56 TS patients (one heterozygous for 1419 + 1G --> C) and 55 controls and 64 patients and 66 controls (one heterozygous for 1419 + 1G --> C), respectively. Transcript analysis of lymphocyte RNA from 5 1419 + 1G --> C carriers revealed no systematic influence on the expression level of the mutated allele. In addition, segregation analysis of 1419 + 1G --> C in affected families gave evidence that 1419 + 1G --> C does not play a causal role in the etiology of TS. We conclude that genetic variations of the CNR1 gene are not a plausible explanation for the clinically observed relation between the cannabinoid system and TS.


**OBJECTIVE:** To demonstrate the clinical characteristics, radiologic findings, and neuroanatomical features of tetrahydrocannabinol-related posterior fossa ischemic stroke in adolescent patients. **DESIGN:** A retrospective case and chart review of 3 cases encountered at a
tertiary care institution over a span of 5 years. SETTING: Inpatient and intensive care hospitalization units managing children and adolescents. SUBJECTS: Male adolescent patients with ischemic cerebellar stroke after use of marijuana. DIAGNOSTIC INVESTIGATIONS: Computed tomography brain scans (3 subjects), magnetic resonance imaging brain study (1 subject), cerebral arteriography (1 subject), cerebellar biopsy (1 subject), and necropsy (2 subjects). RESULTS: Three adolescent males had similar presentations of headache, fluctuating level of consciousness or lethargy, visual disturbance, and variable ataxia after self-administration of marijuana. They developed primary cerebellar infarctions within days after the exposure that could not be attributed to supratentorial herniation syndromes and only minimally involved brainstem structures. CONCLUSIONS: Episodic marijuana use may represent a risk factor for stroke in childhood, particularly in the posterior circulation. Early recognition of the cerebellar stroke syndrome may allow prompt neurosurgical intervention, reducing morbidity.


Understanding the pharmacokinetics of orally administered cannabinoids is vitally important for optimizing therapeutic usage and to determine the impact of positive tests on drug detection programs. In this study, gas chromatography-mass spectrometry (limit of quantitation = 2.5 ng/mL) was used to monitor the excretion of total 11-nor-9-carboxy-Delta(9)-tetrahydrocannabinol (THCCOOH) in 4381 urine voids collected from seven participants throughout a controlled clinical study of multiple oral doses of THC. The National Institute on Drug Abuse Institutional Review Board approved the study and each participant provided informed consent. Seven participants received 0, 0.39, 0.47, 7.5, and 14.8 mg THC/day for five days in this double blind, placebo-controlled, randomized protocol conducted on a closed research ward. No significant differences (P <= 0.05) were observed in mean time of maximum excretion rate, mean maximum excretion rate, and mean terminal elimination half-life (t(1/2)) between the four THC doses, with ranges of 67.4 to 94.9 h, 0.9 to 16.3 micro g/h, and 44.2 to 64.0 h, respectively. Mean apparent elimination t(1/2) of 24.1 +/- 7.8 and 21.1 +/- 4.3 h for the 7.5 and 14.8 mg/day doses, respectively, were calculated from the excretion rate curve prior to the last urine sample with a THCCOOH concentration >/= 15 ng/mL. An average of only 2.9 +/- 1.6%, 2.5 +/- 2.7%, 1.5 +/- 1.4%, and 0.6 +/- 0.5% of the THC in the urine over each 14-day dosing session. This study demonstrated that the terminal urinary elimination t(1/2) of THCCOOH following oral administration was approximately two to three days for doses ranging from 0.39 to 14.8 mg/d. These data also demonstrate that the apparent urinary elimination t(1/2) of THCCOOH prior to reaching a 15 ng/mL concentration is significantly shorter than the terminal urinary elimination t(1/2). These controlled drug administration data should assist in the interpretation of urine cannabinoid results and provide clinicians with valuable information for future pharmacological studies.


Summary Three Cannabidiol Medicinal Extracts (CBMEs) for sublingual use became available in 2000. A total of 34 'N of 1' studies were undertaken using this novel therapy for patients with chronic, mainly neuropathic, pain and associated symptoms to explore efficacy, tolerability, safety and dosages. Three CBMEs (Delta9 Tetrahydrocannabinol (THC), Cannabidiol (CBD) and a 1:1 mixture of them both) were given over a 12-week period. After an initial open-label period, the CBMEs were used in a randomised, double-blind, placebo controlled, crossover trial. Extracts which contained THC proved most effective in symptom control. Regimens for the use of the sublingual spray emerged and a wide range of dosing requirements was observed. Side-effects were common, reflecting a learning curve for both patient and study team. These were generally acceptable and little different to those seen when other psycho-active agents are
used for chronic pain. These initial experiences with CBME open the way to more detailed and extensive studies.


ABSTRACT Aim To study the role of cannabis use in the onset of symptoms and disorders in the schizophrenia spectrum. Design Review of five population-based, longitudinal studies on the relationship between cannabis use and problems ranging from the experience of psychotic symptoms to hospitalization with a confirmed diagnosis of schizophrenia. Several hypotheses are examined that may explain this relationship: (1) self-medication; (2) effects of other drugs; (3) confounding; (4) stronger effect in predisposed people, and (5) etiological hypothesis. Findings Hypotheses 1 and 2 can be dismissed; hypothesis 3 is still open to debate, and converging evidence is found for hypotheses 4 and 5-antecedent cannabis use appears to act as a risk factor in the onset of schizophrenia, especially in vulnerable people, but also in people without prior history. Conclusion There is an intrinsic message here for public health, but how that message is to be translated into action is not immediately clear.


Glaucoma is one of the leading causes of blindness in the world. In spite of the diverse therapeutic possibilities, new and better treatments for glaucoma are highly desirable. Cannabinoids effectively lower the intraocular pressure (IOP) and have neuroprotective actions. Thus, they could potentially be useful in the treatment of glaucoma. The purpose of this article is to provide the reader with an overview of the latest achievements in research into the potential use of cannabinoids for glaucoma.


Obesity is a major health problem and as a result, it is reasonable to consider pharmacological approaches alongside approaches involving diet, physical activity and lifestyle change. The currently available drugs, sibutramine and orlistat, result in modest, clinically worthwhile weight loss, with demonstrable improvements in co-morbidity, but do not meet the often unrealistic expectations of patients or health care professionals managing obese patients. There is insufficient data on efficacy or safety of other agents to support their use. Many new pharmacological approaches are under investigation. These include gut hormones, such as peptide YY (3-36) and cholecystokinin that normally signal satiety, and centrally-acting agents such as serotonin agonists, the anticonvulsants topiramate and zonisamide, cannabinoid receptor antagonists and drugs that act on other peptide neurotransmitter systems such as NPY and the melanocortins. Given the multiple pathways that influence energy balance, it is likely that therapies targeting more than one control system may be required in the future to meet the expectations and needs of patients needing to lose weight for medical reasons.

BEHAVIOURAL SCIENCE


Epidemiological studies have repeatedly shown that cannabis is the most commonly used illegal drug in the United States. Furthermore, individuals with cannabis dependence have high rates of comorbid substance use disorders and depression. A significant proportion of individuals with addictive disorders develop withdrawal symptoms, cannot control their drug use despite substantial adverse psychosocial consequences, and frequently have a coexisting psychiatric disorder. Nevertheless, only a minority of persons with cannabis dependence ever
seek treatment. We were unable to locate epidemiological reports regarding treatment seeking behavior among persons with cannabis dependence. Epidemiological studies of populations with substance disorders have observed that employment, higher educational level, previous use of treatment, major depression, and a co-occurring substance dependency increased the probability of seeking treatment for alcohol dependence. Thus we hypothesized that the same variables would predict service use among persons with cannabis dependence. The main findings of this study were that persons with cannabis dependence were more likely to contact a professional during the past year if they previously sought treatment and had alcohol dependence with major depression. Prospective, longitudinal studies of adolescents would increase our understanding of the processes by which individuals identify themselves as having problems related to their habitual use of marijuana, and why some seek help while others do not.


Although personality measures such as neuroticism (N), extraversion (E) and novelty-seeking (NS) are associated with the use and abuse/dependence of illicit drugs, little is known about the degree to which these associations are due to genetic or environmental factors. The goal of this analysis was to estimate the extent of genetic and environmental overlap between three dimensions of personality (N, E and NS) and illicit psychoactive substance use and abuse/dependence. Using data from adult male and female twins from the Mid-Atlantic Twin Registry, we used the structural equation modeling package Mx to perform bivariate Cholesky decompositions for personality measures of N, E and NS, individually with cannabis, cocaine, sedatives, stimulants and hallucinogens. This was done separately for use and for a polychotomous diagnosis of abuse and/or dependence. Sex differences were tested. The phenotypic relationship between personality and use and abuse/dependence of illicit drugs were moderate and most of the covariance was explained by genetic factors. Sexes could be equated for N and E but not for NS. For NS, use and abuse/dependence of illicit drugs showed greater phenotypic and genetic overlap in males than females. Of the personality measures, NS and illicit drug use and abuse/dependence were most closely related. NS was most closely related to cannabis use while N showed significant genetic overlap with sedative use. NS in males appears to be a good indicator of risk for cannabis use. This result may be useful for candidate gene studies.


AIMS: The aim of this study was to estimate the prevalence of psychiatric disorders among 1439 heavy cannabis users seeking treatment for abuse problems in Denmark. DESIGN: Using two different registers, we compared cannabis users with 9122 abusers of other substances. FINDINGS: (1). Cannabis users were younger and more often males, but otherwise demographic data suggested that the group was as marginalized as users of hard drugs. (2). Additional abuse of other substances was common. (3). Even though cannabis users were generally young, 27.5% had at some point been inpatients at psychiatric hospitals with disorders unrelated to psychoactive substance abuse. (4). Cannabis users had significantly raised levels of depression (p < 0.001) and personality disorders (p < 0.0001) compared with users of other drugs, while the prevalence of schizophrenia was marginally raised (p < 0.05). The results were obtained after adjustment for age, gender and secondary abuse. Analyses were made using logistic regression methods. CONCLUSION: Co-morbid psychiatric disorders are common among heavy cannabis users seeking treatment. Some psychiatric disorders occur more frequently in this group compared with users of other substances.


To test the relationship between schizotypal symptoms and cannabis use in a non-clinical population, cannabis users and non-users were asked to complete the Schizotypal Personality Questionnaire. Significant differences in scores between the groups were observed. There may be a developmental process in the relationship between cannabis use and schizotypal symptoms.

**ABSTRACT**

Aims In the last few years, epidemiological studies in Brazil have detected significant increases in the use and abuse of psychoactive drugs by adolescents; however, there is a paucity of data on the factors associated with this use. Objectives To assess the prevalence of drug use by students from public schools in a Brazilian city and to evaluate the influence of age, school achievement, family, psychosocial, health, demographic and behavioural characteristics on regular drug use. Design This cross-sectional study was conducted using a representative sample of 6417 students attending public schools in the city of Barueri, Brazil and included adolescents from the 5th grade of elementary school to the 3rd year of high school. The Brazilian version of the Drug Use Screening Inventory (DUSI-R) was administered in the classroom by trained educational advisers without teachers being present. Findings Prevalence rates for the previous month were: alcohol: 48%, tobacco: 22.5%, cannabis: 14%, inhalants/solvents: 5%, cocaine: 3%, tranquilizers: 0.5%, amphetamines: 0.9%, anabolic steroids: 0.1% and ecstasy: 0.9%. With the exceptions of tranquilizers and amphetamines, the older students reported significantly higher frequencies and amounts of drug use than the younger ones. Boys reported a significantly higher consumption of alcohol, cannabis, cocaine and ecstasy than girls, as well as higher percentages of frequent/heavy use. Logistic regression analysis detected that poor school achievement, a poor or bad relationship with those with whom they live, studying in the evening period, presence of antisocial behaviour, family problems and friends who use drugs were factors significantly associated with drug use. Conclusions The findings suggest that preventive programmes should be more comprehensive in scope, rather than focusing only on information about the negative consequences of drug use.


The aims of this paper is to study the relations between anxious, depressive and borderline symptomatology and cannabis use and dependence in adolescents and young adults. A convenient sample of 212 subjects composed of high-school and college students from Toulouse, France (85 boys, 127 girls; mean age=18.3 ± 1.8 Years) completed questionnaires assessing the patterns of cannabis use, age of first use, the symptoms of dependence using a questionnaire derived from the Mini International Neuropsychiatric Interview, and the anxious, depressive and borderline symptomatology using the STAI-YA (State-Trait Anxiety Inventory; Spielberger et al., 1970), the CES-D (Center for Epidemiological Studies-Depression scale; Radloff, 1977) and the BPI (Borderline Personality Inventory; Leichsenring, 1999), respectively; 54% of subjects reported having used cannabis once during the last 6 Months (45.3% of girls and 66.6% of boys, p=0.002). Frequency of use was higher in boys: e.g, 61% of boys used cannabis at least almost daily versus 31% of girls (p=0.00001). Age of first use was lower in boys than in girls (14.6 ± 2.6 versus 15.7 ± 2.3, t=-2.46, p=0.02). Length of use was higher in boys than in girls (3.9 ± 2.2 versus 3 ± 1.6, t=2.2, p=0.03). Among users, near of 64% of boys and 36% of girls met the criteria for cannabis dependence (p=0.003). BPI, CES-D and STAI-YA scores were compared between non-users and users and between non-dependent and dependent users: the only significant differences were that BPI scores were higher in users versus non-users and in dependent users versus non-dependent users; CES-D and STAI-YA scores did not distinguished users from non-users and dependent users from non-dependent users. BPI and CES-D scores were correlated with the length of cannabis use (Pearson r=0.19 and r=0.19, respectively, p<0.05). In a multiple regression analysis predicting the frequency of cannabis use, we entered age, sex, CES-D, STAI-YA and BPI scores. This model accounted for 23% of the variance of the frequency of use (F(5,206)=14.4, p<0.0001). Sex, age, and BPI scores were significant predictors (b=0.31, t=5.03, p<0.0001; b=0.29, t=4.87, p<0.0001, b=0.27, t=3.80, p<0.0001, respectively). CES-D scores were a nearly significant predictor (b=-0.17, t=-1.96, p=0.051). STAI-YA scores were not a significant predictor (b=0.11, t=1.29, p=0.20). In a multiple regression analysis predicting the dependence scores, we entered age, sex, frequency of use, CES-D, STAI-YA and BPI scores. This model accounted for 41% of the variance of the dependence score (F(6,107)=12.6, p=0.005). Frequency of use and BPI scores were significant predictors (b=0.51, t=6.12, p<0.0001; b=0.26, t=2.86, p=0.005, respectively). Age, sex, CES-D and STAI-YA scores
were not significant predictors (b=-1.04, t=-1.32, p=0.19; b=0.008, t=0.09, p=0.92; b=0.16, t=1.53, p=0.12; b=-0.14, t=-1.46, p=0.15, respectively). The frequency of use and dependence observed in this study confirm the results obtained in epidemiological studies of use and dependence in France. The high frequency of daily or almost daily users suggests that a high proportion of subjects were "high" while completing the questionnaires. This is a confounding variable now inevitable in epidemiological studies of cannabis use given the high proportion of daily users. The consequence may be that responses to mood questionnaire express both the acute euphoriant effect of cannabis may mask a chronic depressive symptomatology induced by chronic cannabis consumption. The antidepressant and anti-anxiety acute effect of cannabis may explain that CES-D and STAI-YA scores did not distinguished users from non-users and dependent users from non-dependent users. The correlation between length of use and CES-D scores may reveal the depressant chronic effect of long-term use. The correlation between length of use and BPI scores suggest that long-term cannabis use induces an increase in borderline symptomatology. Results of the regression analyses suggest that the borderline symptomatology is highly linked to frequency of use and cannabis dependence. This may be due to the increase in borderline symptomatology induced by both acute and chronic effects of cannabis. The relation between cannabis use and dependence on one hand and anxious and depressive symptomatology on the other hand may have been obscured by the acute mood effect of cannabis consumption. Borderline symptomatology appeared to be highly linked to cannabis use and dependence in adolescents and young adults. Borderline personality disorder in adolescents is not the only risk factor for cannabis use and dependence in adolescents: borderline symptomatology even at a subclinical level seems to be a higher risk factor than anxious or depressive symptomatology. The frequency of daily or almost daily users may be a confounding variable for the study of relations between anxiety and depressive disorders in adolescents and young adults.


Two school surveys measured the consumption of alcohol, tobacco and cannabis among French adolescents (7-12th grades), one in 1993 (N=8435, 48.8% males), another in 1999 (N=11,331, 47.9% males). Increase in all substance use and polydrug use was observed (total sample, by gender and by age). The increase was important (1) for lifetime consumption of cannabis, "tobacco+cannabis," "alcohol+tobacco" and "alcohol+tobacco+cannabis" (OR=3.0); (2) for regular consumption of cannabis and "tobacco+cannabis" (OR=3.0); (3) among girls; (4) among youngsters aged 15 and more. In summary, these patterns of increase were quite different from those we expected for France, a wet and masculine culture.


Substance use disorder is one of the most common mental health problems in the Western world with a significant contribution to the global burden of disease and a high level of unmet treatment need. To assess the use and effectiveness of web-based interventions for substance use disorders. A qualitative review of the published literature across databases Medline, EMBASE, PsychINFO, GrayLIT Network, and Web of Science using relevant key terms. A search of the worldwide web was also conducted using search engines such as Google. There were a number of computerized and internet-based interventions for mental health disorders including substance use disorders located; however, they are largely descriptive with no large randomized controlled trials of internet-delivered interventions for substance use disorders reported. While the literature on internet-based substance use interventions is sparse and flawed, the potential impact of effective intervention is considerable. On the basis of the limited research available it is reasonable to suggest that a demand for such interventions exists and there is a likelihood that they would be as effective as those delivered by therapists for the majority of less severely dependent clients. Further clinical outcome research, particularly in the area of brief interventions for alcohol use disorders and extension to other drugs such as cannabis and club drugs, is certainly justified. (c) 2004 Elsevier Science Inc. All rights reserved.

This study used latent growth mixture modeling to identify discrete developmental patterns of marijuana use from early adolescence (age 13) to young adulthood (age 23) among a sample of 5,833 individuals. After the a priori removal of abstainers, 4 trajectory groups were identified: early high users, who decreased from a relatively high level of use at age 13 to a more moderate level: stable light users, who maintained a low level of use: steady increasers, who consistently increased use; and occasional light users, who began use at age 14 and used at low levels thereafter. Analyses of covariance comparing the trajectory groups on behavioral, socioeconomic, and health outcomes at age 29 revealed that abstainers consistently had the most favorable outcomes, whereas early high users consistently had the least favorable outcomes. ((c) 2004 APA, all rights reserved)


Recent theories propose that repeated drug use is associated with attentional and evaluative biases for drug-related stimuli, and that these cognitive biases are related to individual differences in subjective craving. This study investigated cognitive biases for cannabis-related cues in recreational cannabis users. Seventeen regular cannabis users and 16 non-users completed a visual probe task which assessed attentional biases for cannabis-related words, and an implicit association test (IAT) which assessed implicit positive or negative associations for cannabis-related words. Results from the IAT indicated more negative associations for cannabis-related words in non-users compared to users. Among cannabis users, those with high levels of cannabis craving had a significant attentional bias for cannabis-related words on the visual probe task, but those with low levels of craving did not. Results highlight the role of craving in attentional biases for cannabis-related stimuli.


The consumption of psychotropic drugs among Brazilian secondary school students was examined by comparing data from four surveys using a questionnaire adapted from the WHO's Program on Research and Reporting on the Epidemiology of Drug Dependence. Students filled out the form in their classrooms without the presence of teachers. The target population consisted of 10-18-year-old students (on average, 15,000 students responded to each survey) in Brazil's ten largest state capitals: Belem, Belo Horizonte, Brasilia, Curitiba, Fortaleza, Porto Alegre, Recife, Rio de Janeiro, Salvador, and Sao Paulo. Among the legal drugs, lifetime use (use at least once during life) of tobacco was increased in seven cities (the exceptions were Brasilia, Porto Alegre and Rio de Janeiro). There was also a significant increase in frequent use of alcohol (six times or more per month) in 6 of the cities, from an average of 9.2% in 1987 to 15.0% in 1997. With respect to illegal drugs, there was a significant increase in lifetime use of marijuana (a 3-fold increase from 2.8% in 1987 to 7.6% in 1997). Cocaine use increased 4-fold over the survey period (0.5% in 1987 to 2.0% in 1997). Lifetime use of cocaine significantly increased in eight capitals (except Recife and Rio de Janeiro). However, frequent cocaine use increased in only three capitals (Belem, Fortaleza and Porto Alegre), from an average of 1.0% in 1987 to 3.6% in 1997. Lifetime use of medications such as anxiolytics and amphetamines increased 2-fold on average over the survey period. Comparing the four studies, the main conclusion is that there were significant increases in the frequencies for lifetime use, frequent use and heavy use of many drugs.

Alcohol use, "alcohol abuse," and illicit drug use were investigated in a representative sample of 1076 urban, northern Italian high school students aged 14 to 19 years in 2001. In addition to questions on substance use, the participants were asked about school achievements and perceived substance use among friends. All the students were submitted to Zuckerman Sensation Seeking Scale (SSS) scale, Eysenck Personality Questionnaire (EPQ), Buss-Durkee Hostility Inventory (BDHI), and Parental Bonding Instrument (PBI). Lifetime alcohol use was found in 80.5%, "alcohol abuse" in 37.7%, cannabis use in 26.2%, ecstasy in 2.8%, heroin in 3.8%, and cocaine in 8.3% of the students: gender differences were significant for alcohol use, "alcohol abuse" and ecstasy use, with male subjects outnumbering females, but not for reported cannabis, heroin, and cocaine use. Early substance use onset among adolescents aged 14-16 years was detected. Higher sensation seeking on SSS, social coping impairment on EPQ, direct aggressiveness on BDHI, poor school achievements, and lower parental care on PBI were found associated with illicit drug use and "alcohol abuse" (multiple drugs users). Increased levels of aggressiveness and sensation seeking were evidenced both in minimal experimenters (ME) and habitual users (HU), without any significant difference, in comparison with abstinent students. Similarly, ME scored higher than abstinent subjects on EPQ for social coping impairment, but lower than HU. Parental care perception was lower in HU, but not in ME with, respect to abstinent subjects. Pearson inverse correlation was demonstrated between PBI scores and EPQ maladaptation and BDHI aggressiveness. Data from this preliminary pilot study suggest that temperamental traits and personality changes may be associated to early substance use "proneness" and reduced perception of parental care.


BACKGROUND: Co-occurring substance use disorders, mostly involving alcohol, cannabis or cocaine, occur commonly in patients with schizophrenia and are associated with increased morbidity and mortality. Available but limited data suggest that substance use disorders (especially cannabis use disorders) may also be common in first-episode patients and appear linked to a poor outcome in these patients. Strategies to curtail substance use form an important dimension of the treatment program for both first-episode and chronic patients. We report on rates of co-occurring substance use disorders in patients within their first episode of schizophrenia-related psychosis from a multicenter, international treatment trial of olanzapine vs. haloperidol. METHODS: The study involved 262 patients (of 263 who were randomized and who returned for a post-randomization evaluation) within their first episode of psychosis (schizophrenia, schizoaffective disorder or schizophreniform disorder) recruited from 14 academic medical centers in North America and Western Europe. Patients with a history of substance dependence within 1 month prior to entry were excluded. RESULTS: Of this sample, 97 (37%) had a lifetime diagnosis of substance use disorder (SUD); of these 74 (28% of the total) had a lifetime cannabis use disorder (CUD) and 54 (21%) had a lifetime diagnosis of alcohol use disorder (AUD). Patients with SUD were more likely to be men. Those with CUD had a lower age of onset than those without. Patients with SUD had more positive symptoms and fewer negative symptoms than those without SUD, and they had a longer duration of untreated psychosis. The 12-week response data indicated that 27% of patients with SUD were responders compared to 35% of those without SUD. Patients with AUD were less likely to respond to olanzapine than those without AUD. DISCUSSION: These data suggest that first-episode patients are quite likely to have comorbid substance use disorders, and that the presence of these disorders may negatively influence response to antipsychotic medications, both typical and atypical antipsychotics, over the first 12 weeks of treatment.


BACKGROUND: While there has been substantial research examining the correlates of comorbid substance abuse in psychotic disorders, it has been difficult to tease apart the relative importance of individual variables. Multivariate analyses are required, in which the relative contributions of risk factors to specific forms of substance misuse are examined, while taking into account the effects of other important correlates. METHODS: This study used multivariate correlates of several forms of comorbid substance misuse in a large epidemiological sample of 852 Australians with DSM-III-R-diagnosed psychoses. RESULTS: Multiple substance use was common and equally prevalent in nonaffective and affective psychoses. The most consistent correlate across the substance use disorders was male sex. Younger age groups were more likely to report the use of illegal drugs, while alcohol misuse was not associated with age. Side effects secondary to medication were associated with the misuse of cannabis and multiple substances, but not alcohol. Lower educational attainment was associated with cannabis misuse but not other forms of substance abuse. CONCLUSION: The profile of substance misuse in psychosis shows clinical and demographic gradients that can inform treatment and preventive research.


ABSTRACT Aim This study examines patterns of illicit drug use in a national sample of young men and women in Israel over a 20-year period. Design Annual cross-sectional data are analysed from an ongoing systematic sample of soldiers being discharged from active military service during the years 1982-2001. Setting An anonymous questionnaire is self-administered to soldiers on the day of discharge in an unsupervised setting. Participants Between 1200 and 2800 individuals participated in the survey annually. A total of 40,518 people were included in the analysis. This sample frame is reflective of all Israel Defense Forces (IDF) releasees below the rank of Captain. Military recruits in Israel comprised about 80% of the country's 18-year-old Jewish male cohort in any given year, and about two-thirds of the female population of this age. Findings Time-trends of drug use in Israel parallel those in the United States and European countries, although at much lower rates. Several indicators suggest a recent increase, particularly among women. Drug use is strongly inversely related to education level. Marijuana accounts for 65-75% of drug use in this young adult population. Conclusion Jewish cultural background and the military policy of zero tolerance are assumed contributors to the low drug use levels. Recent upward trends suggest that intensified prevention, surveillance and research efforts are in order.


OBJECTIVE: To describe the risks and risk factors for substance use initiation and progression among a large sample of American Indian (AI) adolescents. METHOD: Data came from surveys completed by 2,356 AI adolescents aged 14 to 20 years who participated in two or more consecutive waves of a longitudinal study between 1993 and 1996 (response rate 74%). Discrete-time survival analysis was used to describe the risks and risk factors for substance use initiation and progression. RESULTS: The risk for initiating use of any substance accelerated in early adolescence and peaked at age 18. The risk for progression from use of alcohol, marijuana, and/or inhalants to the use of other illicit drugs (e.g., cocaine) increased over the first 4.5 years after initiating substance use, then diminished in subsequent years. The risk of substance use initiation and progression varied across the four participating communities and by season of the year. Compared to adolescents who initiated substance use with alcohol only, adolescents who initiated substance use with marijuana or inhalants were more likely to progress to use other illicit drugs. CONCLUSIONS: Prevention programs for AI communities should be designed to address these community, age, and seasonal variations in the risks for substance use initiation and progression.

OBJECTIVE: To estimate the magnitude of and socio-demographic factors related to substance use among street children in Delhi. DESIGN: Observational study. METHODS: 115 male street children aged 6 to 16 years were interviewed at the time of their admission to an observation home. RESULTS: More than half of the subjects had indulged in substance use before coming to the observation home. The agents consumed were nicotine, inhalants, alcohol and cannabis. On application of multiple logistic regression, maltreatment of the child by family members was found significant predictor of substance use in the study group. CONCLUSION: Substance use in street children is associated with unstable homes and maltreatment.


The present study assessed drug use and the validity of self-reports of drug use among young people seeking treatment. On admission the participants (n = 316), 215 males and 101 females, were interviewed about their drug use. Urine samples were collected to screen for alcohol, amphetamine, benzo diazepines, cannabis, cocaine, methylenedioxymethamphetamine (MDMA) and opiate use. Self-reports of substance use were compared with urinalysis results. Seventy-three percent of the participants reported use of two or more substances. Single substance users were primarily alcohol users. Kappa agreement between self-report and urinalysis results was of acceptable concordance (≥ 0.65) except for alcohol (kappa = 0.19). Conditional kappa values were good (≥ 0.85) with exception of opiates (cond. kappa = 0.57). The self-reports were generally reliable among young people seeking treatment. No significant differences (p ≥ 0.54) were found in the validity of self-reports between the genders.


Although the American popular press and films might generally lead one to think otherwise, illegal drug use and drug trafficking occur outside the boundaries of disadvantaged American inner-city neighborhoods. Nonetheless, the occurrence of youthful drug involvement may be determined by similar community conditions in many parts of the world. In Spring 1998, a probability sample of 776 high school students living in Guam, Micronesia, completed a self-report anonymous survey, one that assessed their village and metropolitan neighborhood environments as well as drug involvement. On Guam, higher levels of neighborhood disadvantage were associated with youths being more likely to have been offered a chance to try drugs. This study adds new evidence on the potential importance of environmental and psychosocial contexts of neighborhood environment that might help account for the nonrandom distribution of youthful drug involvement.


Effectiveness of the Preventive Dimensions Program, a K-12 Utah plan for safe and drug-free schools, was assessed among 150 sixth-grade students. Participants' knowledge about drug use increased, as did all children's intent to use marijuana.