INTRODUCTION

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BASIC SCIENCE


Migraine pathophysiology is believed to involve the release of neuropeptides via the activation of trigeminal afferents that innervate the cranial vasculature. Anandamide, the endogenous ligand to the cannabinoid receptor, is able to inhibit neurogenic dural vasodilatation, calcitonin gene-related peptide (CGRP)-induced and nitric oxide-induced dural vessel dilation in the intravital microscopy model. In an in vitro setting anandamide is also able to activate the vanilloid type 1 (TRPV1) receptor and cause vasodilation, via the release of CGRP. In this study we used intravital microscopy to study whether anandamide behaves as a TRPV1 receptor agonist in the trigeminovascular system. We examined if anandamide-induced dural vasodilation involves CGRP release that can be reversed by the CGRP receptor antagonist, CGRP8-37, and whether like capsaicin the anandamide effect could be reversed by the TRPV1 receptor antagonist, capsazepine. Anandamide 1 (19+/−9%, n=12), 3 (29+/−5%, n=37), 5 (74+/−7%, n=13) and 10 mg kg(−1) (89+/−18%, n=6) was able to cause a dose-dependent increase in dural vessel diameter. Capsazepine (3 mg kg(−1), t5=6.2, P<0.05) and CGRP8-37 (300 micro g kg(−1), t6=11.1, P<0.05) attenuated the anandamide-induced dural vessel dilation when compared to control (Student's paired t-test). AM251 (3 mg kg(−1)), a cannabinoid type 1 (CB1) receptor antagonist, was unable to reverse this anandamide-induced dilation. The study demonstrates that anandamide acts as a TRPV1 receptor agonist in the trigeminovascular system, activating TRPV1 receptors that promote CGRP release and cause vasodilation independent of any action at the CB1 receptor. Anandamide has been shown previously to inhibit trigeminovascular neurons and prevent vasodilation, through an action at CB1 receptors.


The vasoactive effects of the synthetic cannabinoid (CB) arachidonyl-2-chloroethylamide (ACEA) was tested in the knee joints of urethane-anæsthetised rats. Experiments were also performed to determine whether these vasomotor responses could be blocked by the selective CB1 receptor antagonists AM251 (N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide) (10(-9) mol) and AM281 (1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-4-morpholinyl-1H-pyrazole-3-carboxamide) (10(-8) mol), as well as the selective CB2 receptor antagonist AM630 (6-iodo-2-methyl-1-[2-(4:morpholinyl)ethyl]-[1H-indol-3-yl][4-methoxyphenyl)methanone) (10(-8) mol). Peripheral application of ACEA (10(-14)-10(-9) mol) onto the exposed surface of the knee joint capsule caused a dose-dependent increase in synovial blood flow. The dilator action of the CB occurred within 1 min after drug administration and rapidly returned to control levels shortly thereafter. The maximal vasodilator effect of ACEA corresponded to a 30% increase in articular perfusion compared to control levels. The hyperaemic action of ACEA was not significantly altered by coadministration of AM251, AM281 or
The transient receptor potential channel vanilloid receptor 1 (TRPV1) antagonist capsazepine (10(-6) mol) significantly reduced the vasodilator effect of ACEA on joint blood vessels (P=0.002). Furthermore, destruction of unmyelinated and thinly myelinated joint sensory nerves by capsaicin (8-methyl-N-vanillyl-6-nonenamide) treatment also attenuated ACEA responses (P<0.0005). These data clearly demonstrate a vasodilator effect of the cannabinomimetic ACEA on knee joint perfusion. Rather than a classic CB receptor pathway, ACEA exerts its vasomotor influence by acting via TRPV1 receptors located on the terminal branches of capsaicin-sensitive afferent nerves innervating the joint.


We have studied behavioural, biochemical and endocrine responses to the cannabinoid agonist WIN 55,212-2 (WIN) in neonatal rats, as well as the effects of weaning on such responses. We used preweanling rats (20 days of age), 25-day-old weaned rats (weaning at Day 22) and 25-day-old nonweaned rats of both sexes. The behavioural effects of WIN were assessed in the nociceptive tail immersion test and in the open field. We also analysed the effect of weaning on corticosterone responses to WIN (radioimmunoassay) as well as on WIN-stimulated [(35)S]GTPgammaS binding in periaqueductal grey (PAG) and striatum. The cannabinoid agonist induced a modest increase in pain thresholds, whereas the effect of the drug on open-field activity, particularly on vertical activity, was much more marked. The weaning process appeared to reduce the baseline nociceptive latencies of the female rats. No significant effect of weaning on the behavioural responses to WIN was found. However, the group of weaned females (but not males) showed a significantly reduced WIN-stimulated [(35)S]GTPgammaS binding in the striatum. The cannabinoid agonist significantly increased the corticosterone levels of 25-day-old rats with the effect being more marked in weaned than in nonweaned animals. The results suggest that the weaning process might produce some sexually dimorphic developmental changes in CB(1) receptor function.


Fatty acid amide hydrolase (FAAH) inactivates the endogenous cannabinoid (endocannabinoid) anandamide and related lipid transmitters in vivo. A single nucleotide polymorphism (SNP) in the human FAAH gene (385C to A) has recently been described that, in homozygous form, is over-represented in subjects with problem drug use. This SNP, which converts a conserved proline residue in FAAH to threonine (P129T), suggests a potential role for the FAAH-endocannabinoid system in regulating addictive behavior. Nonetheless, the impact of the 385A mutation on the biochemical and cellular function of FAAH remains unknown. Here, we report that T lymphocytes isolated from patients homozygous for the P129T-FAAH variant express less than half of the FAAH protein and activity observed in wild type (WT) lymphocytes. Transfected COS-7 cells also expressed significantly lower levels of P129T-FAAH compared to WT-FAAH, indicating that the aberrant expression of the former protein is not a cell type-specific phenomenon. A comparison of the transcription/translation efficiencies and cellular stabilities of WT- and P129T-FAAH proteins revealed that the reduced expression of the mutant enzyme is due to a post-translational mechanism that precedes productive folding. These findings demonstrate that the natural 385A SNP in the human FAAH gene produces a mutant enzyme with reduced cellular stability, thus fortifying a potential link between functional abnormalities in the endocannabinoid system and drug abuse and dependence.


Fatty acid amides (FAAs) constitute a large class of endogenous signaling lipids that modulate several physiological processes, including pain, feeding, blood pressure, sleep, and inflammation. Although FAAs have been proposed to evoke their behavioral effects through both central and peripheral mechanisms, these distinct signaling pathways have remained
experimentally challenging to separate. Here, we report a transgenic mouse model in which the central and peripheral FAA systems have been functionally uncoupled. Mice were generated that express the principle FAA-degrading enzyme FAA hydrolase (FAAH) specifically in the nervous system (FAAH-NS mice) by crossing FAAH(-/-) mice with transgenic mice that express FAAH under the neural specific enolase promoter. FAAH-NS mice were found to possess wild-type levels of FAAs in the brain and spinal cord, but significantly elevated concentrations of these lipid transmitters in peripheral tissues. This anatomically restricted biochemical phenotype correlated with a reversion of the reduced pain sensitivity of FAAH(-/-) mice, consistent with the FAA anandamide producing this effect by acting on cannabinoid receptors in the nervous system. Interestingly, however, FAAH-NS mice still exhibited an antinflammatory phenotype similar in magnitude to FAAH(-/-) mice, indicating that this activity, which was not blocked by cannabinoid receptor antagonists, was mediated by peripherally elevated FAAs. These data suggest that the central and peripheral FAA signaling systems regulate discrete behavioral processes and may be targeted for distinct therapeutic gain.


Cannabinoids (CB) can act as retrograde synaptic mediators of depolarization-induced suppression of inhibition or excitation in hippocampus. This mechanism may underlie the impairment of some cognitive processes produced by these compounds, including short-term memory formation in the hippocampus. In this study, we investigated several compounds known to interact with CB receptors, evaluating their effects on K(+-)evoked release of [3H]D-aspartate ([3H]D-ASP) and [3H]GABA from superfused synaptosomes isolated from the rat hippocampus. [3H]D-ASP and [3H]GABA release were inhibited to different degrees by the synthetic cannabinoids WIN 55,212-2; CP 55,940, and arachidonyl-2'-chloroethylamide/N-(2-chloroethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide (ACEA), as well as by the endocannabinoids, anandamide (AEA), and 2-arachidonoylglycerol (2-AG). Both types of release were also inhibited by capsaicin. The inhibition produced by each of the cannabinoid compounds and capsaicin was unaffected by capsazepine or by the CB1-receptor antagonists AM-251 and SR141716A. The mechanism underlying AEA- and synthetic CB-induced inhibition of the release of [3H]GABA and [3H]D-ASP from rat hippocampal synaptosomes might not involve activation of presynaptic CB1 receptors.

Derbenev, A. V., T. C. Stuart, et al. (2004). "Cannabinoids suppress synaptic input to neurones of the rat dorsal motor nucleus of the vagus nerve." *J Physiol*. Cannabinoids bind central type 1 receptors (CB1R) and modify autonomic functions, including feeding and antiemetic behaviours, when administered peripherally or into the dorsal vagal complex. Western blots and immunohistochemistry indicated CB1R expression in the rat dorsal vagal complex, and tissue PCR confirmed that CB1R message was made within the region. To identify a cellular substrate for the central autonomic effects of cannabinoids, whole-cell patch-clamp recordings were made in brainstem slices to determine the effects of CB1R activation on synaptic transmission to neurones of the dorsal motor nucleus of the vagus (DMV). A subset of these neurones was identified as gastric-related after being labelled retrogradely from the stomach. The CB1R agonists, WIN55,212-2 or anandamide decreased the frequency of spontaneous excitatory or inhibitory postsynaptic currents in a concentration-related fashion, an effect that persisted in the presence of tetrodotoxin. Paired-pulse ratios of electrically-evoked postsynaptic currents were also increased by WIN55,212-2. The effects of WIN55,212-2 were sensitive to the selective CB1R antagonist, AM251. Cannabinoid agonist effects on synaptic input originating from neurones in the nucleus tractus solitarius (NTS) were determined by evoking activity in the NTS with local glutamate application. Excitatory and inhibitory synaptic inputs arising from the NTS were attenuated by WIN55,212-2. Our results indicate that cannabinoids inhibit transfer of synaptic information to the DMV, including that arising from the NTS, in part by acting at receptors located on presynaptic terminals contacting DMV neurones. Inhibition of synaptic input to DMV neurones likely contributes to the suppression of visceral motor responses by cannabinoids.

The endogenous cannabinoid, 2-arachidonoylglycerol (2-AG), is produced by neurons and other cells in a stimulus-dependent manner and undergoes rapid biological inactivation through transport into cells and catalytic hydrolysis. The enzymatic pathways responsible for 2-AG degradation are only partially understood. We have previously shown that overexpression of monoacylglycerol lipase (MGL), a cytosolic serine hydrolase that cleaves 1- and 2-monoacylglycerols to fatty acid and glycerol reduces stimulus-dependent 2-AG accumulation in primary cultures of rat brain neurons. We report now that RNA interference (RNAi)-mediated silencing of MGL expression greatly enhances 2-AG accumulation in HeLa cells. Following stimulation with the calcium ionophore, ionomycin, 2-AG levels in MGL-silenced cells were comparable to those found in cells in which 2-AG degradation had been blocked using methyl arachidonyl fluorophosphonate (MAFP), a non-selective inhibitor of 2-AG hydrolysis. The results indicate that MGL plays an important role in the degradation of endogenous 2-AG in intact HeLa cells. Furthermore, immunodepletion experiments show that MGL accounts for at least 50% of the total 2-AG-hydrolyzing activity in soluble fractions of rat brain, suggesting that this enzyme also contributes to 2-AG deactivation in the central nervous system.


Several lines of evidence indicate that cannabinoids, among other functions, are involved in motor control. Although cannabinoid receptors (CB(1)) mRNA has been observed in medium-sized spiny neurons of the striatum, a description of the precise localization of CB(1) at a protein level among striatal cells is still lacking. Therefore, we performed immunohistochemical studies with light and confocal microscopy to identify neuronal subpopulations that express CB(1) and to assess the distribution of the receptor within these neurons. In our single label light microscopy study, CB(1) was observed in most medium-sized neurons of the caudate-putamen. However, CB(1) was also present in large-sized neurons scattered throughout the striatum. Our dual-label study showed that 89.3% of projection neurons in matrix contain CB(1), and that 56.4% of projection neurons in patch are labeled for CB(1). To investigate the presence of CB(1) among the different subclasses of striatal interneurons we performed a double-labeling study matching CB(1) and each of the striatal interneuron markers, namely, choline acetyl-transferase, parvalbumin, calretinin, and nitric oxide synthase. Our double-label study showed that most parvalbumin immunoreactive interneurons (86.5%), more than one-third (39.2%) of cholinergic interneurons, and about one-third (30.4%) of the NOS-positive neurons are labeled for CB(1). Calretinin-immunolabeled neurons were devoid of CB(1). Synapse 53:159-167, 2004.


Abstract Fatty acid amide hydrolase (FAAH) and monoglyceride lipase (MGL) catalyse the hydrolysis of the endocannabinoids anandamide and 2-arachidonoylglycerol. We investigated their ultrastructural distribution in brain areas where the localization and effects of cannabinoid receptor activation are known. In the hippocampus, FAAH was present in somata and dendrites of principal cells, but not in interneurons. It was located mostly on the membrane surface of intracellular organelles known to store Ca(2+) (e.g. mitochondria, smooth endoplasmic reticulum), less frequently on the somatic or dendritic plasma membrane. MGL immunoreactivity was found in axon terminals of granule cells, CA3 pyramidal cells and some interneurons. In the cerebellum, Purkinje cells and their dendrites are intensively immunoreactive for FAAH, together with a sparse axon plexus at the border of the Purkinje cell/granule cell layers. Immunostaining for MGL was complementary; the axons in the molecular layer were intensively labelled leaving the Purkinje cell dendrites blank. FAAH distribution in the amygdala was similar to that of the CB(1) cannabinoid receptor: evident signal in neuronal somata and proximal dendrites in the basolateral nucleus, and hardly any labelling in the central nucleus. MGL staining was restricted to axons in the neuropil, with similar relative signal intensities seen for FAAH in different nuclei.
Thus, FAAH is primarily a postsynaptic enzyme, whereas MGL is presynaptic. FAAH is associated with membranes of cytoplasmic organelles. The differential compartmentalization of the two enzymes suggests that anandamide and 2-AG signalling may subserve functional roles that are spatially segregated at least at the stage of metabolism.


Cannabinoids are known to modulate GABAergic and glutamatergic transmission in cortical areas, the former via CB1 and the latter via a novel receptor. Pharmacological data demonstrate that several widely used cannabinoid ligands bind to both receptors, which may explain the inconsistencies in their behavioural effects. Earlier we showed that the cannabinoid antagonist SR-141716A affected behaviour in both CB1 knockout and wild-type animals, and its effect (anxiolysis) was different from that of CB1 gene disruption (anxiogenesis). In the present experiments, we studied the effects of the CB1 antagonist AM-251, and the cannabinoid agonist WIN-55,212-2 in wild-type as well as in CB1 knockout mice. CB1 knockout mice showed higher scores of anxiety-like behaviour than the wild-type animals in the elevated plus-maze. Selective blockade of CB1 receptors by AM-251 (0.3, 1 and 3 mg/kg) increased anxiety-like behaviour dose-dependently in the wild-type mice but had no effect in the knockouts. In wild types, the cannabinoid agonist WIN-55,212-2 (1 and 3 mg/kg) caused a decrease in anxiety-like behaviour, which was abolished by the CB1-selective antagonist AM-251 (3 mg/kg). The same agonist did not change plus-maze behaviour in CB1 knockout animals. These data demonstrate at the behavioural level that AM-251 and, at low concentrations, WIN-55,212-2, are selective ligands of the CB1 cannabinoid receptor in mice. Our studies on the behavioural effects of the cannabinoid antagonist SR-141716A and the CB1 antagonist AM-251 show that the CB1 and the novel cannabinoid receptor mediate anxiolytic and anxiogenic effects, respectively. This suggests that agonists of the former, or antagonists of the latter, are promising new compounds in the pharmacotherapy of anxiety.


Abstract Adult male Long-Evans rats were administered the potent cannabinoid 1 receptor agonist HU-210 (100 micro g/kg, i.p.) for 15 days continuously and their performance on a matching-to-place version of the Morris water maze was subsequently evaluated. Overall, experimental animals performed significantly worse initially on the reference memory component of this task, but their performance improved over 5 days until it was indistinguishable from that of control animals. Animals given HU-210 did not exhibit working memory impairments at short intertrial delays (30 s); however, significant impairments were observed in learning performance with longer intertrial delays (300 s). In vivo electrophysiological analyses revealed that long-term potentiation in the CA1 region of the hippocampus was significantly impaired following the administration of HU-210 for 15 days. These results indicate that long-term cannabinoid exposure can produce marked deficits in reference and working memory performance, and also impair hippocampal synaptic plasticity in vivo.


Virodhamine is a recently identified novel endocannabinoid. Cannabinoids may evoke vasorelaxation through novel receptors in the vasculature and/or through release of vasodilator peptides from sensory nerve endings. Virodhamine induced endothelium-dependent relaxation in the rat isolated small mesenteric artery mounted in a myograph and precontracted with methoxamine. Desensitization of vanilloid receptors by capsaicin did not affect relaxation responses to virdhamine. The CB(1) receptor antagonist SR 141716A (3 microM), but not the more CB(1)-selective blocker AM 251 (1 microM), attenuated the response, while two CB(2) receptor antagonists, SR 144528 (1 microM) and AM 630 (10 microM), had no effect. The novel antagonist for the putative endothelial 'abnormal-cannabidiol receptor', O-1918 (30 microM),
inhibited virdodhamine relaxations. Hence virdodhamine may activate this novel receptor, which might also recognize SR 141716A. Inhibition of nitric oxide synthase (L-NAME 300 microM) did not affect relaxation to virdodhamine but the responses were markedly reduced when tone was induced with 60 mM KCl, suggesting a role for the activation of K(+) channels. The Ca(2+)-activated K(+) channel (K(Ca)) blockers, apamin (50 nM) and charybdotoxin (50 nM), inhibited virdodhamine vasorelaxation. Combination of these blockers with SR 141716A (3 microM) caused no further inhibition. It was concluded that virdodhamine relaxes the rat small mesenteric artery by endothelium-dependent activation of K(Ca), perhaps via the putative abnormal-cannabinidiol receptor.


Delta(9)-Tetrahydrocannabinol (the active ingredient of marijuana), as well as endogenous and synthetic cannabinoids, exert many biological functions by activating two types of cannabinoid receptors, CB1 receptors (expressed by central and peripheral neurons) and CB2 receptors (that occur mainly in immune cells). Convincing evidence has accumulated in recent years that cannabinoids inhibit gastric and intestinal motility through activation of enteric CB1 receptors. However, a report in this issue of British Journal of Pharmacology has highlighted the possibility that CB2 receptors in the rat intestine could contribute to reducing the increase of intestinal motility induced by an endotoxic inflammation. By minimizing the adverse psychotropic effects associated with brain cannabinoid receptors, the CB2 receptor represents a new molecular target for the treatment of motility disorders associated with intestinal inflammation.


Pharmacological studies suggest a role for CB1 cannabinoid receptors (CB1R) in regulating neurogenesis in the adult brain. To investigate this possibility, we measured neurogenesis by intraperitoneal injection of bromodeoxyuridine (BrdU), which labels newborn neurons, in wild-type and CB1R-knockout (CB1R-KO) mice. CB1R-KO mice showed reductions in the number of BrdU-labeled cells to approximately 50% of wild-type (WT) levels in dentate gyrus and subventricular zone (SVZ), suggesting that CB1R activation promotes neurogenesis. To test this further, WT mice were given the CB1R antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboximide hydrochloride (SR141716A) before measuring neurogenesis with BrdU. SR141716A paradoxically increased the number of BrdU-labeled cells by approximately 50% in SVZ; another CB1R antagonist, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl-1H-pyrazole-3-carboxamide (AM251), had a similar effect. To investigate this discrepancy, SR141716A was given to CB1R-KO mice, in which it still stimulated neurogenesis, indicating involvement of a non-CB1 receptor. Action at one such non-CB1, SR141716A-sensitive site, the VR1 vanilloid receptor, was tested by administering SR141716A to VR1-KO mice, in which the ability of SR141716A to enhance neurogenesis was abolished. Thus, CB1 and VR1 receptors both seem to have roles in regulating adult neurogenesis.


Three cannabis constituents, cannabidiol (1), Delta(8)-tetrahydrocannabinol (3), and cannabiol (5), were oxidized to their respective para-quinones 2, 4, and 6. In the 1960s, the oxidized product 4 had been assigned a para-quinone structure, which was later modified to an ortho-quinone. To distinguish between the two possible quinone structures, a detailed NMR investigation was undertaken. The original para-quinone structure was confirmed. X-ray crystallography elucidated the structures of the crystalline 2 and 6. All three compounds displayed antiproliferative activity in several human cancer cell lines in vitro, and quinone 2 significantly reduced cancer growth of HT-29 cancer in nude mice.


We investigated the mechanisms by which activation of group I metabotropic glutamate receptors (mGluRs) and CB1 cannabinoid receptors (CB1Rs) leads to inhibition of synaptic currents at the calyx of Held synapse in the medial nucleus of the trapezoid body (MNTB) of the rat auditory brainstem. In approximately 50% of the MNTB neurons tested, activation of group I mGluRs by the specific agonist (s)-3,5-dihydroxyphenylglycine (DHPG) reversibly inhibited AMPA receptor- and NMDA receptor-mediated EPSCs to a similar extent and reduced paired-pulse depression, suggestive of an inhibition of glutamate release. Presynaptic voltage-clamp experiments revealed a reversible reduction of Ca2+ currents by DHPG, with no significant modification of the presynaptic action potential waveform. Likewise, in approximately 50% of the tested cells, the CB1 receptor agonist (R)-(+) [2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone (WIN) reversibly inhibited EPSCs, presynaptic Ca2+ currents, and exocytosis. For a given cell, the amount of inhibition by DHPG correlated with that by WIN. Moreover, the inhibitory action of DHPG was blocked by the CB1 antagonist N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (AM251) and occluded by WIN, indicating that DHPG and WIN operate via a common pathway. The inhibition of EPSCs by DHPG, but not by WIN, was abolished after dialyzing 40 mm BAPTA into the postsynaptic cell, suggesting that DHPG activated postsynaptic mGluRs. Light and electron microscopy immunolabeling indicated a presynaptic expression of CB1Rs and postsynaptic localization of mGluR1a. Our data suggest that activation of postsynaptic mGluRs triggers the Ca2+-dependent release of endocannabinoids that activate CB1 receptors on the calyx terminal, which leads to a reduction of presynaptic Ca2+ current and glutamate release.


The biological effects of cannabinoids (CB) are mediated by CB1 and CB2 receptors. The role of CB2 receptors in the gastrointestinal tract is uncertain. In this study, we examined whether CB2 receptor activation is involved in the regulation of gastrointestinal transit in rats. Basal and lipopolysaccharide (LPS)-stimulated gastrointestinal transit was measured after instillation of an Evans blue-gum Arabic suspension into the stomach, in the presence of specific CB1 and CB2 agonists and antagonists, or after treatment with inhibitors of mediators implicated in the transit process. In control rats a CB1 (ACEA; 1 mg kg(-1)), but not a CB2 (JWH-133; 1 mg kg(-1)), receptor agonist inhibited basal gastrointestinal transit. The effects of the CB1 agonist were reversed by the CB1 antagonist AM-251, which alone increased basal transit. LPS treatment increased gastrointestinal transit. This increased transit was reduced to control values by the CB2, but not the CB1, agonist. This inhibition by the CB2 agonist was dose dependent and prevented by a selective CB2 antagonist (AM-630; 1 mg kg(-1)). By evaluating the inhibition of LPS-enhanced gastrointestinal transit by different antagonists, the effects of the CB2 agonist (JWH-133; 1 mg kg(-1)) were found to act via cyclooxygenase, and to act independently of inducible nitric oxide synthase (NOS) and platelet-activating factor. Interleukin-1beta and constitutive NOS isoforms may be involved in the accelerated LPS transit. The activation of CB2 receptors in response to LPS is a mechanism for the re-establishment of normal gastrointestinal transit after an inflammatory stimulus.


Cannabinoids exhibit medicinal properties including analgesic, anti-inflammatory and immunosuppressive properties. This paper reviews some of the recent findings in the study of cannabinoids in pain and inflammation. Some of the effects of cannabinoids are receptor mediated and others are receptor independent. Endocannabinoids naturally reduce pain and are cerebroprotective. Natural and synthetic cannabinoids have the potential to reduce nociception, reverse the development of allodynia and hyperalgesia, reduce inflammation and inflammatory pain and protect from secondary tissue damage in traumatic head injury.

Abstract GABAergic synaptic transmission is efficiently controlled by endogenous cannabinoids in cortical structures. Fatty acid amide hydrolase (FAAH) is one of the metabolizing enzymes of endocannabinoids in the brain. In this study we investigated the cellular and subcellular distribution of FAAH at various timepoints during the first postnatal weeks, when GABA is still depolarizing, and plays a crucial role in network events. FAAH immunoreactivity is strong in the CA3 region already at postnatal day 0 (P0), but in CA1 only after P8. During this period, FAAH levels in hilar mossy cells decrease and in granule cells slowly increase. Pyramidal cells express FAAH first in the soma and proximal dendrites, and gradually in more distal segments, reaching adult levels in the most distal dendrites only at P22. Transient expression of FAAH was found in a small number of stratum radiatum cells that may be interneurons and in ependymal cells at the border of the alveus and corpus callosum between P2 and P8. At the ultrastructural level, FAAH distribution at all ages was very similar to the adult pattern, i.e. it was largely associated with the membrane of cytoplasmic vesicles, mitochondria and endoplasmic reticulum. During postnatal development of the hippocampus, the spatio-temporal expression of FAAH correlates well with the general pattern of neuronal maturation, but not with the arrival of afferent pathways, which suggests that FAAH - and its major endocannabinoid substrate, anandamide - is unlikely to be involved in the presynaptic control of neurotransmission. Instead, FAAH may subserve general roles as the inactivating enzyme for many fatty acid amides, in addition to anandamide.


Th helper cell type 1 (Th1)-polarizing cytokines are induced by Legionella pneumophila infection and are suppressed by pretreatment with marijuana cannabinoids (CB). Glucocorticoids and prostaglandin E2 (PGE2) are also reported to suppress Th1 polarization and are induced by Delta(9)-tetrahydrocannabinol (THC), so their role in the suppression of polarizing cytokines was examined. Injection of L. pneumophila or THC alone into BALB/c mice induced a rapid and transient rise in serum corticosterone (CS), and the injection of both agents significantly augmented the CS response, demonstrating that THC increased CS in Legionella-infected mice. Pretreatment with the CB1 antagonist SR141716A had no effect on the THC-induced CS response, but CB2 antagonist (SR144528) treatment increased the CS response. To see if increased CS contributed to the down-regulation of Th1 cytokines, mice were pretreated with the steroid antagonist RU486 before THC injection and Legionella infection. The results showed that RU486 did not attenuate the THC-induced suppression of serum interleukin (IL)-12 or interferon-gamma (IFN-gamma). In addition to CS, THC injection increased urinary PGE2 metabolites, and the CB1 antagonist attenuated this increase. Although L. pneumophila infection increased urinary PGE2, THC pretreatment did not enhance this response; in addition, treatment with the cyclooxygenase inhibitor, indomethacin, did not block the THC-induced suppression of IL-12 and IFN-gamma. These results suggest that the elevation of CS and PGE2 does not account for the THC-induced attenuation of the Th1 cytokine response, and it is concluded that other suppressive mediators are induced by THC or that the drug acts directly on immune cells to suppress cytokine production.


Two types of cannabinoid receptors have been characterized so far, CB(1) and CB(2). While CB(1) receptors are present both in the CNS and in the periphery, CB(2) receptors showed an almost exclusive distribution within the immune system. We now report that CB(2) receptors are present in a specific microglial cell type of the human cerebellum. Thus, we have performed immunohistochemical analysis of tissue sections of white matter areas of the human cerebellum and detected the presence of CB(2) receptors in perivascular microglial cells. These findings
match with the well-known immunomodulatory role of CB(2) receptors and open new perspectives on the possible role that these receptors may play in pathophysiological events. Synapse 53:208-213, 2004. Copyright 2004 Wiley-Liss, Inc.


BACKGROUND: Recent studies have raised concerns about subtle long-lasting neurobiological changes that might be triggered by exposure to Cannabis derivatives, especially in a critical phase of brain maturation, such as puberty. The mesolimbic dopamine (DA) system, involved in the processing of drug-induced reward, is a locus of action of cannabinoids and endocannabinoids. Thus, we compared the effects of repeated cannabinoid administration in adolescent and adult rats on DA neuronal functions and responses to drugs of abuse.

METHODS: Single-unit extracellular recordings from antidromically identified mesoaccumbens DA neurons and from their target cells in the nucleus accumbens were carried out in urethane-anesthetized rats. Animals were pretreated during adolescence or adulthood, for 3 days, with the cannabinoid agonist WIN55212.2 (WIN) or vehicle and allowed a 2-week interval. RESULTS: In cannabinoid-administered rats, DA neurons were significantly less responsive to the stimulating action of WIN, regardless of the age of pretreatment; however, in the adolescent group, but not in the adult, long-lasting cross-tolerance developed to morphine, cocaine, and amphetamine.

CONCLUSIONS: Our study suggests that an enduring form of neuronal adaptation occurs in DA neurons after subchronic cannabinoid intake at a young age, affecting subsequent responses to drugs of abuse.


Chronic exposure to cannabinoids was shown to induce long lasting impairment of learning and memory, which was accompanied by morphological damage to the brain. On the other hand, several studies have shown that cannabinoids can protect from various brain traumas. This enigmatic dualism is explained herein by a comprehensive hypothesis, which is based on our recent in vitro studies and on pharmacokinetic in vivo considerations. The hypothesis predicts that low concentrations of cannabinoids will be neurotoxic while high concentrations of the drugs will protect from neuronal damage, and suggests that chronic administration of cannabinoids will induce neuronal death, while their acute administration will protect the brain. We further propose straightforward experiments, both in vivo (animal models for brain damage) and in vitro (cell death in neuronal cultures) to verify this hypothesis. The outcome of these experiments may have practical applications when considering the use of cannabinoids as therapeutic agents and in evaluating the consequences of their use as recreational drugs.


Cannabinoid and opioid receptor agonists show functional interactions in a number of their physiological effects. Regarding the seizure-modulating properties of both classes of receptors, the present study examined the possibility of a functional interaction between these receptors. We used acute systemic administration of cannabinoid selective CB(1) receptor agonist (ACPA) and antagonist (AM251) and opioid receptor agonist (morphine) and antagonists (naltrexone and norbinaltorphimine) in a model of clonic seizure induced by pentylenetetrazole (PTZ). Acute administration of ACPA (1.5-2 mg/kg) increased the PTZ-induced seizure threshold. In contrast, AM251 (0.5-2 mg/kg) dose-dependently decreased the seizure threshold. Low dose of AM251 (0.5 mg/kg), which did not alter seizure threshold by itself, reversed the anticonvulsant effect of ACPA (2 mg/kg), showing a CB(1) receptor-mediated mechanism. Naltrexone (1 or 10 mg/kg) but not specific kappa-opioid receptor antagonist norbinaltorphimine (5 mg/kg) completely reversed the anticonvulsant effect of ACPA (2 mg/kg). Moreover, the combination of the lower doses of AM251 (0.5 mg/kg) and naltrexone (0.3 mg/kg) had an additive effect in blocking the anticonvulsant effect of ACPA. In accordance with previous reports, morphine exerted biphasic
effects on clonic seizure threshold with anticonvulsant effect at lower (0.5-1 mg/kg) and proconvulsant effect at a higher (30 mg/kg) doses. The pretreatment with AM251 blocked the anticonvulsant effect of morphine at 1 mg/kg, while pretreatment with ACPA (1 mg/kg) potentiated the anticonvulsant effect of morphine at 0.5 mg/kg. The proconvulsant effect of morphine at 30 mg/kg was also inhibited by AM251 (2 mg/kg). A similar interaction between cannabinoids and opioids was also detected on their anticonvulsant effects against the generalized tonic-clonic model of seizure. In conclusion, cannabinoids and opioids show functional interactions on modulation of seizure susceptibility.


To determine the moiety that behaves as the steric trigger to activate the CB(1) cannabinoid receptor, conformational properties of the nonclassical cannabinoid CP55244, one of the most potent CB(1) receptor agonists, were characterized by conformational analysis, rotational barrier calculations, and molecular dynamics (MD) simulations. It was shown from the present MD simulations that the torsion angles phi1 and phi4 of the C3 side chain showed the most dramatic change when compared with the ground-state receptor-bound conformation, indicating that rotation around these torsion angles is responsible for releasing the ligand strain energy. Multiple stages would be involved in the ligand conformational change. As a molecular mechanism for the ligand-induced CB(1) receptor conformational change, we propose that the C3 side chain serves as the steric trigger, while the ACD-ring moiety of CP55244 serves as the plug. Steric clash with helices within the binding pocket would induce microconformational adaptation within the protein. This mechanism would suggest that rotational flexibility in a ligand may be as important a determinant of agonist activity as the pharmacophoric elements that can be identified.


This paper reports the effects of pre- and perinatal exposure to delta9-tetrahydrocannabinol (THC) on expression levels of specific AMPA glutamate receptor subunits (GluR1 and GluR2/3) in the cerebellum of male and female rats. Pregnant rats were administered saline or THC from gestational day 5 (ED5) to postnatal day 20 (PD20). Expression of the GluR1 and GluR2/3 subunits of AMPA glutamate receptors was analyzed by immunohistochemistry in THC-exposed rats at three postnatal ages: PD20 (still exposed to THC) to study the direct effect of drug exposure, and PD30 and PD70 (10 and 50 days following THC withdrawal) to analyze the long-term effects of prenatal exposure. Compared to controls, pre- and perinatal THC exposure decreased the immunoreactivity levels of the GluR1 subunit in Bergmann glial cells, as well as levels of the GluR2/3 subunit in Purkinje neurons at PD20. These changes in AMPA receptor subunit levels may correlate with the decreased excitatory neurotransmission described in the cerebellum after cannabidiol treatment, which could play a significant role in the biochemical effects of THC. In addition, the reduced glutamate receptor expression observed at PD20 did not return to normal even after THC withdrawal (PD30 and PD70). The results support the idea that THC exposure during critical stages of cerebellar development may alter the glutamatergic system, not only during the drug exposure period itself but also in adults following THC withdrawal. The decreased expressions of glutamate receptors induced by developmental THC exposure could lead to functional alterations through the inhibition of glutamatergic neurotransmission, and clearly demonstrate an interaction between cannabinoids and the glutamatergic system.


Gliomas, in particular glioblastoma multiforme or grade IV astrocytoma, are the most frequent class of malignant primary brain tumours and one of the most aggressive forms of cancer. Current therapeutic strategies for the treatment of glioblastoma multiforme are usually ineffective or just palliative. During the last few years, several studies have shown that cannabinoids-the active components of the plant Cannabis sativa and their derivatives-slow the
growth of different types of tumours, including gliomas, in laboratory animals. Cannabinoids induce apoptosis of glioma cells in culture via sustained ceramide accumulation, extracellular signal-regulated kinase activation and Akt inhibition. In addition, cannabinoid treatment inhibits angiogenesis of gliomas in vivo. Remarkably, cannabinoids kill glioma cells selectively and can protect non-transformed glial cells from death. These and other findings reviewed here might set the basis for a potential use of cannabinoids in the management of gliomas.


Cannabis is a potential treatment for epilepsy, although the few human studies supporting this use have proved inconclusive. Previously, we showed that a standardized cannabis extract (SCE), isolated Delta(9)-tetrahydrocannabinol (Delta(9)-THC), and even Delta(9)-THC-free SCE inhibited muscarinic agonist-induced epileptiform bursting in rat olfactory cortical brain slices, acting via CB1 receptors. The present work demonstrates that although Delta(9)-THC (1microM) significantly depressed evoked depolarizing postsynaptic potentials (PSPs) in rat olfactory cortex neurones, both SCE and Delta(9)-THC-free SCE significantly potentiated evoked PSPs (all results were fully reversed by the CB1 receptor antagonist SR141716A, 1microM); interestingly, the potentiation by Delta(9)-THC-free SCE was greater than that produced by SCE. On comparing the effects of Delta(9)-THC-free SCE upon evoked PSPs and artificial PSPs (aPSPs; evoked electrotonically following brief intracellular current injection), PSPs were enhanced, whereas aPSPs were unaffected, suggesting that the effect was not due to changes in background input resistance. Similar recordings made using CB1 receptor-deficient knockout mice (CB1(-/-)) and wild-type littermate controls revealed cannabinoid or extract-induced changes in membrane resistance, cell excitability and synaptic transmission in wild-type mice that were similar to those seen in rat neurones, but no effect on these properties were seen in CB1(-/-) cells. It appears that the unknown extract constituent(s) effects over-rode the suppressive effects of Delta(9)-THC on excitatory neurotransmitter release, which may explain some patients' preference for herbal cannabis rather than isolated Delta(9)-THC (due to attenuation of some of the central Delta(9)-THC side effects) and possibly account for the rare incidence of seizures in some individuals taking cannabis recreationally.


The in vitro metabolism of AM-630 was studied by high-performance liquid chromatography coupled with tandem mass spectrometry. AM-630 is an aminoalkylindole analogue that behaves primarily as a potent CB2-selective antagonist. In this study, 17 metabolic products were identified that resulted from the incubation of AM-630 in rat liver microsome preparations. Six metabolic pathways were proposed to account for all detected metabolites: (1) o-demethylation of the methoxyphenyl group, (2) morpholinyl ring opening, (3) hydroxylation on the methoxy/hydroxyl phenyl ring, (4) hydroxylation on the indole ring, (5) hydroxylation on the morpholine ring and (6) loss of the morpholine ring leading to metabolites containing either a hydroxylated or a carboxylated alkyl terminal. Three metabolites were identified as morpholinyl ring-opening products: M1, M6 and M13. Six metabolites (M2-M5, M7 and M8) were proposed to be the products of o-demethylation, hydroxylation on the methoxyphenyl group or the morpholinyl ring, dehydration following morpholinyl ring monohydroxylation, or a combination of the above metabolic pathways. The remaining eight metabolites were attributed to a pathway involving the loss of the morpholine ring at various points during the metabolic processes.

**CLINICAL SCIENCE**

A forty year old cannabis bodypacker was found dead in his flat in November 2000, two
days after arriving back from a trip to Northern India. On his return he had complained to
his family of feeling unwell, although he had refused to let them in or accept medical help. At post-
mortem he was found to have 55 packages of cannabis resin in the large intestine, wrapped in
cellophane. Subsequent search of the flat by the police revealed the presence of a further 133
similar packages in the fridge, suggesting that he had concealed 188 packages in total. The
cause of death was given as peritonitis due to perforation of the distal large intestine caused by
swallowing the packages.

without a "high"." *Life Sci* 75(12): 1513-22.

A long-standing goal in cannabinoid research has been the discovery of potent synthetic
analogues of the natural substances that might be developed as clinically useful drugs. This
requires, among other things, that they be free of the psychotropic effects that characterize the
recreational use of Cannabis. An important driving force for this goal is the long history of the use
of Cannabis as a medicinal agent especially in the treatment of pain and inflammation. While few
compounds appear to have these properties, ajulemic acid (AJA), also known as CT-3 and IP-751,
is a potential candidate that could achieve this goal. Its chemical structure was derived from
that of the major metabolite of Delta(9)-THC, the principal psychotropic constituent of Cannabis.
In preclinical studies it displayed many of the properties of non-steroidal anti-inflammatory drugs
(NSAIDs); however, it seems to be free of undesirable side effects. The initial short-term trials in
healthy human subjects, as well as in patients with chronic neuropathic pain, demonstrated a
complete absence of psychotropic actions. Moreover, it proved to be more effective than placebo
in reducing this type of pain as measured by the visual analog scale. Unlike the narcotic
analgesics, signs of dependency were not observed after withdrawal of the drug at the end of the
one-week treatment period. Data on its mechanism of action are not yet complete; however, the
activation of PPAR-gamma, and regulation of eicosanoid and cytokine production, appear to be
important for its potential therapeutic effects.


**BACKGROUND:** Although cannabis has been used as a medicine for several centuries,
the therapeutic properties of cannabis preparations (essentially haschich and marijuana) make
them far more popular as a recreational drugs. State of the art. Scientific studies on the effects of
cannabis were advanced considerably by the identification in 1964 of cannabinoid D9-
tetrahydrocannabinol (THC), recognized as the major active constituent of cannabis. Cloning of
the centrally located CB1 receptor in 1990 and the identification of the first endogenous ligand of
the CB1 receptor, anandamide, in 1992 further advanced our knowledge. **Perspective and
conclusions.** Progress has incited further research on the biochemistry and pharmacology of the
cannabinoids in numerous diseases of the central nervous system. In the laboratory animal,
cannabinoids have demonstrated potential in motion disorders, demyelinizing disease, epilepsy,
and as anti-tumor and neuroprotector agents. Several clinical studies are currently in progress,
but therapeutic use of cannabinoids in humans could be hindered by undesirable effects,
particularly psychotropic effects. CB1 receptor antagonists also have interesting therapeutic
potential.


Abstract Fear-conditioned analgesia is an important survival response mediated by
substrates controlling nociception and aversion. Cannabinoid(1) (CB(1)) receptors play an
important role in nociception and aversion. However, their role in fear-conditioned analgesia has
not been investigated. This study investigated the effects of systemic administration of the CB(1)
receptor antagonist, SR141716A (1 mg/kg, ip), on fear-conditioned analgesia and conditioned
aversion in rats. Twenty-four hours after receiving footshock, rats exhibited reduced formalin-
evoked nociceptive behaviour, increased freezing and increased defecation when tested in the footshock apparatus, compared with non-footshocked formalin-injected rats. SR141716A attenuated fear-conditioned analgesia, freezing and defecation. Importantly, SR141716A had no effect on formalin-evoked nociceptive behaviour over an equivalent time period in rats not receiving footshock. SR141716A had no effect on contextually induced freezing during the first half of the test trial in rats receiving intra-plantar injection of saline. Administration of SR141716A did, however, attenuate short-term extinction of contextually induced freezing and ultrasound emission in rats receiving intra-plantar saline, compared with vehicle-treated saline controls. These data suggest an important role for the CB(1) receptor in mediating fear-conditioned analgesia and provide evidence for differential modulation of conditioned aversive behaviour by CB(1) receptors during tonic, persistent pain.


The objective of this study was to compare urinary excretion patterns of two cannabinoid metabolites in subjects with a history of chronic marijuana use. The first metabolite analyzed was nor-9-carboxy-Delta(9)-tetrahydrocannabinol (Delta(9)-THC-COOH), the major urinary cannabinoid metabolite that is pharmacologically inactive. The second metabolite 11-OH-Delta(9)-THC is an active cannabinoid metabolite and is not routinely measured. Urine specimens were collected from four subjects on 12-20 occasions >/=96h apart in an uncontrolled clinical setting. Creatinine was analyzed in each urine specimen by the colorimetric modified Jaffe reaction on a SYVA 30R biochemical analyzer. All urine specimens analyzed for 11-OH-Delta(9)-THC had screened positive for cannabinoids with the EMIT ll Plus cannabinoids assay (cut-off 50ng/mL) on a SYVA 30R analyzer and submitted for Delta(9)-THC-COOH confirmation by GC-MS (cut-off concentration 15ng/mL). Eleven-OH-Delta(9)-THC was measured by GC-MS with a cut-off concentration of 3ng/mL. Both GC-MS methods for cannabinoid metabolites used deuterated internal standards for quantitative analysis. The mean (range) of urinary Delta(9)-THC-COOH concentration was 1153ng/mL (78.7-2634) with a cut-off of 15ng/mL. The mean (range) of Delta(9)-THC-COOH/creatinine ratios (ng/mL Delta(9)-THC-COOH/mmol/L creatinine) was 84.1 (8.1-122.1). The mean (range) urinary of 11-OH-Delta(9)-THC concentration was 387.6ng/mL (11.9-783) with a cut-off of 3ng/mL, and the mean (range) of 11-OH-Delta(9)-THC/creatinine ratio (ng/mL 11-OH-Delta(9)-THC/mmol/L creatinine) was 29.7 (1.2-40.7). Of the 63 urine specimens submitted for Delta(9)-THC-COOH confirmation by GC-MS, 59/63 urine specimens (94%) were positive for Delta(9)-THC-COOH and 51/63 (81%) were positive for 11-OH-Delta(9)-THC. Overall, the concentrations of 11-OH-Delta(9)-THC in urine specimens collected >/=96h apart were lower than Delta(9)-THC-COOH concentrations in 50/51 of the urine specimens in this population. Further urinary cannabinoid excretion studies are needed to assess whether 11-OH-Delta(9)-THC analyses have a role when assessing previous marijuana or hashish use in chronic users whose urine specimens remain positive for Delta(9)-THC-COOH for an extended period of time after last drug use.


Cannabis is the most common illicit substance used by adolescents. This paper reports results of a pilot study using fMRI and a working memory task to compare brain function of adolescent cannabis users to that of two control groups, one matched for tobacco use and the other for nonsmokers.


Despite extensive research on the effects of cannabis on cognitive and motor performance, studies administering computerised cognitive batteries and pencil-and-paper tests have not provided consistent results. Contributing factors are the broad range of tests used, together with a lack of sensitivity for assessing specific cognitive processes. This study for the first time assesses a very early cognitive process, information processing, that is sufficiently
fundamental as to be immune from higher cognitive, motivational, and social processes. Information processes are thought to represent the basic building blocks of higher order cognitive processes. The inspection time (IT) task was used to investigate the effects of acute and subacute cannabis use on information processing in 22 heavy users, compared to 22 noncannabis-using controls. Findings indicate that users in the subacute state display significantly slowed information-processing speeds (longer ITs) compared to controls. Paradoxically, this deficit appears to be normalised whilst users are in the acute state. These results may be explained as a withdrawal effect, but may also be due to tolerance development as a result of long-term cannabis use. Furthermore, these results may assist in providing an explanation for the development of dependence with chronic cannabis users.


The present review focuses on articles dealing with clinical or epidemiological studies on the association between cannabis use and psychoses. Included are all articles published since 1990 that were located by a Medline or Psyclit data-base research and those earlier articles that are needed for a correct understanding of studies published during the index episode. The three main topics found are 1) is there evidence for a so called cannabis psychosis 2) do cannabis users exhibit a higher risk of developing a psychotic disorder or 3) does its use worsen the course in established schizophrenia spectrum disorders. The review concludes that very high doses of cannabis can induce a brief psychosis but that this condition is extremely rare. Therefore, such a diagnosis should only be made after careful exclusion of other etiologies. The actual evidence regarding the impact of cannabis use on persons vulnerable to psychosis is not conclusive. Cannabis use seems to worsen the course of schizophrenia spectrum disorders. Adolescents run a higher risk from using cannabis than older people. They should be strongly advised not to indulge in such behaviour.


OBJECTIVE: To evaluate the effect of the oral synthetic delta-9-tetrahydrocannabinol dronabinol on central neuropathic pain in patients with multiple sclerosis. DESIGN: Randomised double blind placebo controlled crossover trial. SETTING: Outpatient clinic, University Hospital of Aarhus, Denmark. PARTICIPANTS: 24 patients aged between 23 and 55 years with multiple sclerosis and central pain. INTERVENTION: Orally administered dronabinol at a maximum dose of 10 mg daily or corresponding placebo for three weeks (15-21 days), separated by a three week washout period. MAIN OUTCOME MEASURE: Median spontaneous pain intensity (numerical rating scale) in the last week of treatment. RESULTS: Median spontaneous pain intensity was significantly lower during dronabinol treatment than during placebo treatment (4.0 (25th to 75th centiles 2.3 to 6.0) v 5.0 (4.0 to 6.4), P=0.02), and median pain relief score (numerical rating scale) was higher (3.0 (0 to 6.7) v 0 (0 to 2.3), P=0.035). The number needed to treat for 50% pain relief was 3.5 (95% confidence interval 1.9 to 24.8). On the SF-36 quality of life scale, the two items bodily pain and mental health indicated benefits from active treatment compared with placebo. The number of patients with adverse events was higher during active treatment, especially in the first week of treatment. The functional ability of the multiple sclerosis patients did not change. CONCLUSIONS: Dronabinol has a modest but clinically relevant analgesic effect on central pain in patients with multiple sclerosis. Adverse events, including dizziness, were more frequent with dronabinol than with placebo during the first week of treatment.


CANNABIS TO TREAT PSYCHOSIS: The nature of the link between cannabis use and psychosis remains to be clarified. Cross-sectional epidemiological studies have shown that individuals with psychosis use cannabis more often than other individuals in the general
population. It has long been considered that this association was explained by the self-medication hypothesis, postulating that cannabis is used to self-medicate psychotic symptoms. This hypothesis has been recently challenged. PSYCHOTIC DISORDERS ENHANCED BY CANNABIS: Several prospective studies carried out in population-based samples, showed that cannabis exposure was associated with an increased risk of psychosis. A dose-response relationship was found between cannabis exposure and risk of psychosis, and this association was independent from potential confounding factors such as exposure to other drugs and pre-existence of psychotic symptoms. The brain mechanisms underlying the association have to be elucidated; they may implicate deregulation of cannabinoid and dopaminergic systems. A RISK FACTOR NOT TO BE NEGLECTED: Cannabis exposure may be a risk factor for psychotic disorders by interacting with a pre-existing vulnerability for these disorders. If further studies confirm that cannabis is a risk factor for psychosis, its impact on the population’s mental health may not be negligible considering the growing number of adolescents exposed to this substance.


BEHAVIOURAL SCIENCE


Cannabis and cocaine are illicit psychoactive substances that have fallen under intense scrutiny by epidemiologists and behavioral geneticists. However, most analyses have used a composite variable to represent the use of these two drugs. For example, the composite variable of cannabis use often includes use of marijuana or hashish. Similarly, cocaine use involves different preparations (crack vs. cocaine hydrochloride) and varying routes of administration (intranasal insufflation vs. smoking). While there is some epidemiological evidence for the difference in addictive potentials between crack and intranasal cocaine, genetically informative studies have not examined the relationship between the forms of cannabis or cocaine. We used data from male and female same-sex twin pairs to examine the extent of genetic, shared environmental, and unique environmental overlap between (i) marijuana and hashish for cannabis use and (ii) intranasal and crack cocaine for cocaine use. Bivariate Cholesky models were fit using the structural equation modeling software Mx. Our results indicate that for both drugs, the individual drug forms show a complete overlap of genetic factors and a substantial overlap of shared environmental influences. While marijuana and hashish share a moderate proportion of their unique environment, crack and intranasal cocaine only show a modest overlap of unique environmental factors, adding some evidence for form-specific environmental factors. In conclusion, there is substantial overlap of familial factors between forms of a single drug and preference is primarily determined by unique environmental influences. These findings also reinforce the validity of composite variables in epidemiological and genetic research. Copyright 2004 Wiley-Liss, Inc.


OBJECTIVE: This study continues the psychometric evaluation of a 31-item Marijuana Screening Inventory (MSI-X) with adults referred to a substance abuse clinic, by determining MSI-X reliability, factor structure, scoring cutoff accuracy, sensitivity, and specificity with a DSM-IV-TR criterion measure. METHOD: A "marijuana inventory" containing demographic, MSI-X, and DSM IV-TR diagnostic items was administered to 107 adults undergoing substance-use evaluation. RESULTS: The MSI-X reliability was .90 with factor analysis deriving nine factors explaining 72.2% of the variance. Varimax rotation supports retention of all 31 items on nine factor-based scales. Receiver operating characteristic analysis determined MSI-X accuracy and cutoff points in relation to four DSM IV-TR diagnostic classifications. The MSI-X obtained the highest probability
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(.91) for accuracy in identifying both cannabis dependence and abuse, with six the optimal cutoff for maximum sensitivity (.83) and specificity (.89). Thus, MSI-X scores of \( \geq 6 \) are considered high risk. A cutoff score of 3 was associated with (probability, .90; sensitivity, .85; specificity, .81) identifying cannabis abuse only risk, providing a 3 to 5 score in the moderate risk range.

CONCLUSIONS: Clinical sample data supports the psychometric usefulness of the MSI-X as a screening tool. Marijuana lifetime use was 90% and past-year use 48%. The MSI-X identified 43% of lifetime users and 29% of past year users with moderate to high risk marijuana patterns deserving comprehensive evaluation. More males (15.9%) than females (7.5%) obtained MSI-X high-risk scores. The MSI-X empirically derived cutoff scores are within one point of the theoretical clinical cutoffs previously reported.


The aim of the study was to compare perceptions of cannabis use effects and risks of tolerance effect, withdrawal syndrome, dependence and repercussions on school, social, and familial functioning among adolescent cannabis users and non users. Subjects were 210 adolescents (121 boys, 89 girls; mean age=16.3 1.3) from the department of Pyrenees-Orientales, France. Subjects completed a questionnaire assessing the frequency of cannabis use, the method of using cannabis, and including open-ended questions (What are the different methods of cannabis use? What are their pleasant and unpleasant or negative effects? What are their risks? Do you think that cannabis effects decrease in intensity when you are used to it? When someone is used to cannabis and stop using it (or has no more of it), does she experience craving for cannabis and withdrawal symptoms? What do you think of cannabis use?). Among the subjects, 118 (56.2%) were cannabis users and 92 (43.8%) were non-users. Among users, 27% used cannabis once a Month or less than once a Month, 21%, more than once a Month; 24%, more than once a weeks; 6%, every day; 20%, more than once a day. The methods of using cannabis were joints (76%), bong (40%), pipe (23%), and ingestion (18%). Knowledge of methods of using cannabis was higher in users than non-users: joint (87% vs 64%, \( p<0.0001 \)), bong (69% vs 21%, \( p<0.0001 \)), pipe (38% vs 7%, \( p<0.0001 \)), ingestion (41% vs 13%, \( p<0.0001 \)). Fifty-four per cent of users reported that cannabis use induces pleasant affects versus 30% of non-users (\( p=0.0006 \)). They were exhilaration (47% vs 9%), relaxation (40% vs 23%), cheerfulness (21% vs 10%). Twenty-seven percent of users reported that cannabis use reduces negative feelings versus 14% of non-users (\( p=0.02 \)). To be more open to social relationships was mentioned by 13% of users versus 1% of non-users (\( p=0.0001 \)). The negative effects that were reported were attention and cognitive impairment (13% of users vs 5% of non users, \( p=0.05 \)), irritability (8% vs 8%), loss of control (8% vs 8%) and feeling faint (13% vs 6%, \( p=0.09 \)). Users reported than bong has much quicker and stronger effects than joints. The effects of bong class cannabis as a hard drug. Physical ne-gative effects or risk were reported by 35% of users versus 30% of non-users (\( p=0.44 \)). Bong users described specific physical risks such as respiratory problems and fainting. No subjects reported the risk of road accidents. Most users and non-users considered that cannabis use causes dependence (60% vs 74%, \( p=0.03 \)), tolerance (68% vs 60%, \( p=0.23 \)), and withdrawal symptoms (76% vs 52%, \( p<0.001 \)). A majority of users and non-users reported that cannabis use causes a deterioration in school functioning (42% vs 20%, \( p=0.69 \), in social activities (23% vs 14%, \( p=0.10 \) and in family relationships (29% vs 20%, \( p=0.14 \)). Most of users (56%) had a global positive opinion of cannabis use whereas most non-users (66%) had a global negative opinion of cannabis use. The frequency and methods of use reported in this study compare with the results of a recent study carried out in another town of the south of France. These results suggest that a high proportion of French adolescents are using cannabis and that a high proportion of users utilize bongs. Perception of cannabis effects and risks of tolerance effect, withdrawal syndrome, dependence and repercussions on school, social, and familial functioning differed between users and non-users. Users have more positive beliefs and less negative beliefs about cannabis than non-users. Users reported more frequently pleasant effects and less frequently unpleasant or negative effects, physical risks, risks of dependence, deterioration in school, social, and familial functioning than non-users. However, only a minority of non-users reported negative effects or consequences of cannabis use. None
subjects reported a risk of road accident. These results suggest that information on negative effects, risks and repercussions of cannabis use may be a target for prevention intervention.


BACKGROUND AND METHOD: As part of the evaluation of the Confederation's measures to reduce drug related problems, a review of available data on drug use and drug related problems in Switzerland has been conducted. Source of data included: population surveys (adults and teenagers), surveys among drug users, health statistics (drug related and AIDS related deaths, HIV case reporting, drug treatments) police statistics (denunciations for consumption). RESULTS: The aims of reducing the number of dependent hard drug users have been achieved where heroin is concerned. In particular, there seems to have been a decrease in the number of people becoming addicted to this substance. For all other illegal substances, especially cannabis, the trend is towards an increased use, as in many European countries. As regards dependent drug users, especially injecting drug users, progress has been made in the area of harm reduction and treatment coverage. CONCLUSION: This epidemiological assessment can be used in the discussions currently engaged about the revision of the Law governing narcotics and will be a baseline for future follow up of the situation.


Many studies have shown that different risk or problem behaviors in adolescence are interrelated. Given the increased use of various substances among adolescents in the United States and in most European countries, the question emerges whether there are more substance use 'specialists' or a progression of a general substance use pattern. If the latter is the case, the interrelatedness of the different substances should remain stable over time in a representative sample and among subgroups characterized by gender and language. Data from 4,146 15-year-olds in Switzerland surveyed in 1986, 1994 and 1998 were analyzed, using confirmatory factor analyses based on polychoric correlations. Smoking, drunkenness and cannabis use greatly increased over the 12-year period. However, in the different survey years, the factor structure did not differ for all 15-year-olds in general or for subgroups. This progression of a general pattern refers to an increased normalization of recreational substance use in general, not only of cannabis use. Favorable attitudes towards general substance use are a challenge to substance use prevention in adolescence, and reveal a need for more research on such a progression in other countries. Copyright 2004 S. Karger AG, Basel


Acute marijuana administration may alter response-reinforcer relationships via a change in reinforcer efficacy, but may also impair coordination and motor function. One approach to evaluating drug effects on both motor function and reinforcer efficacy involves fitting the matching law equation to data obtained under multiple variable interval (VI) schedules. The present report describes an experiment that examined the effects of acute marijuana on response properties using this approach. Six human subjects responded under a multiple VI schedule for monetary reinforcers after smoking placebo and two active doses of marijuana. The low marijuana dose produced unsystematic changes in responding. As measured by the matching law equation parameters (k and rB), at the high dose five subjects showed a decrease-motor-related properties of response rate and four subjects' responding indicated a decrease in reinforcer efficacy. These data raise the possibility that, at high doses, marijuana administration alters both motor function and reinforcer efficacy.


OBJECTIVES: The impact of social participation, trust and the miniaturization of community, i.e. the combination of high social participation and low trust, on cannabis smoking
was investigated. METHODS: The 2000 public health survey in Scania is a cross-sectional study. A total of 13,715 persons aged 18-80 years, of which 3,978 persons aged 18-34 years were included in this study, answered a postal questionnaire, which represents 59% of the random sample. A logistic regression model was used to investigate the association between the social capital variables and ever having experienced cannabis smoking. The multivariate analysis was performed to investigate the importance of possible confounders (age, country of origin and education) on the differences in having experienced cannabis smoking according to social participation, trust and their four combination categories. RESULTS: Cannabis smoking is not associated with social participation, but positively associated with low trust among both men and women, and the miniaturization of community, i.e. the combination of high social participation and low trust, among men. CONCLUSIONS: This study suggests that the miniaturization of community, i.e. the combination of high social participation and low levels of generalized trust of other people, may enhance the experience of cannabis smoking.


BACKGROUND/INTRODUCTION: A paucity of research exists on driving after use of cannabis or cocaine among clients in substance abuse treatment and changes in this behavior after treatment. OBJECTIVES: The objectives of this research are to compare treatment clients and population controls before and after treatment in terms of: 1) amount of driving; 2) alcohol, cannabis, and cocaine consumption; 3) driving after use of alcohol, cannabis, and cocaine; and 4) driving infractions. METHOD: Telephone interviews were conducted with a sample of 110 clients who received treatment in 1995 for a primary problem of alcohol (n = 44), cannabis (n = 37), or cocaine (n = 29) abuse. A random sample of 104 drivers from the general population, frequency matched by age and sex was also interviewed. Participants were asked to describe their driving habits and driving infractions before and after 1995. RESULTS: Both treatment and control groups reported about the same amount of driving. The treatment group reported significantly more consumption of alcohol, cannabis, and cocaine than did the control group before treatment. Significant declines in use for each substance were found for the treatment group after treatment, but use for the control group remained stable over the two time periods. Similarly significant declines in driving after use of alcohol, cannabis, and cocaine were found for the treatment group but the control group remained stable. Finally driving infractions, including speeding tickets, collisions, and license suspensions, significantly declined for the treatment group but not the control group. DISCUSSION: The results confirm that before treatment, the treatment subjects drove more frequently after consuming alcohol, cannabis, or cocaine than the control group. Declines in substance use and driving after treatment were accompanied by reductions in some types of driving infractions. Differences between groups, and over time in terms of driving while under the influence of psychoactive substances better explain the results than differences between groups in impulsivity/risk-taking or sleep problems.


In the past century we have learned that driving performance is impaired by alcohol even in low dosage, and that many other drugs are also linked to impairment. This paper is a summary of some of the more relevant studies in the past fifty years an overview of our knowledge and unanswered questions. There is no evidence of a threshold blood alcohol (BAC) below which impairment does not occur, and there is no defined category of drivers who will not be impaired by alcohol. Alcohol increases not only the probability of collision, but also the probability of poor clinical outcome for injuries sustained when impaired by alcohol. This review samples the results of the myriad studies that have been performed during the last half century as experiments have moved from examination of simple sensory, perceptual and motor behaviours to more complex measures of cognitive functioning such as divided attention and mental workload. These more sophisticated studies show that significant impairment occurs at very low BACs (<0.02 gm/100 ml). However, much remains to be determined regarding the more emotional aspects of behaviour, such as judgment, aggression and risk taking. Considering that the majority of alcohol related accidents occur at night, there is a need for increased examination on the role of fatigue,
circadian cycles and sleep loss. The study of the effects of drugs other than alcohol is more complex because of the number of substances of potential interest, the difficulties estimating drug levels and the complexity of the drug/subject interactions. The drugs of current concern are marijuana, the benzodiazepines, other psychoactive medications, the stimulants and the narcotics. No one test or group of tests currently meets the need for detecting and documenting impairment, either in the laboratory or at the roadside.


Abortion is known to be associated with higher rates of substance abuse, but no studies have compared substance use rates associated with abortion compared to delivery of an unintended pregnancy. This study examines data for women in the National Longitudinal Survey of Youth whose first pregnancy was unintended. Women with no pregnancies were also used as a control group. Use of alcohol, marijuana, cocaine, and behaviors suggestive of alcohol abuse were examined an average of four years after the target pregnancy among women with prior histories of delivering an unintended pregnancy (n = 535), abortion (n = 213), or those who reported no pregnancies (n = 1144). Controls were instituted for age, race, marital status, income, education, and pre-pregnancy self-esteem and locus of control. Compared to women who carried an unintended first pregnancy to term, those who aborted were significantly more likely to report use of marijuana (odds ratio: 2.0), with the difference in these two groups approaching significance relative to the use of cocaine (odds ratio: 2.49). Women with a history of abortion also reported more frequent drinking than those with a history of unintended birth. With the exception of less frequent drinking, the unintended birth group was not significantly different from the no pregnancy group. Resolution of an unintended pregnancy by abortion was associated with significantly higher rates of subsequent substance use compared to delivering an unintended pregnancy. A history of abortion may be a useful marker for identifying women in need of counseling for substance use.


The primary purpose of this study was to determine associations between measures of prior incarceration and marijuana use with self-reported HIV/AIDS risk behaviors among a sample of soon-to-be-released adult male inmates. Analyses presented exclusively involve calculating two multiple logistic regression models to test the study hypothesis. The general model specified self-reported marijuana use as an outcome with selected demographic variables including ethnicity, age, education, and income prior to incarceration as predictor variables. Significant bivariate associations were recorded for age, education, and sexual self-expectation with respect to reincarceration. Specifically, the least amount of education reported, the more likely study participants were to have been incarcerated more than once.


This paper reports the prediction of marijuana use cessation among young adults who were regular users 5 years earlier. Social, attitude, intrapersonal, violence-related, drug use, and demographic baseline measures served as predictors of whether or not 339 teenage marijuana users reported having quit use 5 years later. Young adult social role variables were included as additional predictors. Quitting was defined as having not used marijuana in the last 30 days (42% of the sample at follow-up). After controlling for covariation among predictors, in a three-step analysis, only baseline level of marijuana use, male gender, young adult marital status, and friends’ marijuana use (marginal) remained statistically direct predictors. Implications of these results include the need to reduce psychological dependence on marijuana and increase social unacceptability of marijuana use across genders to help increase prevalence of quit attempts.

Chronic consumption of several drugs of abuse (cannabis, stimulants, opioids) has been associated with the presence of neuropsychological impairments in a broad range of functions. Nevertheless, in recent years neuropsychological research on substance abuse has focused on the study of impairments in the executive functions linked to the prefrontal cortex and their influence on the personality, cognitions, and behaviors of the substance abusers. The aim of our review is, first, to summarize the main neuropsychological impairments shown by classic studies, as well as these new discoveries in executive functioning; second, to consider the mediating role of neuropsychological status on treatment outcomes and analyze the impact of these impairments in clinical practice with drug addicts; and third, to review the principal methodological challenges associated with research in the field of the neuropsychology of substance abuse. We also highlight the convenience of intervening in those functions most relevant to the abusers' persistence in consumption and risk of relapse.


The objectives of this research were to (1) determine the incidence and prevalence of alcohol and other drug use among motor vehicle crash (MVC) victims admitted to a regional Level-I trauma center, and (2) to examine the utility of using a rapid point-of-collection (POC) drug-testing device to identify MVC patients with drug involvement. Blood and urine specimens were routinely collected per clinical protocol for each MVC victim at the time of admission. Blood alcohol concentration (BAC) levels were determined per standard clinical protocol. Clinical urine specimens were routinely split so that a POC drug-testing device for the detection of commonly abused drugs (Marijuana, Cocaine, Amphetamines, Methamphetamines, and Opiates) could be compared to that of the standard hospital laboratory analysis of each urine specimen (which also included Barbiturates and Benzodiazepines). In the six-month period of this study, nearly two-thirds of trauma center admissions were victims of motor vehicle crashes. During this time, blood and urine was collected from 322 MVC victims. Toxicology results indicated that 59.3% of MVC victims tested positive for either commonly abused drugs or alcohol. More patients tested positive for drug use than tested positive for alcohol, with 33.5% testing positive for drug use only, 15.8% testing positive for alcohol use only, and 9.9% testing positive for both drugs and alcohol. Less than half (45.2%) of the substance-abusing patients in this study would have been identified by an alcohol test alone. After alcohol, marijuana and benzodiazepines were the most frequently detected drugs. Point of collection (POC) test results correlated well with laboratory results and provide important information to initiate rapid intervention/treatment for substance use problems among injured patients.


A key issue that came to the forefront during the welfare reform debate in the United States during the 1990s concerned the relationship between welfare receipt and drug use and abuse. This paper examines the relationship between persistent welfare assistance, welfare background, and marijuana and cocaine use among African-American women. We hypothesize that women who have received welfare assistance for a period of 5 years or more will be more likely to use drugs compared to those who have never received welfare assistance or who have received it for a shorter duration. Data for this analysis comes from a longitudinal study of African-Americans living in a Chicago community followed from first grade (Formula: see text) to age 32. Multinomial logistic regression analyses were performed to examine the relationship between years of welfare receipt and three categories of marijuana and cocaine use (never, past, and current) among female respondents (Formula: see text). Results indicate an increased risk of past-year cocaine and marijuana use for women who reported receiving welfare benefits for 5 years or more. Growing up in a family that received welfare did not significantly predict adult drug use, but did significantly predict an adult welfare experience. Implications of results are discussed.
This newsletter is supported by an unrestricted educational grant from Valeant/ICN Pharmaceuticals (Canada)