The Canadian Consortium for the Investigation of Cannabinoids in Human Therapeutics

INTRODUCTION
Here is the latest summary of research abstracts. Please note that the International Cannabinoid Research Society (ICRS) meeting will be held in Cornwall, Ontario from June 25-28th, 2003. Details may be found at www.cannabinoidsociety.org

BASIC SCIENCE
Dexanabinol [HU 211, dexamabinone, sinnabidol, PA 50211, PRS 211007] is a synthetic, non-psychotropic tetrahydro-cannabinoid. This profile has been selected from R&D Insight trade mark, a pharmaceutical intelligence database produced by Adis International Ltd. Dexanabinol lacks cannabinomimetic activity, and is a functional antagonist of the NMDA receptor with antioxidant and anti-tumour necrosis factor-alpha properties. Dexanabinol is in clinical trials for traumatic brain injury (head injuries), glaucoma and mild cognitive impairment, and is being investigated preclinically for its potential in the treatment of multiple sclerosis. Pharmos has a licensing agreement with the Hebrew University, Israel, and is seeking a partner for development and commercialisation of the dexamabinol family of compounds. The Financial Times (ft.com) reported in March 2001 that the market for brain trauma could be worth approximately $US500 million, according to estimates by Pharmos. The company was said to have $US26 million in capital at the time, most of which would be used taking dexamabinol through regulatory submission, according to the Financial Times.

Neuronal excitability and long-term synaptic plasticity at excitatory synapses are critically dependent on the level of inhibition, and accordingly, changes of inhibitory synaptic efficacy should have great impact on neuronal function and neural network processing. We describe here a form of activity-dependent long-term depression at hippocampal inhibitory synapses that is triggered postsynaptically via glutamate receptor activation but is expressed presynaptically. That is, glutamate released by repetitive activation of Schaffer collaterals activates group I metabotropic glutamate receptors at CA1 pyramidal cells, triggering a persistent reduction of GABA release that is mediated by endocannabinoids. This heterosynaptic form of plasticity is involved in changes of pyramidal cell excitability associated with long-term potentiation at excitatory synapses and could account for the effects of cannabinoids on learning and memory.

A number of recent in vitro studies have described a role for endogenous cannabinoids ("endocannabinoids") as transsynaptic modulators of neuronal activity in the hippocampus and other brain regions. However, the impact that endocannabinoid signals may have on activity-dependent neural events in vivo remains mostly unknown and technically challenging to address because of the short half-life of these chemical messengers in the brain. Mice lacking the enzyme
fatty acid amide hydrolase [FAAH (-/-) mice] are severely impaired in their ability to degrade the endocannabinoid anandamide and therefore represent a unique animal model in which to examine the function of this signaling lipid in vivo. Here, we show that the administration of anandamide dramatically augments the severity of chemically induced seizures in FAAH (-/-) mice but not in wild-type mice. Anandamide-enhanced seizures in FAAH (-/-) mice resulted in significant neuronal damage in the CA1 and CA3 regions of the hippocampus for the bicuculline and kainate models, respectively. Notably, in the absence of anandamide treatment, FAAH (-/-) mice exhibited enhanced seizure responses to high doses of kainate that correlated with greatly elevated endogenous levels of anandamide in the hippocampus of these animals. Collectively, these studies suggest that both exogenously administered and endogenously produced anandamide display FAAH-regulated proconvulsant activity and do not support a general neuroprotective role for this endocannabinoid in response to excitotoxic stimuli in vivo. More generally, these findings demonstrate that the disinhibitory actions of endocannabinoids observed in hippocampal slices in vitro may also occur in vivo.


Fatty acid amide hydrolase (FAAH) catalyses hydrolysis of the endocannabinoid arachidonoyl ethanolamide ("anandamide") in vitro and regulates anandamide levels in the brain. In the cerebellar cortex, hippocampus and neocortex of the rat brain, FAAH is located in the somata and dendrites of neurons that are postsynaptic to axon fibers expressing the CB(1) cannabinoid receptor [Proc R Soc Lond B 265 (1998) 2081]. This complementary pattern of FAAH and CB(1) expression provided the basis for a hypothesis that endocannabinoids may function as retrograde signaling molecules at synapses in the brain [Proc R Soc Lond B 265 (1998) 2081; Phil Trans R Soc Lond 356 (2001) 381] and subsequent experimental studies have confirmed this [Science 296 (2002) 678]. To assess more widely the functions of FAAH in the brain and the potential impact of FAAH activity on the spatiotemporal dynamics of endocannabinoid signaling in different regions of the brain, here we have employed immunocytochemistry to compare the distribution of FAAH and CB(1) throughout the mouse brain, using FAAH(-/-) mice as negative controls to validate the specificity of FAAH-immunoreactivity observed in wild type animals. In many regions of the brain, a complementary pattern of FAAH and CB(1) expression was observed, with FAAH-immunoreactive neuronal somata and dendrites surrounded by CB(1)-immunoreactive fibers. In these regions of the brain, FAAH may regulate postsynaptic formation of anandamide, thereby influencing the spatiotemporal dynamics of retrograde endocannabinoid signaling. However, in some regions of the brain such as the globus pallidus and substantia nigra pars reticulata, CB(1) receptors are abundant but with little or no associated FAAH expression and in these brain regions the spatial impact and/or duration of endocannabinoid signaling may be less restricted than in regions enriched with FAAH. A more complex situation arises in several regions of the brain where both FAAH and CB(1) are expressed but in a non-complementary pattern, with FAAH located in neurons and/or oligodendrocytes that are proximal but not postsynaptic to CB(1)-expressing axon fibers. Here FAAH may nevertheless influence endocannabinoid signaling but more remotely. Finally, there are regions of the brain where FAAH-immunoreactive neurons and/or oligodendrocytes occur in the absence of CB(1)-immunoreactive fibers and here FAAH may be involved in regulation of signaling mediated by other endocannabinoid receptors or by receptors for other fatty acid amide signaling molecules. In conclusion, by comparing the distribution of FAAH and CB(1) in the mouse brain, we have provided a neuroanatomical framework for comparative analysis of the role of FAAH in regulation of the spatiotemporal dynamics of retrograde endocannabinoid signaling in different regions of the brain.


Previous work has suggested a role for retrograde synaptic signaling via endogenous cannabinoids in regulating the inhibitory control of neuronal activity. In this issue of Neuron,
Chevaleyre and Castillo provide evidence for another form of endocannabinoid-mediated depression of hippocampal inhibition, which is activity dependent and long lasting.


Cannabinoid CB1 receptors and vanilloid VR1 receptors are co-localized to some extent in sensory neurons of the spinal cord and dorsal root ganglia. In this study, we over-expressed both receptor types in human embryonic kidney (HEK)-293 cells and investigated the effect of the CB1 agonist HU-210 on the VR1-mediated increase in intracellular Ca2+ ([Ca2+]i), a well-known response of the prototypical VR1 agonist capsaicin. After a 5-min pre-treatment, HU-210 (0.1 microM) significantly enhanced the effect of several concentrations of capsaicin on [Ca2+]i in HEK-293 cells over-expressing both rat CB1 and human VR1 (CB1-VR1-HEK cells), but not in cells over-expressing only human VR1 (VR1-HEK cells). This effect was blocked by the CB1 receptor antagonist SR141716A (0.5 microM), and by phosphoinositide-3-kinase and phospholipase C inhibitors. The endogenous agonist of CB1 and VR1 receptors, anandamide, was more efficacious in inducing a VR1-mediated stimulation of [Ca2+]i in CB1-VR1-HEK cells than in VR1-HEK cells, and part of its effect on the former cells was blocked by SR141716A (0.5 microM). Pre-treatment of CB1-VR1-HEK cells with forskolin, an adenylate cyclase activator, enhanced the capsaicin effect on [Ca2+]i. HU-210, which in the same cells inhibits forskolin-induced enhancement of cAMP levels, blocked the stimulatory effect of forskolin on capsaicin. Our data suggest that in cells co-expressing both CB1 and VR1 receptors, pre-treatment with CB1 agonists inhibits or stimulates VR1 gating by capsaicin depending on whether or not cAMP-mediated signalling has been concomitantly activated.


Endocannabinoid production by platelets and macrophages is increased in circulatory shock. This may be protective of the cardiovascular system as blockade of CB(1) cannabinoid receptors exacerbates endothelial dysfunction in haemorrhagic and endotoxin shock and reduces survival. Now evidence suggests that blockade of CB(1) receptors starting 24 h after myocardial infarction in rats has a deleterious effect on cardiac performance, while use of a nonselective cannabinoid receptor agonist prevents hypotension and reduces endothelial dysfunction, although left ventricular end diastolic pressure is elevated. Cannabinoids and endocannabinoid systems may therefore present useful targets for therapy following myocardial infarction. British Journal of Pharmacology (2003) 138, 1183-1184. doi:10.1038/sj.bjp.0705155


1 The nonpsychoactive cannabinoid abnormal-cannabidiol (trans-4-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol) (abn-cbd) produced concentration-dependent relaxation of methoxamine-precontracted rat small mesenteric artery. Endothelial removal reduced abn-cbd potency six-fold without affecting the maximum relaxation. 2 In endothelium-intact vessels, abn-cbd was less potent under 60 mM KCl-induced tone and inhibited by combination of L-N(G)-nitroarginine methyl ester (L-NNAME) (nitric oxide synthase inhibitor; 300 micro M), apamin (small conductance Ca(2+)-activated K(+) channels inhibitor; 50 nM) and charybdotoxin (inhibitor of intermediate conductance Ca(2+)-activated K(+) channels and large conductance Ca(2+)-activated K(+) channels BK(Ca); 50 nM). L-NNAME alone or in combination with either toxin alone had little effect. 3 In intact vessels, relaxations to abn-cbd were inhibited by SR 141716A (cannabinoid receptor antagonist; 1 or 3 micro M). Concomitant addition of L-NNAME, apamin and charybdotoxin had no further effect. Other cannabinoid receptor antagonists either had little (SR 144528; 1 micro M and AM 251; 1 micro M) or no effect (AM 630; 10 micro M and AM 281; 1 micro M). Inhibition of gap junctions, G(i/o) protein coupling and protein kinase A also had no effect. 4 Endothelium-independent relaxation to abn-cbd was unaffected by L-NNAME, apamin plus charybdotoxin or capsaicin (10 micro M). Abn-cbd inhibited CaCl(2)-induced contractions in vessels with depleted intracellular Ca(2+) stores and stimulated with methoxamine or KCl. This was insensitive to SR 141716A (3 micro M) but greatly reduced in vessels stimulated
with ionomycin (Ca(2+) ionophore; 1 micro M). We conclude that abn-cbd relaxes the rat small mesenteric artery by endothelium-dependent activation of K(+) channels via SR 141716A-sensitive pathways, which do not involve CB(1) and CB(2) receptors. It also causes endothelium-independent, SR 141716A-insensitive, relaxation by inhibiting Ca(2+) entry through voltage-gated Ca(2+) channels. British Journal of Pharmacology (2003) 138, 1320-1332. doi:10.1038/sj.bjp.0705160


Dopamine and endocannabinoids are neurotransmitters known to play a role in the activity of the basal ganglia motor circuit. While a number of studies have demonstrated functional interactions between type 1 cannabinoid (CB1) receptors and dopaminergic systems, we still lack detailed neuroanatomical evidence to explain their relationship. Single- and double-labeling methods (in situ hybridization and immunohistochemistry) were employed to determine both the expression and localization of CB1 receptors and tyrosine hydroxylase (TH) in the basal ganglia. In the striatum, we found an intense signal for CB1 receptor transcripts but low signal for CB1 receptor protein, whereas in the globus pallidus and substantia nigra we found the opposite; no hybridization signal but intense immunoreactivity. Consequently, CB1 receptors are synthesized in the striatum and mostly transported to its target areas. No co-expression or co-localization of CB1 receptors and TH was found. In the caudate-putamen, globus pallidus and substantia nigra, TH-immunoreactive fibers were interwoven with the CB1 receptor-immunoreactive neuropil and fibers. Our data suggest that the majority of the striatal CB1 receptors are located presynaptically on inhibitory GABAergic terminals, in a position to modulate neurotransmitter release and influence the activity of substantia nigra dopaminergic neurons. In turn, afferent dopaminergic fibers from the substantia nigra innervate CB1 receptor-expressing striatal neurons that are known to also express dopamine receptors. In conclusion, these data provide a neuroanatomical basis to explain functional interactions between endocannabinoid and dopaminergic systems in the basal ganglia.

Kishimoto, S., M. Gokoh, et al. (2003). "2-Arachidonoylglycerol induces the migration of HL-60 cells differentiated into macrophage-like cells and human peripheral blood monocytes through the cannabinoid CB2 receptor-dependent mechanism." J Biol Chem.

2-Arachidonoylglycerol is an endogenous ligand for the cannabinoid receptors (CB1 and CB2) and has been shown to exhibit a variety of cannabimimetic activities in vitro and in vivo. Recently, we proposed that 2-arachidonoylglycerol is the true endogenous ligand for the cannabinoid receptors, and both receptors (CB1 and CB2) are primarily 2-arachidonoylglycerol receptors. The CB1 receptor is assumed to be involved in the attenuation of neurotransmission. On the other hand, the physiological roles of the CB2 receptor, which is abundantly expressed in several types of leukocytes such as macrophages, still remain unknown. In this study, we examined the effects of 2-arachidonoylglycerol on the motility of HL-60 cells differentiated into macrophage-like cells. We found that 2-arachidonoylglycerol induces the migration of differentiated HL-60 cells. The migration induced by 2-arachidonoylglycerol was blocked by treatment of the cells with either SR144528, a CB2 receptor antagonist, or pertussis toxin, suggesting that the CB2 receptor and Gi/Go are involved in the 2-arachidonoylglycerol-induced migration. Several intracellular signaling molecules such as Rho kinase and mitogen-activated protein kinases were also suggested to be involved. In contrast to 2-arachidonoylglycerol, anandamide, another endogenous cannabinoid receptor ligand, failed to induce the migration. The 2-arachidonoylglycerol-induced migration was also observed for two other types of macrophage-like cells, the U937 cells and THP-1 cells, as well as human peripheral blood monocytes. These results strongly suggest that 2-arachidonoylglycerol induces the migration of several types of leukocytes such as macrophages/monocytes through a CB2 receptor-dependent mechanism thereby stimulating inflammatory reactions and immune responses.

Cannabinoid receptors and their endogenous ligands are potent inhibitors of neurotransmitter release in the brain. Here, we show that in a rat model of Parkinson's disease induced by unilateral nigral lesion with 6-hydroxydopamine (6-OHDA), the striatal levels of the endocannabinoid anandamide (AEA) were increased, while the activity of its membrane transporter and hydrolase (fatty-acid amide hydrolase, FAAH) were decreased. These changes were not observed in the cerebellum of the same animals. Moreover, the frequency and amplitude of glutamate-mediated spontaneous excitatory post-synaptic currents were augmented in striatal spiny neurones recorded from parkinsonian rats. Remarkably, the anomalies in the endocannabinoid system, as well as those in glutamatergic activity, were completely reversed by chronic treatment of parkinsonian rats with levodopa, and the pharmacological inhibition of FAAH restored a normal glutamatergic activity in 6-OHDA-lesioned animals. Thus, the increased striatal levels of AEA may reflect a compensatory mechanism trying to counteract the abnormal corticostratal glutamatergic drive in parkinsonian rats. However, this mechanism seems to be unsuccessful, since spontaneous excitatory activity is still higher in these animals. Taken together, these data show that anomalies in the endocannabinoid system induced by experimental parkinsonism are restricted to the striatum and can be reversed by chronic levodopa treatment, and suggest that inhibition of FAAH might represent a possible target to decrease the abnormal cortical glutamatergic drive in Parkinson's disease.


Fatty acid amide hydrolase (FAAH)1 is a mammalian amidase signature (AS) enzyme that inactivates neuromodulatory fatty acid amides, including the endogenous cannabinoid anandamide and the sleep-inducing substance oleamide. The recent determination of the three-dimensional structures of FAAH and two distantly related bacterial AS enzymes indicates that these enzymes employ an unusual serine-serine-lysine triad for catalysis (S241-S217-K142 in FAAH). Mutagenesis of each of the triad residues in FAAH has been shown to severely reduce amidase activity; however, how these residues contribute, both individually and in cooperation, to catalysis remains unclear. Here, through a combination of site-directed mutagenesis, enzyme kinetics, and chemical labeling experiments, we provide evidence that each FAAH triad residue plays a distinct role in catalysis. In particular, mutation of K142 to alanine indicates that this residue functions as both a base involved in activation of the S241 nucleophile and an acid that participates in the protonation of the substrate leaving group. This latter property appears to support the unusual ability of FAAH to hydrolyze amides and esters at equivalent rates. Interestingly, although structural evidence indicates that the impact of K142 on catalysis likely occurs through the bridging S217, mutation of this latter residue to alanine impaired catalytic activity, but left the amide/ester hydrolysis ratios of FAAH intact. Collectively, these findings suggest that FAAH possesses a specialized active site structure dedicated to a mechanism for competitive amide and ester hydrolysis where nucleophile attack and leaving group protonation occur in a coordinated manner dependent on K142.


Novel aromatic analogues of N-oleoylethanolamine and N-arachidonoylthanolamine (anandamide, AEA) were synthesized and, based on the capability of similar compounds to interact with proteins of the endocannabinoid and endovanilloid signaling systems, were tested on: (i) cannabinoid CB(1) and CB(2) receptors; (ii) vanilloid VR1 receptors; (iii) anandamide cellular uptake (ACU); and (iv) the fatty acid amide hydrolase (FAAH). The (R)- and, particularly, the (S)-1'-4-hydroxybenzyl) derivatives of N-oleoylthanolamine and AEA (OMDM-1, OMDM-2, OMDM-3, and OMDM-4) inhibited to a varied extent ACU in RBL-2H3 cells (K(i) ranging between 2.4 and 17.7&mang;M), the oleoyl analogues (OMDM-1 and OMDM-2, K(i) 2.4 and 3.0&mang;M, respectively) being 6- to 7-fold more potent than the arachidonoyl analogues (OMDM-3 and OMDM-4). These four compounds exhibited: (i) poor affinity for either CB(1) (K(i)>/=5&mang;M) or CB(2) (K(i)>10&mang;M) receptors in rat brain and spleen membranes, respectively; (ii) almost no activity at vanilloid receptors in the intracellular calcium assay carried out with intact cells over-expressing the human VR1 (EC(50)>/=10&mang;M); and (iii) no activity as inhibitors of FAAH in
N18TG2 cell membranes (K(i)>50&mug;M). The oleoyl- and arachidonoyl-N'-4-hydroxy-3-methoxybenzyl)hydrazines (OMDM-5 and OMDM-6), inhibited ACU (K(i) 4.8 and 7.0&mug;M, respectively), and were more potent as VR1 agonists (EC(50) 75 and 50nM, respectively), weakly active as CB(1) receptor ligands (K(i) 4.9 and 3.2&mug;M, respectively), and inactive as CB(2) ligands (K(i)>5&mug;M) as well as on FAAH (K(i)/=40&mug;M). In conclusion, we report two novel potent and selective inhibitors of ACU (OMDM-1 and OMDM-2) and one "hybrid" agonist of CB(1) and VR1 receptors (OMDM-6). Unlike other compounds of the same type, OMDM-1, OMDM-2, and OMDM-6 were very stable to enzymatic hydrolysis by rat brain homogenates.


The effect of the endogenous cannabinoid ligand anandamide on the function of the cloned alpha7-subunit of the chick nicotinic ACh receptor expressed in Xenopus oocytes was investigated by using the two-electrode voltage-clamp technique. Anandamide reversibly inhibited nicotine (10 micro M) induced-currents in a concentration-dependent manner (10 nM to 30 micro M), with an IC50 value of 218 nM. The effect of anandamide was neither dependent on the membrane potential nor mediated by endogenous Ca(2+) dependent Cl(-) channels since it was unaffected by intracellularly injected BAPTA and perfusion with Ca(2+)-free bathing solution containing 2 mM Ba(2+). Anandamide decreased the maximal nicotine-induced responses without significantly affecting its potency, indicating that it acts as a noncompetitive antagonist on nACh alpha7 receptors. This effect was not mediated by CB1 or CB2 receptors, as neither the selective CB1 receptor antagonist SR 141716A nor CB2 receptor antagonist SR 144528 reduced the inhibition by anandamide. In addition, inhibition of nicotinic responses by anandamide was not sensitive to either pertussis toxin treatment or to the membrane permeable cAMP analogue 8-Br-cAMP (0.2 mM). Inhibitors of enzymes involved in anandamide metabolism including phenylmethylsulfonyl fluoride, superoxide dismutase and indomethacin or the anandamide transport inhibitor AM404 did not prevent anandamide inhibition of nicotinic responses, suggesting that anandamide, itself, acted on nicotinic receptors. In conclusion, these results demonstrate that the endogenous cannabinoid anandamide inhibits the function of nACh alpha7 receptors expressed in Xenopus oocytes in a cannabinoid-receptor independent and noncompetitive manner.


Administration of the cannabinoid CB1 receptor antagonist SR141716 (3-10 mg/kg i.p.) abolished neuropeptide Y-induced overeating and significantly reduced ethanol and sucrose intake in CB1 wild-type (+/+) mice. In CB1 receptor knockout (-/-) mice, neuropeptide Y totally lost its capacity to increase food consumption. Similarly, sucrose and ethanol intakes were significantly lower in CB1-/- vs. CB1+/+ mice. In CB1 deficient mice, SR141716 had no effect in these models.


1 The cannabinoid CB(1) receptor inverse agonist/antagonist SR 141716 increases acetylcholine release in rodent hippocampus and improves memory in some experimental paradigms. Since drugs like SR 141716 may represent a novel class of cognition-enhancing drugs, we wanted to check whether the function of the CB(1) receptor is preserved during ageing. 2 Hippocampal and striatal slices from 2- to 3- and 24- to 28-month-old C57BL/6J mice were preincubated with [3H]-choline or [3H]-noradrenaline ([3H]-NA) and superfused. 3 The cannabinoid receptor agonist WIN 55,212-2 inhibited, and SR 141716 facilitated, the electrically (3 Hz) evoked tritium overflow in hippocampal slices (preincubated with [3H]-choline) from young and aged mice to the same extent. The evoked overflow per se was less by 33% in slices from aged animals. 4 WIN 55,212-2 and SR 141716 did not affect, but the muscarinic receptor agonist oxotremorine inhibited, the evoked (3 Hz) overflow in striatal slices (preincubated with [3H]-choline) from young and aged mice to the same extent. The evoked overflow per se tended to be less in slices from aged animals. 5 The evoked (0.3 Hz) overflow in hippocampal slices
(preincubated with [(3)H]-NA) was not affected by WIN 55,212-2 and SR 141716, but was inhibited by histamine (via H(3) receptors) in slices from young mice and, to a somewhat less extent, in slices from aged mice. The evoked overflow per se did not differ between age groups.

In conclusion, the function of the CB(1) receptor involved in the tonic inhibition of hippocampal acetylcholine release is preserved in aged mice. British Journal of Pharmacology (2003) 138, 1425-1430. doi:10.1038/sj.bjp.0705194


Cannabinoid modulation of immune responses is a pathological consequence of marijuana abuse and a potential outcome of therapeutic application of the drug. Moreover, endogenous cannabinoids are physiological immune regulators. In the present report, we describe alterations in gene transcription that occur after cannabinoid exposure in a mast cell line, RBL2H3. Cannabinoid exposure causes marked changes in the transcript levels for numerous genes, acting both independently of and in concert with immunoreceptor stimulation via FcepsilonRI. In two mast cell lines, we observed mRNA and protein expression corresponding to both CB1 and CB2 cannabinoid receptor isoforms, contrary to the prevailing view that CB1 is restricted to the CNS. We show that coexpression of the two isoforms is not functionally redundant in mast cells. Analysis of signaling pathways downstream of cannabinoid application reveals that activation of extracellular signal-regulated kinase, AKT, and a selected subset of AKT targets is accomplished by CB2 ligands and nonselective CB1/CB2 agonists in mast cells. CB1 inhibition does not affect AKT or extracellular signal-regulated kinase activation by cannabinoids, indicating that CB2 is the predominant regulatory receptor for these kinases in this cell context. CB1 receptors are, however, functional in these mast cells, since they can contribute to suppression of secretory responses.


Association of cannabimimetic compounds such as cannabinoids, aminoalkylindoles (AAIs), and arachidonylethanolamide (anandamide) with the brain cannabinoid (CB(1)) receptor activates G-proteins and relays signals to regulate neuronal functions. A CB(1) receptor homology model was constructed using the published x-ray crystal structure of bovine rhodopsin (Palczewski et al., Science,2000, Vol. 289, pp. 739-745) in the conformation most likely to represent the "high-affinity" state for agonist binding to G-protein coupled receptors (GPCRs). A molecular docking approach that combined Monte Carlo and molecular dynamics simulations was used to identify the putative binding conformations of nonclassical cannabinoid agonists, including AC-bicyclic CP47497 and CP55940, and ACD-tricyclic CP55244. Placement of these ligands was based upon the assumption of a critical hydrogen bond between the A-ring OH and the side chain N of Lys192 in transmembrane helix 3. We evaluated two alternative binding conformations, C3-in and C3-out, denoting the directionality of the ligand C3 side chain within the receptor with respect to the inside or the outside of the cell. Assuming both the C3-in or C3-out conformation, the calculated ligand-receptor binding energy (DeltaE(bind)) was correlated with the experimentally observed binding affinity (K(i)) for a series of nonclassical cannabinoid agonists. The C3-in conformation was marginally better than the alternative C3-out conformation in predicting the rank order of the tested nonclassical cannabinoid analogs. Adopting the C3-in conformation due to the greater number of receptor interactions with known pharmacophoric elements of the ligand, key residues were identified comprising the presumed hydrophobic pocket that interacts with the C3 side chain of cannabinoid agonists. Key hydrogen bonds would form between both K3.28(192) and E(258) and the A-ring OH, and between Q(261) and the C-ring C-12 hydroxypropyl. In summary, the present study represents one of the first attempts to construct a homology model of the CB(1) cannabinoid receptor based upon the published bovine rhodopsin x-ray crystal structure and to elucidate the putative ligand binding site for nonclassical cannabinoid agonists. We postulated sites of the CB(1) receptor critical for the ligand interaction, including the hydrophobic pocket interacting with the key pharmacophoric moiety, the C3 side chain. More work is needed to delineate between two alternative (and possibly other) binding conformations of the nonclassical cannabinoid ligands within the CB(1) receptor. The present
study provides a consistent framework for further investigation of the CB(1) receptor-ligand interaction and for the study of CB(1) receptor activation.


Using a well-established songbird model of juvenile vocal development, we have found that daily cannabinoid exposure at modest dosages alters sensory-motor vocal learning. Adult exposure did not change song that had already been learned. Our results demonstrate the potential for cannabinoid exposure to produce distinct effects during post-natal CNS development.


Cannabinoid CB1 receptors have been detected in retinas of numerous species, with prominent labeling in photoreceptor terminals of the chick and monkey. CB1 labeling is well-conserved across species, suggesting that CB1 receptors might also be present in photoreceptors of the tiger salamander. Synaptic transmission in vertebrate photoreceptors is mediated by L-type calcium currents that are modulated by CB1 receptors in bipolar cells of the tiger salamander. Presence of CB1 receptors in photoreceptor terminals would therefore be consistent with presynaptic modulation of synaptic transmission, a role seen for cannabinoids in other parts of the brain. Here we report immunohistochemical and electrophysiological evidence for the presence of functional CB1 receptors in rod and cone photoreceptors of the tiger salamander. The cannabinoid receptor agonist WIN 55212-2 enhances calcium currents of rod photoreceptors by 39% but decreases calcium currents of large single cones by 50%. In addition, WIN 55212-2 suppresses potassium currents of rods and large single cones by 44 and 48%, respectively. Thus functional CB1 receptors, present in the terminals of rod and cone photoreceptors, differentially modulate calcium and potassium currents in rods and large single cones. CB1 receptors are therefore well positioned to modulate neurotransmitter release at the first synapse of the visual system.


Type 1 vanilloid receptors (VR1) have been identified recently in the brain, in which they serve as yet primarily undefined purposes. The endocannabinoid anandamide (AEA) and some of its oxidative metabolites are ligands for VR1, and AEA has been shown to afford protection against ouabain-induced in vivo excitotoxicity, in a manner that is only in part dependent on the type 1 cannabinoid (CB1) receptor. In the present study, we assessed whether VR1 is involved in neuroprotection by AEA and by arvanil, a hydrolysis-stable AEA analog that is a ligand for both VR1 and CB1. Furthermore, we assessed the putative involvement of lipoxigenase metabolites of AEA in conveying neuroprotection. Using HPLC and gas chromatography/mass spectroscopy, we demonstrated that rat brain and blood cells converted AEA into 12-hydroxy-N-arachidoyl ethanolamine (12-HAEA) and 15-hydroxy-N-arachidonoylethanolamine (15-HAEA) and that this conversion was blocked by addition of the lipoxigenase inhibitor nordihydroguaiaretic acid. Using magnetic resonance imaging we show the following: (1) pretreatment with the reduced 12-lipoxigenase metabolite of AEA, 12-HAEA, attenuated cytotoxic edema formation in a CB1 receptor-independent manner in the acute phase after intracranial injection of the Na+/K+-ATPase inhibitor ouabain; (2) the reduced 15-lipoxigenase metabolite, 15-HAEA, enhanced the neuroprotective effect of AEA in the acute phase; (3) modulation of VR1, as tested using arvanil, the VR1 agonist capsaicin, and the antagonist capsazepine, leads to neuroprotective effects in this model, and arvanil is a potent neuroprotectant, acting at both CB1 and VR1; and (4) the in vivo neuroprotective effects of AEA are mediated by CB1 but not by lipoxigenase metabolites or VR1.

CB(1) cannabinoid receptor agonists show a different profile compared to other drugs of abuse on the basis of experimental data that reveal their reinforcing properties. Thus, there are controversial data in the literature concerning the ability of CB(1) receptor agonists to reinforce behavioral responses in experimental animals, i.e. to lower self-stimulation thresholds, and to support self-administration or conditioned place preference. The aim of the present study was to examine the effects of WIN 55,212-2, a potent CB(1) receptor agonist (graded doses 0.1, 0.3, 1mg/kg, i.p.), on the rewarding efficacy of lateral hypothalamic self-stimulation and on the systemic cocaine-induced potentiation of brain-stimulation reward. WIN 55,212-2 did not affect lateral hypothalamic self-stimulation thresholds both in drug naïve rats and in rats pretreated with the drug, whereas it produced a significant, dose-dependent decrease in the maximal rate of responding, i.e. in the performance of the animals. Cocaine (5.0mg/kg, i.p.) produced a significant reduction in self-stimulation threshold, without altering maximal rates of responding. Importantly, WIN 55,212-2 attenuated the effect of cocaine at the two higher doses tested. The effects of the CB(1) receptor agonist were reversed by pretreatment with the selective CB(1) receptor antagonist SR 141716A (0.02mg/kg, i.p.) that did not by itself affect cocaine's action. These results indicate that acute stimulation of CB(1) receptors per se does not affect baseline self-stimulation, but reduces the reinforcing effects induced by cocaine. Taken together these findings suggest that cannabinoids may interfere with brain-reward systems responsible for the expression of acute reinforcing properties of drugs of abuse, such as cocaine, and provide evidence that the cannabinoid system could be an interesting drug discovery and development target for the treatment of drug addiction.


1 To study the long-term effects of altered cannabinoid receptor activity on myocardial and vascular function, Wistar rats were treated with the selective CB(1) antagonist AM-251 (0.5 mg kg(-1) d(-1)), the potent synthetic cannabinoid HU-210 (50 micro g kg(-1) d(-1)) or vehicle for 12 weeks after coronary artery ligation or sham operation. 2 AM-251 further reduced the pressure-generating capacity, shifted the pressure volume curve to the right (P<0.05) and increased the left-ventricular operating volume (AM-251: 930+/−40 micro l vs control: 820+/−40 micro l; P<0.05) in rats with large myocardial infarction (MI). 3 Left-ventricular CB(1) immunoactivity in rats 12 weeks after large MI was unaltered as compared with noninfarcted hearts. 4 Cannabinoid receptor activation through HU-210, a cannabinoid that alters cardiovascular parameters via CB(1) receptors, increased the left-ventricular end-diastolic pressure (LVEDP, P<0.05). However, it prevented the drop in left-ventricular systolic pressure (HU-210: 142+/−5 mm Hg; P<0.05 vs control: 124+/−3 mm Hg; and P<0.001 vs AM-251: 114+/−3 mm Hg) and prevented endothelial dysfunction (ED) in aortic rings of rats with large MI (P<0.05). 5 Compared with AM-251, HU-210 prevented the decline in the maximal rate of rise of left-ventricular pressure and the maximum pressure-generating ability (P<0.05). In rats with small MI, HU-210 increased cardiac index (P<0.01) and lowered the total peripheral resistance (P<0.05). 6 The study shows that during the development of congestive heart failure post-large MI, cannabinoid treatment increases LVEDP and prevents hypotension and ED. Presumed CB(1) antagonism promotes remodeling despite unchanged myocardial CB(1) expression. British Journal of Pharmacology (2003) 138, 1251-1258. doi:10.1038/sj.bjp.0705156


Demyelinating diseases can be associated with painful sensory phenomena such as tactile allodynia and hyperalgesia. To study the mechanisms underlying demyelination-induced pain, we have characterized a novel model of demyelination of the sciatic or saphenous nerve. Topical lysolecithin application causes focal demyelination of afferent nerve A-fibers without axonal loss, as assessed either by electron and light microscopy or by immunohistochemical analysis of dorsal root ganglia (DRG) for a neuronal injury marker, activating transcription factor 3. Focal demyelination is accompanied by spontaneous action potentials in afferents and
increased expression of neuropeptide Y and Na(v)1.3 sodium channels specifically in DRG neurons that coexpress a specific marker of myelinated afferents. In contrast, expression of tetrodotoxin-resistant, Na(v)1.8 sodium channels is specifically decreased in the same subgroup of DRG cells. Central sensitization of somatosensory processing is also induced, with increased behavioral reflex responsiveness to thermal and mechanical stimuli. These changes are reversed by intrathecal administration of an NMDA receptor antagonist or cannabinoïd (CB) receptor agonist, but not by a mu-opiod receptor agonist. Recovery of behavioral reflexes occurred approximately 3 weeks after lysolecithin treatment. This is the first time that demyelination of afferent A-fibers has been shown to specifically induce neuropathic pain and indicates that axonal damage is not a prerequisite for development of the pain state. The profile of phenotypic changes in DRG is distinct from other pain models and displays a sensitivity to NMDA and CB receptor agents that may be exploitable therapeutically.


The cannabinoïd receptor one (CB1) is responsible for the effects of cannabis on motor and cognitive function in the CNS. There is to date very limited information about the CB1 gene expression in the human brain, in particular during fetal development. In the present study, in situ hybridization experiments were used to examine the microscopic and macroscopic organization of the CB1 mRNA expression in normal human fetal (approximately 20 weeks of development) and adult brains. The fetal brain showed a distinct heterogeneous pattern of the CB1 mRNA expression which was low to moderate in many brain areas. The most striking feature of the fetal brain was the intense expression in the hippocampal CA region and basal nuclear group of the amygdaloid complex. Many of the same brain areas that showed positive expression of the CB1 mRNA in the fetal brain also expressed the gene in the adult brain. However, aside from an intense expression in the hippocampus which resembled that in fetal brain, the adult brain showed very high expression throughout the cerebral cortex, caudate nucleus, putamen and cerebellar cortex. These results document a different pattern of the anatomical organization of the CB1 mRNA expression in the mid-gestation fetal and adult human brain. Overall, the high CB1 mRNA expression in the fetal hippocampus and amygdala indicates that these limbic structures might be most vulnerable to prenatal cannabis exposure.


Anandamide (AEA), an endogenous cannabinoïd, is generated by macrophages during shock conditions, and is thought to be a causative mediator of septic shock. Thus, we hypothesized that AEA plays a crucial role in endothelial cell (EC) injury. Here, we demonstrate that AEA induces apoptosis in a time-and dose-dependent manner in human umbilical vein endothelial cells (HUVECs). AEA triggered phosphorylation of c-Jun NH(2)-terminal kinase (JNK) and p38 mitogen activated protein kinase. AEA also showed a marked increase of interleukin 1beta- converting enzyme (ICE)CED-3 family protease (caspase-3) activity. AEA-induced EC death was inhibited by a selective vanilloid receptor 1 (VR1) antagonist, capsazepine, and was enhanced by a VR1 agonist, capsaicin, indicating that AEA induces apoptosis in ECs via VR1. In conclusion, we propose that AEA may play a crucial role in EC injury under conditions of shock, and that the use of inhibitors of the AEA regulation system may have a therapeutic effect under these conditions.

**CLINICAL SCIENCE**


Subjects with a history of chronic marijuana use were screened for cannabinoïd metabolites in urine specimens with the EMIT((R)) II Plus cannabinoid assay with a cut-off value of 50ng/ml. All presumptively positive specimens were submitted for confirmatory analysis for the major urinary cannabinoïd metabolite (Delta(9)-THC-COOH) by GC-MS with a cut-off value of 15ng/ml.
Creatinine was analyzed in each specimen as an index of dilution. Huestis and Cone [J. Anal. Toxicol. 22 (1998) 445] reported that serial monitoring of Delta(9)-THC-COOH to creatinine ratios in paired urine specimens collected at least 24h apart could differentiate new drug use from residual Delta(9)-THC-COOH excretion. The best accuracy (85.4%) for predicting new marijuana use was a Delta(9)-THC-COOH/creatinine ratio $\geq 0.5$ (dividing the Delta(9)-THC-COOH to creatinine ratio of specimen 2 by the specimen 1 ratio). In a previous study in this laboratory [J. Anal. Toxicol. 23 (1999) 531], urine specimens were collected from chronic marijuana users at least 24h apart and dilute urine specimens (creatinine values $<2.2\mu g/mol/l$) were excluded from the data analysis. The objective of the present study was to determine whether creatinine corrected urine specimens positive for cannabinoids could differentiate new marijuana use from the excretion of residual Delta(9)-THC-COOH in chronic users of marijuana based on the Huestis 0.5 ratio. Urine specimens (N=946) were collected from 37 individuals with at least 48h between collections. All urine specimens were included in the data review irrespective of creatinine concentration. The mean urinary Delta(9)-THC-COOH concentration was 302.4ng/ml, mean Delta(9)-THC-COOH/creatinine ratio (ng/ml Delta(9)-THC-COOH/(mmol/l) creatinine) was 29.3 and the Huestis ratio calculation indicated new drug use in 83% of all sequentially paired urine specimens. The data were sub-divided into three groups (A-C) based on the mean Delta(9)-THC-COOH/creatinine values. Interindividual Delta(9)-THC-COOH/creatinine mean values ranged from 2.2 to 13.8 in group A (264 specimens, N=15 subjects) where 80.7% of paired specimens indicated new drug use. In group B, mean Delta(9)-THC-COOH/creatinine values ranged from 15.3 to 37.8 in 444 specimens (N=14 subjects) and 83.3% of paired specimens indicated new drug use. In group C, individual mean Delta(9)-THC-COOH/creatinine values were $>40.1$ (41.3-132.5) in 238 urine specimens (N=8 subjects) and 85.3% of paired specimens indicated new marijuana use. Correcting Delta(9)-THC-COOH excretion for urinary dilution and comparing Delta(9)-THC-COOH/creatinine concentration ratios of sequentially paired specimens (collected at least 48h apart) provided an objective indicator of new marijuana use in this population.


The active compound in herbal cannabis, Delta(9)-tetrahydrocannabinol, exerts all of its known central effects through the CB(1) cannabinoid receptor. Research on cannabinoid mechanisms has been facilitated by the availability of selective antagonists acting at CB(1) receptors and the generation of CB(1) receptor knockout mice. Particularly important classes of neurons that express high levels of CB(1) receptors are GABAergic interneurons in hippocampus, amygdala and cerebral cortex, which also contain the neuropeptides cholecystokinin. Activation of CB(1) receptors leads to inhibition of the release of amino acid and monoamine neurotransmitters. The lipid derivatives anandamide and 2-arachidonylglycerol act as endogenous ligands for CB(1) receptors (endocannabinoids). They may act as retrograde synaptic mediators of the phenomena of depolarization-induced suppression of inhibition or excitation in hippocampus and cerebellum. Central effects of cannabinoids include disruption of psychomotor behaviour, short-term memory impairment, intoxication, stimulation of appetite, antinociceptive actions (particularly against pain of neuropathic origin) and anti-emetic effects. Although there are signs of mild cognitive impairment in chronic cannabis users there is little evidence that such impairments are irreversible, or that they are accompanied by drug-induced neuropathology. A proportion of regular users of cannabis develop tolerance and dependence on the drug. Some studies have linked chronic use of cannabis with an increased risk of psychiatric illness, but there is little evidence for any causal link. The potential medical applications of cannabis in the treatment of painful muscle spasms and other symptoms of multiple sclerosis are currently being tested in clinical trials. Medicines based on drugs that enhance the function of endocannabinoids may offer novel therapeutic approaches in the future.

This study tested whether performance would be more impaired when marijuana use followed partial sleep deprivation (PSD) than when marijuana use followed a typical night of sleep. Seven recreational marijuana users (mean 15 of last 30 days) completed six test sessions in a double-blind randomized within-subject design. Each session began with an overnight stay in a sleep laboratory. Bed and wake times were calculated from mean data on individual sleep diaries. Time-in-bed was either regular (mean=8.2 h) or shortened (first 65% of regular time-in-bed deprived). At 3 and 5 h after waking, daytime sleepiness was measured with self-report questionnaires and a sleep latency test. Approximately 6.5 h after waking, subjects smoked a marijuana cigarette (0.003, 2, or 3.5% delta-9 tetrahydrocannabinol [THC]). Test batteries were completed 2, 62, and 122 min after smoking ended. Sleepiness was significantly greater following PSD than after regular sleep. Following regular sleep, heart rate increases with active THC doses were comparable, but heart rate with 2% THC was significantly less elevated following PSD. Ratings of 'impaired' and 'stoned' increased with both THC doses after regular sleep and were further increased with 3.5% THC after PSD. High-potency marijuana increased body sway similarly across sleep conditions. There were no significant effects of marijuana or PSD, alone or in combination, on brake latency. Thus, while PSD increased the dose-dependence of THC effects on heart rate and subjective impairment, it did not enhance the effects of marijuana on standing balance and brake latency.


**BACKGROUND:** Preliminary studies suggested that delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient of Cannabis sativa L., might be effective in the treatment of Tourette syndrome (TS). This study was performed to investigate for the first time under controlled conditions, over a longer-term treatment period, whether THC is effective and safe in reducing tics in TS. **METHOD:** In this randomized, double-blind, placebo-controlled study, 24 patients with TS, according to DSM-III-R criteria, were treated over a 6-week period with up to 10 mg/day of THC. Tics were rated at 6 visits (visit 1, baseline; visits 2-4, during treatment period; visits 5-6, after withdrawal of medication) using the Tourette Syndrome Clinical Global Impressions scale (TS-CGI), the Shapiro Tourette-Syndrome Severity Scale (STSSS), the Yale Global Tic Severity Scale (YGTSS), the self-rated Tourette Syndrome Symptom List (TSSL), and a videotape-based rating scale. **RESULTS:** Seven patients dropped out of the study or had to be excluded, but only 1 due to side effects. Using the TS-CGI, STSSS, YGTSS, and video rating scale, we found a significant difference (p <.05) or a trend toward a significant difference (p <.10) between THC and placebo groups at visits 2, 3, and/or 4. Using the TSSL at 10 treatment days (between days 16 and 41) there was a significant difference (p <.05) between both groups. ANOVA as well demonstrated a significant difference (p =.037). No serious adverse effects occurred. **CONCLUSION:** Our results provide more evidence that THC is effective and safe in the treatment of tics. It, therefore, can be hypothesized that the central cannabinoid receptor system might play a role in TS pathology.

**BEHAVIOURAL SCIENCE**


Cannabis, more often than alcohol, is the drug mentioned in substance-related reasons for treatment of an adolescent in an emergency department (ED). This study examined the prevalence of DSM-IV cannabis and alcohol diagnoses in an adolescent ED sample, evaluated the performance (i.e. sensitivity and specificity) of DSM-IV cannabis symptoms and other screening items as indicators of cannabis diagnosis status, and examined parent-adolescent agreement on the presence of cannabis and alcohol diagnoses. Adolescents (ages 13-19, n=442) admitted to an ED for a non-substance-related injury were administered the diagnostic interview schedule for children (DISC). Parents (n=272) of adolescents younger than age 18 completed the
DISC-parent version to report on their child's drug use. A minority met criteria for a current DSM-IV cannabis or alcohol diagnosis: 7.9% for both alcohol and cannabis, 7.5% for cannabis-only, and 9.0% for alcohol-only. Frequency of cannabis use had the best overall performance in discriminating those with and without a cannabis diagnosis compared with items on perceived risk of cannabis use, peer cannabis use, and alcohol and cigarette use. Parent reports generally underestimated the adolescent's substance use. Questions on level of substance use generally provide an efficient method of screening adolescents for substance-related problems in an ED setting.


A collaborative case-control study was conducted in France in order to determine the prevalence of alcohol, cannabinoids, opiates, cocaine metabolites, amphetamines and therapeutic psychoactive drugs in blood samples from drivers injured in road accidents and to compare these values with those of a control population. Recruitment was performed in emergency departments of six university or general hospitals and comprised 900 drivers involved in a non-fatal accident and 900 patients (controls) who attended the same emergency units for a non-traumatic reason. Drivers and controls were matched by sex and age. Alcohol was determined by flame ionization-gas chromatography, drugs of abuse (DOA) by gas chromatography-mass spectrometry with the same analytical procedures in the six laboratories, and medicines by high performance liquid chromatography with diode array detection. Blood alcohol concentration exceeding 0.5g/l (i.e. the legal French threshold) was found in 26% of drivers and 9% of controls. In the 18-27 years age range, alcohol was the only toxic found in blood samples of 17% drivers and 5% controls, leading to an odds-ratio (OR) of 3.8. A significant relationship was found between alcohol blood concentrations and OR values. All age groups confounded, the main active substance of cannabis, Delta(9) tetrahydrocannabinol (THC), was found in 10% of drivers and 5% of controls. In the less than 27 years old, THC (>1ng/ml) was detected alone in the blood of 15.3% drivers and of 6.7% controls, giving OR=2.5, whereas there was no link between THC blood concentrations and OR value. THC was found alone in 60% of cases and associated with alcohol in 32%, with OR=4.6 between drivers and controls for this association. The difference in morphine prevalence between drivers (2.7%) and controls (0.03%) was highly significant (P<0.001), with OR=8.2. The number of positive cases for amphetamines and cocaine metabolites was too low for reaching any interpretation. The most frequently observed psychoactive therapeutic drugs were by far benzodiazepines, that were found alone in 9.4% of drivers and 5.8% of controls, which led to OR=1.7 (P<0.01). This study demonstrates a higher prevalence of opiates, alcohol, cannabinoids and the combination of these last two compounds in blood samples from drivers involved in road accidents than in those from controls, which suggests a causal role for these compounds in road crashes.


We present a series of 12 cases of violent crime, which were all committed under the influence of cannabis in Geneva, Switzerland, between 1996 and 2000. The crimes were committed by eleven males and one female, with a mean age of 26 years, who were using only cannabis at the time they acted. Most of them were chronic users. Five subjects had a past psychiatric history. Five had a personality disorder. Only three had been sentenced in the past for violent acts. At the time of the aggression, all of them exhibited adverse and acute effects of cannabis. All of them were judged by the court to be partially or totally non-responsible. Three cases are presented in more detail. Our data suggests that cannabis could have a specific role in the development of violent behaviour patterns and that detection of its adverse effects should be systematic in criminal responsibility evaluation.


BACKGROUND Reports from clinical and experimental (animal) research converge on the suggestion that prenatal exposure to alcohol, cocaine, or marijuana undermines executive
functioning (EF) and its neurological underpinnings. However, large, adequately controlled, prospective studies of alcohol and marijuana effects on EF have reported conflicting findings, and there have been no such studies of cocaine exposure.METHODSEF was investigated in a cohort (n = 316) of 4-year-old children the majority of whose mothers had used varying combinations of cocaine, alcohol, and marijuana during pregnancy. With use of postpartum maternal report and biological assay, children were assigned to overlapping prenatal cocaine-exposed, alcohol-exposed, and marijuana-exposed groups and to complementary control groups. The postnatal environmental assessment included measures of maternal intellectual and psychosocial functioning, current drug or alcohol use, and home environment.RESULTSThe children in the alcohol-exposed group had worse tapping-inhibition performance than children in the non-alcohol-exposed group, and this effect persisted when potential confounding environmental variables, other drug variables, and concurrent verbal intelligence were controlled for.CONCLUSIONSPrenatal alcohol is predictive of decreased EF in early childhood that could not be attributed to environmental factors. The results are discussed in terms of the age and overall high-risk status of the children.


The study's objective was to investigate in a non-clinical population the association between cannabis use and anxiety in daily life using the Experience Sampling Method (ESM). Seventy-nine subjects with high or low levels of cannabis use were selected among a sample of 685 undergraduate university students. ESM was used to collect information on cannabis use and state-anxiety in daily life. DSM-IV diagnoses were assessed using a structured clinical interview. Statistical analyses were performed using multilevel linear random regression models. There was no significant association between the level of state anxiety and cannabis use in daily life. However, a diagnosis of agoraphobia was significantly associated with increased likelihood of cannabis use, independent of state anxiety and other confounding factors. No evidence was found for an anxiolytic or anxiogenic effect of cannabis in daily life. This finding does not support the hypothesis that subjects with high levels of anxiety use cannabis as a means of self-medication. The association between agoraphobia and cannabis use in daily life may be explained by anticipatory anxiety secondary to previous cannabis-induced panic-like symptoms.

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