INTRODUCTION

Here is the latest summary of research abstracts. Readers are reminded of the IACM meeting in Oxford, UK on September 10-11, 2004 (http://www.cannabis-med.org/english/nav/home-conference.htm); abstracts are due by June 15th.

BASIC SCIENCE


The cannabinoid-1 (CB1) receptor plays a role in the regulation of appetitive behavior. Exogenously administered cannabinoid receptor agonists stimulate food consumption in animals and humans. Endogenous cannabinoid receptor agonists are present in the brain, and the brain level of these agonists increases with greater demand of food by rodents. Specific CB1 receptor antagonist compounds have been discovered that display high affinity and selectivity for the CB1 receptor. CB1 receptor antagonists inhibit both acute and long-term food intake in rodents. Chronic treatment with CB1 antagonists results in a sustained reduction in body weight in rodents (5 weeks), and weight loss in humans (16 weeks). Patent literature indicates CB1 receptor antagonist discovery efforts at a number of pharmaceutical companies. The CB1 receptor antagonist, rimonabant (SR-141716), discovered by Sanofi-Synthelabo, is in phase III clinical trials for the treatment of obesity and has been found to decrease appetite and body weight in humans.


Dopaminergic neurotransmission has been highly implicated in the reinforcing properties of many substances of abuse, including marijuana. Cannabinoids activate ventral tegmental area dopaminergic neurons, the main ascending projections of the mesocorticolimbic dopamine system, and change their spiking pattern by increasing the number of impulses in a burst and elevating the frequency of bursts. Although they also increase time-averaged striatal dopamine levels for extended periods of time, little is known about the temporal structure of this change. To elucidate this, fast-scan cyclic voltammetry was used to monitor extracellular dopamine in the nucleus accumbens of freely moving rats with subsecond timescale resolution. Intravenous administration of the central cannabinoid (CB1) receptor agonist, R(+)-[2,3-dihydro-5-methyl-3-[(morpholiny)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-[1-naphthalenyl]methanone mesylate, dose-dependently produced catalepsy, decreased locomotion, and reduced the amplitude of electrically evoked dopamine release while markedly increasing the frequency of detected (nonstimulated) dopamine concentration transients. The CB1 receptor antagonist [N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide] reversed and prevented all agonist-induced effects but did not show effects on dopamine release when injected alone. These data demonstrate that doses of a cannabinoid agonist known to increase burst firing produce ongoing fluctuations in extracellular dopamine on a previously unrecognized temporal scale in the nucleus accumbens.

3-[2-Cyano-3-(trifluoromethyl)phenoxy]phenyl-4,4,4-trifluoro-1-butanesulfonate (BAY 59-3074) is a novel, selective cannabinoid CB1/CB2 receptor ligand (Ki = 55.4, 48.3 and 45.5 nM, at rat and human cannabinoid CB1, and human CB2 receptors, respectively), with partial agonist properties at these receptors in [(35)S]GTPgammaS binding assays. In rats, generalization of BAY 59-3074 to the cue induced by the cannabinoid CB1 receptor agonist (-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl-4,4,4-trifluoro-1-butanesulfonate (BAY 38-7271) in a drug discrimination procedure, as well as its hypothermic and analgesic effects in a hot plate assay, were blocked by the cannabinoid CB1 receptor antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR 141716A). BAY 59-3074 (0.3-3 mg/kg, p.o.) induced antihyperalgesic and anti-allodynic effects against thermal or mechanical stimuli in rat models of chronic neuropathic (chronic constriction injury, spared nerve injury, tibial nerve injury, and spinal nerve ligation models), and inflammatory pain (carrageenan and complete Freund's adjuvant models). Anti-allodynic efficacy of BAY 59-3074 (1 mg/kg, p.o.) in the spared nerve injury model was maintained after two weeks of daily administration. However, tolerance developed rapidly (within 5 days) for cannabinoid-related side-effects which occur at doses above 1 mg/kg (e.g., hypothermia). Uptitration from 1 to 32 mg/kg, p.o. (doubling of daily dose each 4(th) day) prevented the occurrence of such side-effects, whereas antihyperalgesic and anti-allodynic efficacy was maintained/increased. No withdrawal symptoms were seen after abrupt withdrawal following 14 daily applications of 1-10 mg/kg, p.o. It is concluded that BAY 59-3074 may offer a valuable therapeutic approach to treat diverse chronic pain conditions.


Noladin ether has recently been reported to be an endocannabinoid, with selectivity for the cannabinoid (CB) CB1 receptor. In the present study, we investigated the effects of noladin ether in the rat isolated mesenteric arterial bed, cultured dorsal root ganglia (DRG) cells and human vanilloid (TRPV1)-receptor-expressing HEK293 cells (TRPV1-HEK293 cells). Electrical field stimulation of the mesenteric bed evoked frequency-dependent vasorelaxation due to the action of calcitonin gene-related peptide (CGRP) released from sensory nerves. Noladin ether (0.1-3 micro M) attenuated sensory neurogenic relaxation in a concentration-dependent manner. Noladin ether (1 micro M) reduced vasorelaxation at a submaximal frequency (8 Hz), from 57.3+-6.8 to 23.3+-3.8% (P<0.05, n=4). The inhibitory effects of noladin ether were unaffected by the CB1 antagonists SR141716A and LY320135, and the CB2 antagonist SR144528 (1 micro M). Noladin ether had no effect on vasorelaxation elicited by exogenous CGRP or capsaicin. These data suggest that noladin ether is acting at a presynaptic site and no interaction with TRPV1 is involved. In mesenteric beds from pertussis toxin (PTX)-pretreated rats, the inhibitory actions of noladin ether on sensory neurotransmission were abolished, indicating the involvement of Gi/o protein-coupled receptors. Noladin ether evoked a concentration-dependent increase in intracellular Ca(2+) concentration in TRPV1-HEK293 cells at 10 micro M (36.5+-3.2% of maximal capsaicin-induced response), but it was a less potent agonist than both capsaicin and anandamide and at 1 micro M it was essentially inactive. Noladin ether (1 micro M) had no effect on capsaicin-evoked Ca(2+) responses in DRG cells, and produced no response alone, indicating it neither modulates nor acts directly on TRPV1 receptors.7 These data demonstrate that noladin ether attenuates sensory neurotransmission in rat mesenteric arteries via a non-CB1 non-CB2 PTX-sensitive presynaptic site, independently of TRPV1 receptors.


Dopamine is a light-adaptive signal that desensitizes the retina, while cannabinoids reportedly increase photosensitivity. The presynaptic membrane of goldfish retinal cones has
dopamine D2 receptors and cannabinoid CB1 receptors. This work focused on whether dopamine D2 receptor agonist quinpirole and cannabinoid CB1 receptor agonist WIN 55212-2 (WIN) interacted to modulate voltage-dependent membrane currents of cones. A conventional patch-clamp method was used to record depolarization evoked whole-cell outward currents (Iout) and an inward calcium current (ICa) from the inner segment of cones in goldfish retinal slices. WIN had biphasic actions: low concentrations (<1 microM) increased the currents via Gs, while higher concentrations (>1 microM) decreased the currents via Gi/Go. Neither dopamine nor the D2 agonist quinpirole (1-20 microM) had a significant effect on either Iout or ICa. Quinpirole at 50 microM had a mild suppressive (approximately 20%) effect on Iout. However, quinpirole (<10 microM) completely blocked the enhancement of both currents seen with 0.7 microM WIN. The effect of quinpirole was blocked by sulpiride and by pertussis toxin, indicating that quinpirole was acting via a D2 receptor-Gi/o coupled mechanism. The suppressive action of 50 microM quinpirole (approximately 20%) was not additive with the suppressive effect of 3 microM WIN (approximately 40%). D2 agonists via Gi/o oppose the action of low concentrations of CB1 agonists acting via Gs to modulate cone membrane currents, suggesting a role in shaping the cone light response and/or sensitivity to changes in ambient light conditions. The nonadditive effect of high concentrations of WIN and quinpirole suggests that both decrease membrane currents via the same transduction pathway, Gi/Go protein kinase A (PKA).

Fegley, D., S. Kathuria, et al. (2004). "Anandamide transport is independent of fatty-acid amide hydrolase activity and is blocked by the hydrolysis-resistant inhibitor AM1172." Proc Natl Acad Sci U S A.

The endogenous cannabinoid anandamide is removed from the synaptic space by a high-affinity transport system present in neurons and astrocytes, which is inhibited by N-(4-hydroxyphenyl)-arachidonamide (AM404). After internalization, anandamide is hydrolyzed by fatty-acid amide hydrolase (FAAH), an intracellular membrane-bound enzyme that also cleaves AM404. Based on kinetic evidence, it has recently been suggested that anandamide internalization may be mediated by passive diffusion driven by FAAH activity. To test this possibility, in the present study, we have investigated anandamide internalization in wild-type and FAAH-deficient (FAAH(-/-)) mice. Cortical neurons from either mouse strain internalized [(3)H]anandamide through a similar mechanism, i.e., via a rapid temperature-sensitive and saturable process, which was blocked by AM404. Moreover, systemic administration of AM404 to either wild-type or FAAH(-/-) mice enhanced the hypothermic effects of exogenous anandamide, a response that was prevented by the CB1 cannabinoid antagonist rimonabant (SR141716A). The results indicate that anandamide internalization in mouse brain neurons is independent of FAAH activity. In further support of this conclusion, the compound N-(5Z, 8Z, 11Z, 14Z eicosatetraenyl)-4-hydroxybenzamide (AM1172) blocked [(3)H]anandamide internalization in rodent cortical neurons and human astrocytoma cells without acting as a FAAH substrate or inhibitor. AM1172 may serve as a prototype for novel anandamide transport inhibitors with increased metabolic stability.


Endogenous cannabinoids (endocannabinoids) and their cannabinoid CB1 and CB2 receptors, are present from the early stages of gestation and play a number of vital roles for the developing organism. Although most of these data are collected from animal studies, a role for cannabinoid receptors in the developing human brain has been suggested, based on the detection of "atypically" distributed CB1 receptors in several neural pathways of the fetal brain. In addition, a role for the endocannabinoid system for the human infant is likely, since the endocannabinoid 2-arachidonoyl glycerol has been detected in human milk. Animal research indicates that the Endocannabinoid-CB1 Receptor ('ECBR') system fulfills a number of roles in the developing organism: 1. embryonal implantation (requires a temporary and localized reduction in anandamide); 2. in neural development (by the transient presence of CB1 receptors in white matter areas of the nervous system); 3. as a neuroprotectant (anandamide protects the developing brain from trauma-induced neuronal loss); 4. in the initiation of suckling in the newborn (where activation of the CB1 receptors in the neonatal brain is critical for survival). 5. In
addition, subtle but definite deficiencies have been described in memory, motor and addictive behaviors and in higher cognitive ("executive") function in the human offspring as result of prenatal exposure to marihuana. Therefore, the endocannabinoid-CB1 receptor system may play a role in the development of structures which control these functions, including the nigrostriatal pathway and the prefrontal cortex. From the multitude of roles of the endocannabinoids and their receptors in the developing organism, there are two distinct stages of development, during which proper functioning of the endocannabinoid system seems to be critical for survival: embryonal implantation and neonatal milk sucking. We propose that a dysfunctional Endocannabinoid-CB1 Receptor system in infants with growth failure resulting from an inability to ingest food, may resolve the enigma of "non-organic failure-to-thrive" (NOFTT). Developmental observations suggest further that CB1 receptors develop only gradually during the postnatal period, which correlates with an insensitivity to the psychoactive effects of cannabinoid treatment in the young organism. Therefore, it is suggested that children may respond positively to medicinal applications of cannabinoids without undesirable central effects. Excellent clinical results have previously been reported in pediatric oncology and in case studies of children with severe neurological disease or brain trauma. We suggest cannabinoid treatment for children or young adults with cystic fibrosis in order to achieve an improvement of their health condition including improved food intake and reduced inflammatory exacerbations.


The recent explosion of knowledge on cannabinoid (CB1 and CB2) receptors and their endogenous ligands, impact on virtually all areas of biomedicine, including neuroendocrinology, immunology and reproductive medicine. In recognition of these developments, the NEL editorship has graciously initiated the idea to devote a special section to the Endocannabinoid-CB-Receptor (ECBR) system. The compilation of papers, which make up this special edition of NEL, reflects the astonishing, almost all-encompassing involvement of the ECBR system in health and disease, from early development throughout adulthood. First, Franjo Grotenhermen reviews the basic and clinical pharmacology of cannabinoids. Developmental aspects, covering the early embryonal period through postnatal development, and including fertility, nutritional and neuroprotective issues, are discussed in the second paper. Ethan Russo discusses the available literature on the medicinal usefulness of cannabis-based medicine for migraine, fibromyalgia and irritable bowel syndrome. Dr. Russo also considers a putative "endocannabinoid deficiency" as the biological basis for these and related disorders. Ruediger Lorenz describes the outcome of a unique clinical study, in which he prescribed delta-9 Tetrahydrocannabinol (THC), the major psychoactive component of the cannabis plant, to eight children/adolescents suffering from a variety of neurological/neuropsychiatric conditions. Lastly, Gauter, Rukwied and Konrad report on a clinical case, in which for the first time, and successfully, THC (dronabinol) was given to a patient suffering from severe, painful blepharospasm. It is our hope that the current collection of articles will inspire clinicians and scientists alike, to actively participate in the exciting world of cannabis research and cannabis-based therapeutics.


Abstract The cholinergic system in the CNS plays important roles in higher brain functions, primarily through muscarinic acetylcholine receptors. At cellular levels, muscarinic activation produces various effects including modulation of synaptic transmission. Here we report that muscarinic activation suppresses hippocampal inhibitory transmission through two distinct mechanisms, namely a cannabinoid-dependent and cannabinoid-independent mechanism. We made paired whole-cell recordings from cultured hippocampal neurons of rats and mice, and monitored inhibitory postsynaptic currents (IPSCs). When cannabinoid receptor type 1 (CB1) was blocked, oxotremorine M (oxo-M), a muscarinic agonist, suppressed IPSCs in a subset of neuron pairs. This suppression was associated with an increase in paired-pulse ratio, blocked by the M(2)-preferring antagonist gallamine, and was totally absent in neuron pairs from M(2)-knockout mice. When CB1 receptors were not blocked, oxo-M suppressed IPSCs in a gallamine-resistant manner in cannabinoid-sensitive pairs. This suppression was associated with an increase in
paired-pulse ratio, blocked by the CB1 antagonist AM281, and was completely eliminated in neuron pairs from M(1)/M(3)-compound-knockout mice. Our immunohistochemical examination showed that M(2) and CB1 receptors were present at inhibitory presynaptic terminals of mostly different origins. These results indicate that two distinct mechanisms mediate the muscarinic suppression. In a subset of synapses, activation of M(2) receptors at presynaptic terminals suppresses GABA release directly. In contrast, in a different subset of synapses, activation of M(1)/M(3) receptors causes endocannabinoid production and subsequent suppression of GABA release by activating presynaptic CB1 receptors. Thus, the muscarinic system can influence hippocampal functions by controlling different subsets of inhibitory synapses through the two distinct mechanisms.


Our study was undertaken to investigate whether bacterial endotoxin/lipopolysaccharide (LPS) affects the neurogenic vasopressor response in rats in vivo by presynaptic mechanisms and, if so, to characterize the type of presynaptic receptor(s) operating in the initial phase of septic shock. In pithed and vagotomized rats treated with pancuronium, electrical stimulation (ES) (1 Hz, 1 ms, 50 V for 10 s) of the preganglionic sympathetic nerve fibers or intravenous bolus injection of noradrenaline (NA) (1-3 nmol kg(-1)) increased the diastolic blood pressure (DBP) by about 30 mmHg. Administration of LPS (0.4 and 4 mg kg(-1)) under continuous infusion of vasopressin inhibited the neurogenic vasopressor response by 25 and 50%, respectively. LPS did not affect the increase in DBP induced by exogenous NA. The LPS-induced inhibition of the neurogenic vasopressor response was counteracted by the cannabinoid CB1 receptor antagonist SR 141716A (0.1 micro mol kg(-1)), but not by the CB2 receptor antagonist SR 144528 (3 micro mol kg(-1)), the vanilloid VR1 receptor antagonist capsazepine (1 micro mol kg(-1)) or the histamine H3 receptor antagonist clobenpropit (0.1 micro mol kg(-1)). The four antagonists by themselves did not affect the increase in DBP induced by ES or by injection of NA in rats not exposed to LPS. We conclude that in the initial phase of septic shock, the activation of presynaptic CB1 receptors by endogenously formed cannabinoids contributes to the inhibition of the neurogenic vasopressor response.


Dronabinol (Delta 9-tetrahydocannabinol, THC), the main source of the pharmacological effects caused by the use of cannabis, is an agonist to both the CB1 and the CB2 subtype of cannabinoid receptors. It is available on prescription in several countries. The non-psychoactive cannabinoid (CBD), some analogues of natural cannabinoids and their metabolites, antagonists at the cannabinoid receptors and modulators of the endogenous cannabinoid system are also promising candidates for clinical research and therapeutic uses. Cannabinoid receptors are distributed in the central nervous system and many peripheral tissues including spleen, leukocytes; reproductive, urinary and gastrointestinal tracts; endocrine glands, arteries and heart. Five endogenous cannabinoids have been detected so far, of whom anandamide and 2-arachidonylglycerol are best characterized. There is evidence that besides the two cannabinoid receptor subtypes cloned so far additional cannabinoid receptor subtypes and vanilloid receptors are involved in the complex physiological functions of the cannabinoid system that include motor coordination, memory procession, control of appetite, pain modulation and neuroprotection. Strategies to modulate their activity include inhibition of re-uptake into cells and inhibition of their degradation to increase concentration and duration of action. Properties of cannabinoids that might be of therapeutic use include analgesia, muscle relaxation, immunosuppression, anti-inflammation, anti-allergic effects, sedation, improvement of mood, stimulation of appetite, anti-emesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects.

Preclinical and clinical studies suggest that cannabidiol (CBD), a major component of Cannabis sativa, could produce antipsychotic effects without causing extra-pyramidal side-effects. In the present paper we employed the detection of Fos protein to investigate neuronal activation in the dorsal striatum and nucleus accumbens of male Wistar rats after systemic administration of CBD (120 mg/kg), haloperidol (1 mg/kg) or clozapine (20 mg/kg). Only haloperidol was able to increase the number of Fos immunoreactive neurons (FIr) in the dorsal striatum (vehicle: 0.07 +/- 0.07/0.1 mm(2), haloperidol: 28.3 +/- 8.9/0.1 mm(2), p < 0.01). In contrast, both haloperidol and CBD significantly increased FIr in the nucleus accumbens (Vehicle: 0 +/- 0/0.1 mm(2), haloperidol: 7.2 +/- 2.7/0.1 mm(2), CBD: 4.0 +/- 1.9/0.1 mm(2), p < 0.05). Clozapine also produced a barely significant increase in FIr (3.0 +/- 1.7/0.1 mm(2), p = 0.062). These results show that CBD is able to induce FIr in a limbic- but not in a motor-related area.


Amides of fatty acids with ethanolamine (FAE) are biologically active lipids that participate in a variety of biological functions, including the regulation of feeding. The polyunsaturated FAE anandamide (arachidonylethanolamide) increases food intake by activating G protein-coupled cannabinoid receptors. On the other hand, the monounsaturated FAE oleylethanolamide (OEA) reduces feeding and body-weight gain by activating the nuclear receptor PPAR-alpha (peroxisome proliferator-activated receptor-alpha). In the present report, we examined whether OEA can also influence energy utilization. OEA (1-20 M) stimulated glycerol and fatty acid release from freshly dissociated rat adipocytes in a concentration-dependent and structurally-selective manner. Under the same conditions, OEA had no effect on glucose uptake or oxidation. OEA enhanced fatty-acid oxidation in skeletal muscle strips, dissociated hepatocytes and primary cardiomyocyte cultures. Administration of OEA in vivo (5mg-kg(-1)), intraperitoneally) produced lipolysis in both rats and wild-type mice, but not in mice in which PPAR-alpha had been deleted by homologous recombination (PPAR-alpha(-/-)). Likewise, OEA was unable to enhance lipolysis in adipocytes or stimulate fatty-acid oxidation in skeletal muscle strips isolated from PPAR-alpha mice. The synthetic PPAR-alpha agonist Wy-14643 produced similar effects, which also were dependent on the presence of PPAR-alpha. Sub-chronic treatment with OEA reduced body-weight gain and triacylglycerol content in liver and adipose tissue of diet-induced obese rats and wild-type mice, but not in obese PPAR-alpha(-/-) mice. The results suggest that OEA stimulates fat utilization through activation of PPAR-alpha and that this effect may contribute to its anti-obesity actions.


A new series of 1,2,4-triazoles have been prepared and the evaluation of their cannabinoid properties have been carried out. Compound 8 showed cannabinoid silent antagonist activity in mouse vas deferens and guinea pig ileum preparations and in vivo assays (cannabinoid tetrad) in mouse. It did not have intrinsic activity in these bioassays, and therefore, it did not behave as a partial agonist or an inverse agonist.


Inhibition of spinal and trigeminal withdrawal reflexes by morphine and by the cannabinoid agonist HU 210 has been studied in anaesthetized and in decerebrated rabbits. In intact, pentobarbitone-anaesthetized animals, the jaw-depressor reflex (JDR) evoked by stimulation of the tongue, and the reflex elicited in the ankle flexor tibialis anterior (TA) by stimulation of the toes were inhibited to the same extent by morphine (1-30 mg kg(-1) i.v. cumulative). In spinalized, anaesthetized rabbits morphine depressed the JDR to the same level as in non-spinal preparations, but the effect of the opioid on the TA reflex was significantly reduced. All effects of morphine were reversed by naloxone (0.25 mg kg(-1), i.v.). In anaesthetised intact animals, HU 210 depressed the JDR at a dose of 100 nmol kg(-1) i.v. cumulative, reduced reflexes evoked in the knee flexor muscle semitendinosus (ST) by
stimulation at the toes at a dose of 30 nmol kg\(^{-1}\) i.v. cumulative, but had no consistent or significant effects on the TA reflex to toe stimulation. The same results were obtained in spinalized, anaesthetised animals. In decerebrated, spinalized rabbits with no anaesthesia, HU 210 (30 nmol kg\(^{-1}\)) depressed both ST and TA reflexes evoked by toe stimulation. These data reveal that trigeminal and spinal withdrawal reflexes are equally sensitive to morphine provided the spinal cord is intact, suggesting that at least part of the action of systemic morphine is due to activation of descending inhibition. The present results also show for the first time that cannabinoid agonists can inhibit trigeminal withdrawal reflexes. HU 210 had differential effects on the three reflexes studied depending on the presence or absence of anaesthesia. This is the first occasion on which we have found pharmacological distinctions between withdrawal reflexes, and indicates that spinal sensorimotor processing is more heterogeneous than has been suspected previously.


Accumulating evidence suggests that cannabinoids can produce antinociception through peripheral mechanisms. In the present study, we determined whether cannabinoids attenuated existing hyperalgesia produced by a mild heat injury to the glabrous hindpaw and whether the antihyperalgesia was receptor-mediated. Anesthetized rats received a mild heat injury (55 degrees C for 30 s) to one hindpaw. Fifteen minutes after injury, animals exhibited hyperalgesia as evidenced by lowered withdrawal latency to radiant heat and increased withdrawal frequency to a von Frey monofilament (200mN force) delivered to the injured hindpaw. Separate groups of animals were then treated with an intraplantar (i.pl.) injection of vehicle or the cannabinoid receptor agonist WIN 55,212-2 at doses of 1, 10, or 30 microg in 100 microl. WIN 55,212-2 attenuated both heat and mechanical hyperalgesia dose-dependently. The inactive enantiomer WIN 55,212-3 did not alter mechanical or heat hyperalgesia, suggesting the effects of WIN 55,212-2 were receptor-mediated. The CB1 receptor antagonist AM 251 (30 microg) co-injected with WIN 55,212-2 (30 microg) attenuated the antihyperalgesic effects of WIN 55,212-2. The CB2 receptor antagonist AM 630 (30 microg) co-injected with WIN 55,212-2 attenuated only the early antihyperalgesic effects of WIN 55,212-2. I.pl. injection of WIN 55,212-2 into the contralateral paw did not alter the heat-injury induced hyperalgesia, suggesting that the antihyperalgesia occurred through a peripheral mechanism. These data demonstrate that cannabinoids primarily activate peripheral CB1 receptors to attenuate hyperalgesia. Activation of this receptor in the periphery may attenuate pain without causing unwanted side effects mediated by central CB1 receptors.


2-Arachidonoylglycerol is an endogenous ligand for the cannabinoid receptors (CB1 and CB2). Previously, we provided evidence that 2-arachidonoylglycerol, but not anandamide (N-arachidonoylethanolamine), is the true natural ligand for the cannabinoid receptors. In the present study, we examined in detail the effects of 2-arachidonoylglycerol on the production of chemokines in human promyelocytic leukemia HL-60 cells. We found that 2-arachidonoylglycerol induced a marked acceleration in the production of interleukin 8. The effect of 2-arachidonoylglycerol was blocked by treatment of the cells with SR144528, a cannabinoid CB2 receptor antagonist, indicating that the effect of 2-arachidonoylglycerol is mediated through the CB2 receptor. Augmented production of interleukin 8 was also observed with CP55940, a synthetic cannabinoid, and an ether-linked analog of 2-arachidonoylglycerol. On the other hand, neither anandamide nor the free arachidonic acid induced the enhanced production of interleukin 8. A similar effect of 2-arachidonoylglycerol was observed in the case of the production of macrophage-chemotactic protein-1. The accelerated production of interleukin 8 by 2-arachidonoylglycerol was observed not only in undifferentiated HL-60 cells, but also in HL-60 cells differentiated into macrophage-like cells. Noticeably, 2-arachidonoylglycerol and lipopolysaccharide acted synergistically to induce the dramatically augmented production of interleukin 8. These results strongly suggest that the CB2 receptor and its physiological ligand, i.e., 2-arachidonoylglycerol, play important regulatory roles such as stimulation of the production
of chemokines in inflammatory cells and immune-competent cells. Detailed studies on the cannabinoid receptor system are thus essential to gain a better understanding of the precise regulatory mechanisms of inflammatory reactions and immune responses.


Although the N-arachidonoyl ethanolamine (anandamide) binds to cannabinoid receptors and has been implicated in the suppression of pain, its rapid catabolism in vivo by fatty acid amide hydrolase (FAAH) has presented a challenge in investigating the physiological functions of this endogenous cannabinoid. In order to test whether anandamide and other non-cannabinoid fatty amides modulate nociception, we compared FAAH (+/+) and (-/-) mice in the tail immersion, hot plate, and formalin tests, as well as for thermal hyperalgesia in the carrageenan and the chronic constriction injury (CCI) models. FAAH (-/-) mice exhibited a CB(1) receptor-mediated phenotypic hypoalgesia in thermal nociceptive tests. These mice also exhibited CB(1) receptor-mediated hypoalgesia in both phases of the formalin test accompanied with a phenotypic anti-edema effect, which was not blocked by either CB(1) or CB(2) antagonists. Additionally, FAAH (-/-) mice displayed thermal anti-hyperalgesic and anti-inflammatory effects in the carrageenan model that were mediated, in part, by CB(2), but not CB(1) receptors. In contrast, no genotype differences in pain behavior were evident following CCI, which was instead found to obliterate the phenotypic hypoalgesia displayed by FAAH (-/-) mice in the tail immersion and hot plate tests, suggesting that nerve injury may promote adaptive changes in these animals. Collectively, these findings demonstrate a cannabinoid receptor-mediated analgesic phenotype in FAAH (-/-) mice. In more general terms, these findings suggest that selective inhibitors of FAAH might represent a viable pharmacological approach for the clinical treatment of pain disorders.


The relationship of agonist efficacy to the rate of G protein-coupled receptor signaling desensitization is controversial. Expressing inwardly rectifying potassium channels (GIRKs) in Xenopus oocytes, we have devised a signaling assay that clearly identifies CB1 cannabinoid receptor agonists with low intrinsic efficacy. In this assay, the synthetic CB1 agonists, AM411, AM782, AM1902, AM2233 and WIN55,212-2 and the endogenous cannabinoid, 2-arachidonoyl ester, were full agonists. The synthetic CB1 agonist AM356 (methanandamide), the endogenous cannabinoids, anandamide and 2-arachidonoyl ether, and the phytocannabinoid, Delta(9)THC, were partial agonists. The rate of desensitization of CB1 was independent of agonist efficacy. WIN55,212-2, AM782, AM1902, AM2233, and 2-arachidonoyl glycerol ester all desensitized quickly, with desensitization rates varying from 14% min(-1) to 10% min(-1). AM356, AM411, anandamide, and Delta(9)THC all desensitized considerably slower, at a rate of 5% min(-1). Despite high potency and efficacy, AM411 desensitized as slowly as anandamide and Delta(9)THC. CB1 agonist efficacy and rate of desensitization are not necessarily related.


Endogenous cannabinoids (eCB) mediate synaptic plasticity in brain regions involved in learning and reward. Here we show that in mice, a single in-vivo exposure to Delta9-tetrahydrocannabinol (THC) abolishes the retrograde signaling that underlies eCB-mediated synaptic plasticity in both nucleus accumbens (NAc) and hippocampus in vitro. This effect is reversible within 3 days and is associated with a transient modification in the functional properties of cannabinoid receptors.


The results of vasorespiratory studies in rats anaesthetised with pentobarbital show that (+/-) cannabidiol, a cannabinoid that lacks psychotropic actions and is inactive at cannabinoid (CB) receptors, does not affect respiration or blood pressure when injected (1-2000 microg; 3.2-
6360 nmol i.a.). Cannabidiol in doses up to 2 mg (6360 nmol) i.a. or i.v. did not affect the fall in mean blood pressure or the increase in ventilation (respiratory minute volume) caused by capsaicin and high doses of anandamide, responses that are mediated by activation of vanilloid VR1 (TRPV1) receptors in this species. Similar results were obtained with (-) cannabidiol (30-100 microg i.a.; 95-318 nmol). It has previously been shown using human embryonic kidney (HEK) cells over-expressing vanilloid human VR1 (hVR1) receptors that cannabidiol is a full agonist at vanilloid VR1 receptors in vitro. However, in the intact rat cannabidiol lacked vanilloid VR1 receptor agonist effects. We conclude that there are substantial functional differences between human and rat vanilloid VR1 receptors with respect to the actions of cannabidiol as an agonist at vanilloid VR1 receptors. Studies in vivo show that cannabidiol lacks any significant effect on mean blood pressure or respiratory minute volume when injected i.a. or i.v., and that this cannabinoid does not modulate the vanilloid VR1 receptor-mediated cardiovascular and ventilatory changes reflexly evoked by capsaicin or anandamide in rats anaesthetised with pentobarbital.


We studied the effect of cannabinoids on the activity of N-methyl-d-aspartate (NMDA) receptors in the locus coeruleus from rat brain slices by single-unit extracellular recordings. As expected, NMDA (100 microM) strongly excited (by nine fold) the cell firing activity of the locus coeruleus. Perfusion with the endocannabinoid anandamide (1 and 10 microM) or the anandamide transport inhibitor AM 404 (30 microM) enhanced the NMDA-induced excitation of locus coeruleus neurons. Similarly, the synthetic agonists R(+)-WIN 55212-2 (10 microM) and CP 55940 (30 microM) enhanced the effect of NMDA. In the presence of the CB(1) receptor antagonists SR 141716A (1 microM) or AM 251 (1 microM), the enhancement induced by anandamide (10 microM) was blocked. Our results suggest that cannabinoids modulate the activity of NMDA receptors in the locus coeruleus through CB(1) receptors.


Multiple sclerosis (MS) is the most common of the immune demyelinating disorders of the central nervous system (CNS). Leukocyte/endothelial interactions are important steps in the progression of the disease and substances that interfere with these activities have been evaluated as potential therapeutic agents. Cannabinoid receptor agonists have been shown to downregulate immune responses and there is preliminary evidence that they may slow the progress of MS. The purpose of this investigation was to determine how cannabinoid receptor agonists interfere with leukocyte rolling and adhesion. This was investigated in an experimental autoimmune encephalomyelitis (EAE) model using six to eight week old C57BL/6 mice. Mouse myelin oligodendrocyte protein and pertussis toxin were used to induce EAE. WIN 55212-2, CB1 and CB2 antagonist were given. By use of in vivo intravital microscopy, leukocyte/endothelial interactions were evaluated via a cranial window implanted two days before. The results demonstrated that EAE increases leukocyte rolling and firm adhesion in the brain, and that this increased leukocyte/endothelial interaction can be attenuated by administration of WIN 55212-2. Furthermore, use of the selective antagonists for the CB1 receptor (SR 141716A) and the CB2 receptor (SR144528) in this study demonstrated that the cannabinoid's inhibitory effects on leukocyte/endothelial interactions can be mediated by activating CB2 receptor.


In order to address mechanistic differences between arterial vessel types, we have compared the vasorelaxant actions of anandamide in resistance (G3) and conduit (G0)
mesenteric arteries. Anandamide produced concentration-dependent relaxations of pre-
constricted G3 arteries with a maximal response that was significantly greater than seen in G0. The CB1 receptor selective antagonists SR141716A (100 nM) and AM251 (100 nM) caused
reductions in the vasorelaxant responses to anandamide in both arteries. Maximal vasorelaxant
responses to anandamide were reduced in both arteries after treatment with capsaicin to deplete
sensory neurotransmitters (10 micro M for 1 h). Vasorelaxation to anandamide was not affected
by the nitric oxide synthase inhibitor N(G)-nitro-L-arginine methyl ester (L-NAME, 300 micro M) in
either artery. Only responses in G3 arteries were sensitive to removal of the endothelium. In G3
vessels only, vasorelaxation to anandamide was reduced by inhibition of EDHF activity with a
combination of charybdotoxin (100 nM) and apamin (500 nM) in the presence of L-NAME (300
micro M) and indomethacin (10 micro M). Antagonism of the novel endothelial cannabinoid
receptor (O-1918, 1 micro M) caused a reduction in the sensitivity to anandamide in G3 but not
g0. G3, but not G0, vessels showed a small reduction in vasorelaxant responses to anandamide
after inhibition of gap junctional communication with 18alpha-GA (100 micro M). These results
demonstrate that there are differences in the mechanisms of vasorelaxation to anandamide
between conduit and resistance mesenteric arteries. In small resistance vessels, vasorelaxation
occurs through stimulation of vanilloid receptors, CB1 receptors, and an endothelial receptor
coupled to EDHF release. By contrast, in the larger mesenteric artery, vasorelaxation is almost
entirely due to stimulation of vanilloid receptors and CB1 receptors, and is endothelium-

Pacher, P., S. Batkai, et al. (2004). "Haemodynamic profile and responsiveness to anandamide of
TRPV1 receptor knock-out mice." J Physiol.

The endocannabinoid anandamide and cannabinoid (CB) receptors have been implicated
in the hypotension in various forms of shock and in advanced liver cirrhosis. Anandamide also
activates vanilloid TRPV1 receptors on sensory nerve terminals, triggering the release of
calcitonin gene-related peptide that elicits vasorelaxation in isolated blood vessels in vitro.
However, the contribution of TRPV1 receptors to the in vivo hypotensive effect of anandamide is
equivocal. We compared the cardiac performance of anaesthetised TRPV1 knockout (TRPV1-/-)
mice and their wild-type (TRPV1+/+) littermates and analysed in detail the haemodynamic effects
of anandamide using the Millar pressure-volume conductance catheter system. Baseline
cardiovascular parameters as well as systolic and diastolic function at different preloads were
similar in TRPV1-/- and TRPV1+/+ mice. The predominant hypotensive response to bolus
intravenous injections of anandamide and the associated decrease in cardiac contractility and
total peripheral resistance (TPR) were similar in TRPV1+/+ and TRPV1-/- mice, as was the ability
of the CB1 receptor antagonist SR141716 to completely block these effects. In TRPV1+/- mice,
this hypotensive response was preceded by a transient, profound drop in cardiac contractility
and heart rate and increase in TPR, followed by a brief pressor response, which were unaffected by
SR141716 and were absent in TRPV1-/- mice. These results indicate that mice lacking TRPV1
receptors have a normal cardiovascular profile and their predominant cardiovascular depressor
response to anandamide is mediated through CB1 receptors. The role of TRPV1 receptors is
limited to the transient activation of the Bezold-Jarisch reflex by very high initial plasma
concentrations of anandamide.

cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place
preference learning in rats." Psychopharmacology (Berl).

RATIONALE. Using the place-preference conditioning paradigm, we evaluated the potential of the two most prominent cannabinoids found in marijuana, the psychoactive
component Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and the nonpsychoactive component
cannabidiol (CBD), to potentiate extinction of a cocaine-induced and an amphetamine-induced
conditioned place preference in rats. METHODS. To determine the effects of pretreatment with
Delta(9)-THC or CBD on extinction, a cocaine-induced and amphetamine-induced place
preference was first established. Rats were then given an extinction trial, during which they were
confined to the treatment-paired floor for 15 min. Thirty minutes prior to the extinction trial, they
were injected with a low dose of Delta(9)-THC (0.5 mg/kg), CBD (5 mg/kg) or vehicle. The
potential of the CB(1) receptor antagonist, SR141716, to reverse the effects of Delta(9)-THC or CBD was also evaluated. To determine the hedonic effects of CBD, one distinctive floor was paired with CBD (5 mg/kg) and another with saline. Finally, to determine the effect of Delta(9)-THC or CBD on the establishment of place preference and the expression of a place preference during four cycles of conditioning trials, rats were injected with Delta(9)-THC (0.25-1 mg/kg), CBD (5 mg/kg) or vehicle 25 min prior to receiving an injection of amphetamine followed by placement on the treatment floor; on alternate days, they received injections of vehicle followed by saline and placement on the nontreatment floor. The rats then received two test trials; on one trial they were pretreated with the cannabinoid and on the other trial with vehicle.

RESULTS. Delta(9)-THC and CBD potentiated the extinction of both cocaine-induced and amphetamine-induced conditioned place preference learning, and this effect was not reversed by SR141716. The cannabinoids did not affect learning or retrieval, and CBD was not hedonic on its own. CONCLUSIONS. These results are the first to show that both Delta(9)-THC, which acts on both CB1 and CB2 receptors, and CBD, which does not bind to CB(1) or CB(2) receptors, potentiate the extinction of conditioned incentive learning.


The prototypical aminoalkylindole cannabinoid WIN 55,212-2 (WIN-2) has been shown to produce antihyperalgesia through a peripheral mechanism of action. However, it is not known whether WIN-2 exerts this action directly via cannabinoid receptors located on primary afferents or if other, perhaps indirect or noncannabinoid, mechanisms are involved. To address this question, we have examined the specific actions of WIN-2 on trigeminal ganglion (TG) neurons in vitro by quantifying its ability to modulate the evoked secretion of the proinflammatory neuropeptide CGRP as well as the inflammatory mediator-induced generation of cAMP. WIN-2 evoked CGRP release from TG neurons in vitro (EC(50)=26 microm) in a concentration- and calcium-dependent manner, which was mimicked by the cannabinoid receptor-inactive enantiomer WIN 55,212-3 (WIN-3). Moreover, WIN-2-evoked CGRP release was attenuated by the nonselective cation channel blocker ruthenium red but not by the vanilloid receptor type 1 (TRPV1) antagonist capsazepine, suggesting that, unlike certain endogenous and synthetic cannabinoids, WIN-2 is not a TRPV1 agonist but rather acts at an as yet unidentified cation channel. The inhibitory effects of WIN-2 on TG neurons were also examined. WIN-2 neither inhibited capsaicin-evoked CGRP release nor did it inhibit forskolin-, isoproteranol- or prostaglandin E(2)-stimulated cAMP accumulation. On the other hand, WIN-2 significantly inhibited (EC(50)=1.7 microm) 50 mm K(+) evoked CGRP release by approximately 70%. WIN-2 inhibition of 50 mm K(+) evoked CGRP release was not reversed by antagonists of cannabinoid type 1 (CB1) receptor, but was mimicked in magnitude and potency (EC(50)=2.7 microm) by its cannabinoid-inactive enantiomer WIN-3. These findings indicate that WIN-2 exerts both excitatory and inhibitory effects on TG neurons, neither of which appear to be mediated by CB1, CB2 or TRPV1 receptors, but by a novel calcium-dependent mechanism. The ramifications of these results are discussed in relation to our current understanding of cannabinoid/vanilloid interactions with primary sensory neurons.


A polyketide synthase has been suggested to play an important role in cannabinoid biosynthesis in Cannabis sativa L. This enzyme catalyzes the biosynthesis of olivetolic acid, one of the precursors for cannabinoid biosynthesis. Using a reverse transcriptase-polymerase chain reaction (RT-PCR) based on the DNA homology of chalcone synthase (EC 2.3.1.156) and valerophenone synthase (EC 2.3.1.156) of hop (Humulus lupulus), a cDNA encoding a polyketide synthase in C. sativa was identified. The coding region of the gene is 1170 bp long encoding a 389 amino acid protein of a predicted 42.7 kDa molecular mass and with a pl of 6.04. The gene shares a high homology with a chalcone synthase gene of H. lupulus, 85% and 94% homology on the level of DNA and protein, respectively. Over-expression of the construct in Escherichia coli M15 resulted in a 45 kDa protein. The protein has chalcone synthase activity as well as
valerophenone synthase activity, a chalcone synthase-like activity. Using n-hexanoyl-CoA and malonyl-CoA as substrates did not give olivetol or olivetolic acid as a product.


Various methods for the analysis of cannabinoids in biological materials, including plant and human body materials, are reviewed. Chromatographic methods, such as TLC, GC and HPLC, and non-chromatographic methods, mainly immunoassays, are discussed and compared. Chromatography is most commonly used in the analysis of plant material, with GC apparently offering the most advantages. Immunoassays, such as radioimmunoassay and fluorescence polarisation immunoassay, and enzyme immunoassay methods, such as enzyme multiplied immunoassay technique and enzyme-linked immunosorbent assay, can be used for human body materials; however, GC-MS is still necessary for confirmation and accurate quantification. Preferred methods are suggested for various specific purposes.


The cardiovascular actions of cannabinoids are complex. In general they cause vasorelaxation in isolated blood vessels, while in anaesthetised animals they cause multiphasic responses which involve an early bradycardia and long-lasting hypotension. However, in conscious animals, the picture is one of bradycardia followed by pressor responses. Clearly, the responses to cannabinoids are dependent on the experimental conditions and synthetic cannabinoids and endocannabinoids exhibit different pharmacologies. In terms of mechanisms involved in the vascular responses to cannabinoids, the following have been implicated: the involvement of 'classical' cannabinoid receptors, the involvement of a novel endothelial cannabinoid receptor, the release of nitric oxide, the release of endothelium-derived hyperpolarising factor (EDHF), the activation of vanilloid receptors, metabolism of endocannabinoids to vasoactive molecules, and both peripheral inhibition and central excitation of the sympathetic nervous system. British Journal of Pharmacology (2004) 142, 20-26. doi:10.1038/sj.bjp.0705725


Cannabinoids evoke hypothermia by stimulating central CB(1) receptors. GABA induces hypothermia via GABA(A) or GABA(B) receptor activation. CB(1) receptor activation increases GABA release in the hypothalamus, a central locus for thermoregulation, suggesting that cannabinoid and GABA systems may be functionally linked in body temperature regulation. We investigated whether GABA receptor agonists modulate the hypothermic actions of [4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6 H-pyrrolo[3,2,1ij]quinolin-6-one] (WIN 55212-2), a selective cannabinoid agonist, in male Sprague-Dawley rats. WIN 55212-2 (2.5 mg/kg im) produced a rapid hypothermia that peaked 45-90 min postinjection. The hypothermia was attenuated by bicuculline (2 mg/kg ip), a GABA(A) antagonist. However, SCH 50911 (1-10 mg/kg ip), a GABA(B) blocker, did not antagonize the hypothermia. Neither bicuculline (2 mg/kg) nor SCH 50911 (10 mg/kg) by itself altered body temperature. We also investigated a possible role for CB(1) receptors in GABA-generated hypothermia. Muscimol (2.5 mg/kg ip), a GABA(A) agonist, or baclofen (5 mg/kg ip), a GABA(B) agonist, evoked a significant hypothermia. Blockade of CB(1) receptors with SR141716A (2.5 mg/kg im) did not antagonize muscimol- or baclofen-induced hypothermia, indicating that GABA-evoked hypothermia does not contain a CB(1)-sensitive component. Our results implicate GABA(A) receptors in the hypothermic actions of cannabinoids and provide further evidence of a functional link between cannabinoid and GABA systems.

Based on binding, functional and pharmacological data, this study introduces SR147778 as a highly potent, selective and orally active antagonist for the CB1 receptor. This compound displays nanomolar affinity (Ki = 0.56 and 3.5 nM) for both the rat brain and human CB1 recombinant receptors, respectively. It has low affinity (Ki = 400 nM) for both the rat spleen and human CB2 receptors. Furthermore it shows no affinity for any of the over 100 targets investigated (IC50 >1 micro M). In vitro, SR147778 antagonizes the inhibitory effects of CP 55,940 on both the mouse vas deferens contractions (pA2 value = 8.1) and on forskolin-stimulated adenylyl cyclase activity in the U373 MG cell lines (pA2 value = 8.2) but not in CHO cells permanently expressing the hCB2. SR147778 is able to block the MAP kinase activity induced by CP 55,940 in CHO cell line expressing hCB1 (IC50 = 9.6 nM) but was inactive in cells expressing hCB2. After oral administration, SR147778 displaced the ex vivo [(3)H]-CP 55,940 binding to mouse brain membranes (ED50 = 3.8 mg/kg) with a long duration of action whereas it did not interact with the CB2 receptor expressed in the mouse spleen. Using different routes of administration, SR147778 (0.3 to 3 mg/kg) is shown to antagonize pharmacological effects (hypothermia, analgesia and gastrointestinal transit) induced by WIN55212-2, in mice. Finally, per se, SR147778 (0.3 to 10 mg/kg) is able to reduce both ethanol or sucrose consumption in mice and rats and food intake in fasted and non-deprived rats.


Mouse fibroblast cells overexpressing phosphatidylinositol transfer protein alpha (PI-TPalpha, SPIalpha cells) show a significantly increased rate of proliferation as compared to wtNIH3T3 cells. In addition, SPIalpha cells are extremely resistant towards UV- or TNFalpha-induced apoptosis. Incubation of quiescent wtNIH3T3 cells with the conditioned medium (CM) from SPIalpha cells or with the neutral lipid extract from CM stimulated the proliferation of these cells. CM was also highly effective in increasing resistance towards induced apoptosis in both wtNIH3T3 cells and the highly apoptosis-sensitive SPIbeta cells (i.e. wild-type cells overexpressing PI-TPbeta). CM from SPIalpha cells grown in the presence of NS398, a specific cyclooxygenase-2 (COX-2) inhibitor, expressed a diminished mitogenic and anti-apoptotic activity. This strongly suggests that the bioactive factor(s) is an eicosanoid. In accordance, SPIalpha cells express enhanced levels of COX-1 and COX-2 when compared to wtNIH3T3 and SPIbeta cells. The anti-apoptotic activity of CM from SPIalpha cells tested on SPIbeta cells was inhibited for about 50% by pertussis toxin and suramin as well as by SR141716A, a specific antagonist of the cannabinoid 1 receptor, but not by SR144538, the antagonist of cannabinoid 2 receptor. These inhibitors had virtually no effect on the anti-apoptotic activity of CM from SPIalpha cells prepared in the presence of the COX-2 inhibitor. The latter results imply that PI-TPalpha mediates the production of a COX-2-dependent eicosanoid that activates a G-protein-coupled receptor, most probably a cannabinoid 1-like receptor, thereby enhancing proliferation and cell survival.


The hypothesis of the present work was that activation of CB1 cannabinoid receptors inhibits GABAergic neurotransmission between basket and Purkinje cells in the cerebellar cortex. The aim was to test this hypothesis under near-physiological conditions. Action potentials of basket cells and spontaneous inhibitory postsynaptic currents (sIPSCs) in synaptically coupled Purkinje cells were recorded simultaneously in rat brain slices. The cannabinoid agonists WIN55212-2 and CP55940 decreased the amplitude of sIPSCs occurring simultaneously with basket cell action potentials and lowered the success rate of synaptic transmission. These effects were prevented by the CB1 receptor antagonist SR141716. Depolarisation of Purkinje cells also led to suppression of neurotransmission; prevention of this suppression by CP55940 and SR141716 indicates that endocannabinoids released from Purkinje cells were involved. WIN55212-2 lowered the amplitude of autoreceptor currents recorded in basket cells (autoreceptor currents are due to the action of GABA released from axon terminals on GABAA
Autoreceptors of the same axon terminals); this is a novel proof of the presynaptic action of cannabinoids. Autoreceptor current experiments also indicated that endogenous cannabinoids are not released by basket cell axon terminals. A presynaptic action is additionally supported by the observation that WIN55212-2 lowered the frequency of miniature IPSCs recorded in the presence of tetrodotoxin and the calcium ionophore ionomycin. In conclusion, activation of CB1 receptors by exogenous cannabinoids and by endogenous cannabinoids released by Purkinje cells presynaptically inhibits GABAergic neurotransmission between basket and Purkinje cells. This was demonstrated under near-physiological conditions: transmitter release was elicited by action potentials generated by spontaneously firing intact presynaptic neurons.


Synthetic cannabinoids have a promising future as treatments for nausea, appetite modulation, pain, and many neurological disorders. Transdermal delivery is a convenient and desirable dosage form for these drugs and health conditions. The aim of the present study was to investigate the in vitro transdermal permeation of two synthetic cannabinoids, WIN 55,212-2 and CP 55,940. Transdermal flux, drug content in the skin, and lag times were measured in split-thickness human abdominal skin in flow-through diffusion cells with receiver solutions of 4% bovine serum albumin (BSA) or 0.5% Brij 98. Differential thermal analysis (DSC) was performed in order to determine heats of fusion, melting points, and relative thermodynamic activities. The in vitro diffusion studies in 0.5% Brij 98 indicated that WIN 55,212-2 diffuses across human skin faster than CP 55,940. The WIN 55,212-2 skin disposition concentration levels were also significantly higher than that of CP 55,940. Correspondingly, CP 55,940 was significantly metabolized in the skin. WIN 55,212-2 flux and skin disposition were significantly lower into 4% BSA than into 0.5% Brij 98 receiver solutions. There was no significant difference in the flux, lag time, and drug content in the skin of CP 55,940 in 4% BSA versus 0.5% Brij 98 receiver solutions. The DSC studies showed that CP 55,940 had a significantly lower melting point, smaller heat of fusion, and corresponding higher calculated thermodynamic activity than the more crystalline WIN 55,212-2 mesylate salt. The permeation results indicated that WIN 55,212-2 mesylate, CP 55,940, and other potent synthetic cannabinoids with these physicochemical properties could be ideal candidates for the development of a transdermal therapeutic system.


Central cannabinoid receptors (CB1 receptors) are densely located in the output nuclei of the basal ganglia (globus pallidus, substantia nigra pars reticulata). Endogenous cannabinoids appear to modulate transmitter systems (e.g. dopamine) within the basal ganglia. In the striatum, CB1 receptors are localized on the same neurons as Gi-coupled dopamine D2 receptors. Striatal CB1 receptors are also negatively linked to adenylcyclase, and may modulate dopamine release. The presence of CB1 receptors in dopaminergic neurons strongly suggests that cannabinoids play a modulatory role in dopaminergic neuronal pathways. This co-localization may postulate "cross talk" between endocannabinoids and dopamine-dependent reward mechanisms.

**CLINICAL SCIENCE**


The 4th Amendment of the United States Constitution protects American citizens against unreasonable search and seizure without probable cause. Although law enforcement officials routinely rely solely on the sense of smell to justify probable cause when entering vehicles and dwellings to search for illicit drugs, the accuracy of their perception in this regard has rarely been questioned and, to our knowledge, never tested. In this paper, we present data from two empirical studies based upon actual legal cases in which the odor of marijuana was used as probable
cause for search. In the first, we simulated a situation in which, during a routine traffic stop, the odor of packaged marijuana located in the trunk of an automobile was said to be detected through the driver's window. In the second, we investigated a report that marijuana odor was discernable from a considerable distance from the chimney effluence of diesel exhaust emanating from an illicit California grow room. Our findings suggest that the odor of marijuana was not reliably discernable by persons with an excellent sense of smell in either case. These studies are the first to examine the ability of humans to detect marijuana in simulated real-life situations encountered by law enforcement officials, and are particularly relevant to the issue of probable cause.


The discovery of cannabinoid receptors in the immune system and a family of endogenous ligands of these receptors provides a basis for understanding the cellular and molecular mechanisms of cannabis-induced immunotoxicity. The present study was conducted on 90 nonsmoker males of high school and university students living in Tanta city of matched age and socioeconomic lifestyle. They were divided into a control group (30 males) and a bhang user group (60 males), which used bhang by eating its sweet juice after boiling with a little water and drying in an oven, 'fola'. The bhang group was divided equally into two subgroups: subgroup 1 used bhang for 6-24 months (average 19 +/- 1.2) and subgroup 2 used bhang for 24-36 months (average 31 +/- 1.7). The immunotoxic effects of using bhang appeared in the form of a significant decrease in serum immunoglobulins (IgG and IgM), and C3 and C4 complement protein concentrations (P < 0.05). In addition, our results demonstrated a significant decrease in the absolute number of functionally different subsets of peripheral blood mononuclear lymphocytes, T and B lymphocytes and natural killer (NK) cells in bhang users as compared to controls (P < 0.05). Moreover, the fatty acid amide hydrolase (FAAH) showed significant decrease in bhang users as compared to controls and in subgroup 2 as compared to subgroup 1 (P < 0.05), indicating that the decrease in FAAH protein level is closely related to the duration of bhang use. Positive correlations were found between FAAH level and the absolute number of mononuclear cells (T, B lymphocytes and NK cells) among bhang user subgroups. The present study is the first study to report on the effect of bhang on complement proteins and immunoglobulins in humans. Our study revealed that bhang-induced immunotoxicity could be attributed to decrease in FAAH protein.


Rimonabant, an antagonist of central cannabinoid type 1 (CB1) receptors, is being developed by Sanofi-Synthelabo for the potential treatment of obesity and as a potential smoking cessation agent. Phase III trials were initiated for obesity in August 2001 and were ongoing in September 2003. By September 2002, the compound had entered phase III trials for smoking cessation, and these trials were ongoing in September 2003.


The goal of this study was to describe and compare the prevalence, predictors and patterns of marijuana use, specifically medicinal marijuana use among patients with HIV in Ontario, Canada. Any marijuana use in the year prior to interview and self-defined medicinal use were evaluated. A cross-sectional multicenter survey and retrospective chart review were conducted between 1999 and 2001 to evaluate overall drug utilization in HIV, including marijuana use. HIV-positive adults were identified through the HIV Ontario Observational Database (HOOD), 104 consenting patients were interviewed. Forty-three percent of patients reported any marijuana use, while 29% reported medicinal use. Reasons for use were similar by gender although a significantly higher number of women used marijuana for pain management. Overall, the most commonly reported reason for medicinal marijuana use was appetite stimulation/weight gain. Whereas male gender and history of intravenous drug use were predictive of any marijuana use, only household income less than $20,000 CDN was associated with medicinal marijuana
use. Age, gender, HIV clinical status, antiretroviral use, and history of intravenous drug use were not significant predictors of medicinal marijuana use. Despite the frequency of medicinal use, minimal changes in the pattern of marijuana use upon HIV diagnosis were reported with 80% of current medicinal users also indicating recreational consumption. Although a large proportion of patients report medicinal marijuana use, overlap between medical and recreational consumption is substantial. The role of poverty in patient choice of medicinal marijuana despite access to care and the large proportion of women using marijuana for pain constitute areas for further study.


The benign essential blepharospasm is a subliminal form of primary torsion dystonia with still uncertain aetiology. It is characterized by involuntary convulsive muscle contractions of the M. orbicularis occuli, accompanied by unbearable pain of the cornea, eye bulb and the muscle itself. It has been suggested that blepharospasm is neurobiologically based on a dysfunction of the basal ganglia and an impairment of the dopamine neurotransmitter system. Therefore, therapy of blepharospasm contains administration of anticholinergic- and tranquilizing drugs as well as botulinum toxin as neuromuscular blocking agent. However serious side effects can be observed as well as failure of therapy. In the brain a dense co-localisation of cannabinoid (CB1) and dopamine (D2)-receptor was identified which had been associated with the influence of cannabinoids on the dopaminergic reward system. Additionally, it has been demonstrated that cannabinoids may have an impact on the central GABAergic and glutaminergic transmitter system and thus might be involved in the influence of movement control. In the present case we administered the cannabinoid receptor agonist Dronabinol (Delta-9-Tetrahydrocannabinol) to a woman suffering from severe blepharospasm. Multiple treatments with botulinum toxin did not reveal a long-lasting beneficial effect. By contrast, treatment with 25 mg Dronabinol for several weeks improved the patients' social life and attenuated pain perception remarkably. This case study demonstrates that the therapy with a cannabinoid agonist may provide a novel tool in the treatment of blepharospasm and maybe of other multifactorial related movement disorders.


RATIONALE. The primary psychoactive constituent of marijuana, Delta(9)-THC, activates cannabinoid receptors, which are especially abundant in the frontal cortex and hippocampus. Acute marijuana smoking can disrupt working memory (WM) and episodic memory (EM) functions that are known to rely on these regions. However, the effects of marijuana on the brain activity accompanying such cognitive processes remain largely unexplored. OBJECTIVES. To examine such effects on performance and neurophysiological signals of these functions, EEG recordings were obtained from ten subjects (5M, 5F) performing cognitive tasks before and after smoking marijuana (3.45% Delta(9)-THC) or a placebo. WM was assessed with a spatial N-back task, and EM was evaluated with a test requiring recognition of words after a 5-10 min delay between study and test. RESULTS. Marijuana increased heart rate and decreased global theta band EEG power, consistent with increased autonomic arousal. Responses in the WM task were slower and less accurate after smoking marijuana, accompanied by reduced alpha band EEG reactivity in response to increased task difficulty. In the EM task, marijuana was associated with an increased tendency to erroneously identify distracter words as having been previously studied. In both tasks, marijuana attenuated stimulus-locked event-related potentials (ERPs).

CONCLUSIONS. The results suggest that marijuana disrupted both sustained and transient attention processes resulting in impaired memory task performance. In subjects most affected by marijuana a pronounced ERP difference between previously studied words and new distracter words was also reduced, suggesting disruption of neural mechanisms underlying memory for recent study episodes.


An initial report on the therapeutic application of delta 9-THC (THC) (Dronabinol, Marinol) in 8 children resp. adolescents suffering from the following conditions, is given:
neurodegenerative disease, mitochondrialopathy, posthypoxic state, epilepsy, posttraumatic reaction. THC effected reduced spasticity, improved dystonia, increased initiative (with low dose), increased interest in the surroundings, and anticonvulsive action. The doses ranged from 0.04 to 0.12 mg/kg body weight a day. The medication was given as an oily solution orally in 7 patients, via percutaneous gastroenterostomy tube in one patient. At higher doses disinhibition and increased restlessness were observed. In several cases treatment was discontinued and in none of them discontinuing resulted in any problems. The possibility that THC-induced effects on ion channels and transmitters may explain its therapeutic activity seen in epileptic patients is discussed.


Based on patient reports, animal data, and in vitro experiments, evidence has emerged indicating a positive effect of cannabinoids as symptomatic treatment of spasticity and pain in multiple sclerosis. The recently published CAMS study was the first multicenter, randomized, placebo-controlled phase III trial to examine the efficacy of cannabinoids on symptoms related to MS. There was no treatment effect of cannabinoids on the primary outcome measure, a difference in the reduction of spasticity as assessed by the so-called Ashworth score. In contrast, significant effects on patient-reported spasticity and pain were documented. A major problem of the study was a high degree of patient unmasking in the active treatment group. In this review, the results of the CAMS study are discussed in the context of previous trials, the putative mechanism of action of cannabinoids and their adverse event profile.


: The effects of cannabis extracts on nocturnal sleep, early-morning performance, memory, and sleepiness were studied in 8 healthy volunteers (4 males, 4 females; 21 to 34 years). The study was double-blind and placebo-controlled with a 4-way crossover design. The 4 treatments were placebo, 15 mg Delta-9-tetrahydrocannabinol (THC), 5 mg THC combined with 5 mg cannabidiol (CBD), and 15 mg THC combined with 15 mg CBD. These were formulated in 50:50 ethanol to propylene glycol and administered using an oromucosal spray during a 30-minute period from 10 pm. The electroencephalogram was recorded during the sleep period (11 pm to 7 am). Performance, sleep latency, and subjective assessments of sleepiness and mood were measured from 8:30 am (10 hours after drug administration). There were no effects of 15 mg THC on nocturnal sleep. With the concomitant administration of the drugs (5 mg THC and 5 mg CBD to 15 mg THC and 15 mg CBD), there was a decrease in stage 3 sleep, and with the higher dose combination, wakefulness was increased. The next day, with 15 mg THC, memory was impaired, sleep latency was reduced, and the subjects reported increased sleepiness and changes in mood. With the lower dose combination, reaction time was faster on the digit recall task, and with the higher dose combination, subjects reported increased sleepiness and changes in mood. Fifteen milligrams THC would appear to be sedative, while 15 mg CBD appears to have alerting properties as it increased awake activity during sleep and counteracted the residual sedative activity of 15 mg THC.


OBJECTIVES: This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis. METHODS: Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other resources. RESULTS: Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT1A and inhibits 5-HT2A receptors supporting therapeutic efficacy in acute and preventive migraine treatment. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is
tonically active in the periaqueductal gray matter, a migraine generator. THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging. CONCLUSION: Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines.


BACKGROUND: Cannabis use is commonly identified in people who present with psychosis. OBJECTIVE: This case study aims to provide a practical approach for general practitioners seeing patients with comorbid cannabis and mental health concerns. DISCUSSION: Cannabis related comorbidity is commonly seen in general practice. General practitioners can manage most presentations and help to reduce the likely occurrence of cannabis induced psychosis through the use of psychosocial support, brief interventions and harm minimisation.


Evolving information technology has raised the possibility of new methods of data collection in multiple sclerosis (MS) research. An anonymous, self-report, Internet-based survey was developed, which asked people with MS their opinion on how various extrinsic factors affected their condition. From September 2001 to July 2002, a total of 2529 people completed the questionnaire. The demographic and clinical profiles of the anonymous respondents indicated that most were likely to have MS. Common factors reported as beneficial were cannabis, cold baths, meditation and dietary factors. Common adverse factors reported were high stress, exposure to high temperatures and viral infections. There was an increasing report of high temperatures as being adverse with increasing respondent age (test for trend, P < 0.001). The adverse report of high temperatures correlated significantly with the report of strong sunlight apparently making MS worse (r = 0.35, P < 0.0001). In Australia, high temperatures were more likely to be reported as adverse in warmer, lower latitude regions. The association between strong sunlight as adverse and age or region did not persist after adjustment for high temperatures. Thus, this apparent adverse factor appeared to relate to solar heat, not solar light. People with MS may risk vitamin D deficiency because of sun avoidance due to heat-related fatigue or intolerance. This is of clinical significance not only for bone health but because vitamin D may have beneficial immunomodulatory properties. The present study provides new information from people with MS on factors that may influence symptoms or clinical course. This information will now be used in the design of formal epidemiological cohort studies.


BEHAVIOURAL SCIENCE


The usefulness of the Diagnostic and Statistical Manual's (4th ed.; DSM-IV; American Psychiatric Association, 1994) tolerance criterion as an indicator of dependence has been debated. The authors of this study evaluated the performance of DSM's cannabis tolerance criterion, operationally defined as a percentage increase in quantity needed to get high, in distinguishing adolescents with and without cannabis dependence. Two samples of adolescent cannabis users (ages 12-19) provided data (n = 417 and 380). Tolerance, defined as a
percentage increase (median increase = 300% and 175%, respectively, in the samples), had only moderate overall sensitivity and specificity in distinguishing those with and without cannabis dependence. Results suggest limitations of the DSM-IV and change-based operational definition of tolerance in adolescents. (c) 2004 APA, all rights reserved)


CONTEXT: Among illicit substance use disorders, marijuana use disorders are the most prevalent in the population. Yet, information about the prevalence of current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) marijuana use disorders and how prevalence has changed is lacking. OBJECTIVE: To examine changes in the prevalence of marijuana use, abuse, and dependence in the United States between 1991-1992 and 2001-2002.

DESIGN, SETTING, AND PARTICIPANTS: Face-to-face interviews were conducted in 2 large national surveys conducted 10 years apart: the 1991-1992 National Longitudinal Alcohol Epidemiologic Survey ([NLAES] n = 42 862) and the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions ([NESARC] n = 43 093). MAIN OUTCOME MEASURES: Rates of past year marijuana use, abuse, and dependence. RESULTS: Among the adult US population, the prevalence of marijuana use remained stable at about 4.0% over the past decade. In contrast, the prevalence of DSM-IV marijuana abuse or dependence significantly (P =.01) increased between 1991-1992 (1.2%) and 2001-2002 (1.5%), with the greatest increases observed among young black men and women (P<.001) and young Hispanic men (P =.006). Further, marijuana use disorders among marijuana users significantly increased (P =.002) in the absence of increased frequency and quantity of marijuana use, suggesting that the concomitant increase in potency of delta-9-tetrahydrocannabinol (Delta(9)-THC) may have contributed to the rising rates. CONCLUSIONS: Despite the stability in the overall prevalence of marijuana use, more adults in the United States had a marijuana use disorder in 2001-2002 than in 1991-1992. Increases in the prevalence of marijuana use disorders were most notable among young black men and women and young Hispanic men. Although rates of marijuana abuse and dependence did not increase among young white men and women, their rates have remained high. The results of this study underscore the need to develop and implement new prevention and intervention programs targeted at youth, particularly minority youth.


The present study takes a developmental approach to subgrouping and examines the trajectories of substance use from early adolescence through young adulthood among a community sample of 481 individuals. The patterns of use were examined, subgroups were identified separately for men and women and for alcohol and marijuana, and psychosocial predictors and psychopathology outcomes that differentiated the groups were identified. The results revealed three substantially overlapping subgroups for both alcohol and marijuana: early onset, late onset, and nonuser. Although the general patterns of which dependent variables were related to group were similar for alcohol and marijuana, a closer examination revealed important subgroup differences. For alcohol use, the early-onset group was more dysfunctional in terms of predictors and outcomes whereas the late-onset and nonuser groups were better adjusted. In contrast, for marijuana, the early- and late-onset groups were both more dysfunctional than the nonuser group. In a final analysis, we examined the predictive utility of our developmental approach to subgrouping compared to a traditional, static approach.


The objective of this study was to evaluate the impact of a revised state-of-the-art drug prevention program, Project ALERT, on risk factors for drug use in mostly rural midwestern schools and communities. Fifty-five middle schools from South Dakota were randomly assigned to treatment or control conditions. Treatment-group students received 11 lessons in Grade 7 and 3 more in Grade 8. Effects for 4276 eighth graders were assessed 18 months after baseline.
Results indicate that Project ALERT had statistically significant effects on all the targeted risk factors associated with cigarette and marijuana use and more modest gains with the pro-alcohol risk factors. The program helped adolescents at low, moderate, and high risk for future use, with the effect sizes typically stronger for the low- and moderate-risk groups. Thus, school-based drug prevention programs can lower risk factors that correlate with drug use, help low- to high-risk adolescents, and be effective in diverse school environments.


Cannabis is evermore present in society, whether within the general public or as a subject for scientific debate. Mass consumption of cannabis, for example, is stabilising around 22 percent of 18-year old who admit to having used it at least once during the previous month; however, this consumption rate falls off as they enter later adulthood. This article describes the emerging scientific consensus about the effects of this drug. The psychotropic effects of cannabis—the result of cannabinoids contained in its resin that activate specific receptors—include general euphoria, a mild release from inhibitions and, in certain cases, some distortion of sensory perception. Some patients also experience drowsiness, a stimulated appetite and anxiolytics, while others anticipate a more intense experience such as an altered state of consciousness. The toxicity of smoked cannabis and its acute, chronic secondary effects are described, as well as the problematic relationship between cannabis consumption and psychosis. The damages and toxic effects attributed to such consumption are presented via three, related themes: the growth of dependency, negative somatic consequences (including cognitive impairment and its consequences for driving an automobile, and damaging psychosocial effects. "Escalation theory" is criticized. In their conclusion, the authors cast doubt on the scientific grounds for penalisation of cannabis consumption, and recommend a "de-demonisation" of the drug. An analysis and discussion of the current penalties applied in Belgium are presented.


BACKGROUND: Use of illicit drugs, particularly cannabis, by young people is widespread and is associated with several types of psychological and social harm. These relations might not be causal. Causal relations would suggest that recreational drug use is a substantial public health problem. Non-causal relations would suggest that harm-reduction policy based on prevention of drug use is unlikely to produce improvements in public health. Cross-sectional evidence cannot clarify questions of causality; longitudinal or interventional evidence is needed. Past reviews have generally been non-systematic, have often included cross-sectional data, and have underestimated the extent of methodological problems associated with interpretation. METHODS: We did a systematic review of general population longitudinal studies reporting associations between illicit drug use by young people and psychosocial harm. FINDINGS: We identified 48 relevant studies, of which 16 were of higher quality and provided the most robust evidence. Fairly consistent associations were noted between cannabis use and both lower educational attainment and increased reported use of other illicit drugs. Less consistent associations were noted between cannabis use and both psychological health problems and problematic behaviour. All these associations seemed to be explicable in terms of non-causal mechanisms. INTERPRETATION: Available evidence does not strongly support an important causal relation between cannabis use by young people and psychosocial harm, but cannot exclude the possibility that such a relation exists. The lack of evidence of robust causal relations prevents the attribution of public health detriments to illicit drug use. In view of the extent of illicit drug use, better evidence is needed.

**OBJECTIVES:** We tested the premise that punishment for cannabis use deters use and thereby benefits public health. **METHODS:** We compared representative samples of experienced cannabis users in similar cities with opposing cannabis policies-Amsterdam, the Netherlands (decriminalization), and San Francisco, Calif (criminalization). We compared age at onset, regular and maximum use, frequency and quantity of use over time, intensity and duration of intoxication, career use patterns, and other drug use. **RESULTS:** With the exception of higher drug use in San Francisco, we found strong similarities across both cities. We found no evidence to support claims that criminalization reduces use or that decriminalization increases use. **CONCLUSIONS:** Drug policies may have less impact on cannabis use than is currently thought.


**OBJECTIVE:** To determine the prevalence of the heavy use of drugs among elementary and high school students in a sample of public and private schools, and to identify associated demographic, psychological, cultural and social factors. **METHODS:** This report describes a cross-sectional study using an intention-type sampling technique that compared public schools in central and peripheral areas and private schools. An anonymous self-administered questionnaire was applied. The sample consisted of 2,287 elementary and high school students in the city of Campinas in 1998. Heavy use of drugs was defined as the use of drugs on 20 or more days during the 30 days preceding the survey (WHO, 1981). For the statistical analysis, polytomic logistic regression analysis (logit model) was utilized to identify factors that influenced this manner of using drugs. **RESULTS:** Heavy use of legal and illegal drugs was found as follows: alcohol (11.9%), tobacco (11.7%), marijuana (4.4%), solvents (1.8%), cocaine (1.4%), medications (1.1%) and ecstasy (0.7%). The heavy use of drugs was greatest among students at the city-center public school who had daytime jobs and studied in the evenings. These students were in the A and B socioeconomic classes and had had little religious education during childhood. **CONCLUSIONS:** Greater availability of cash and specific socialization patterns were identified as factors associated with the heavy use of drugs among students.


Adolescent tobacco smokers have higher rates of marijuana (MJ) use than nonsmokers. Because MJ smoking typically involves deeper inhalation and longer breathholding than tobacco smoking, we hypothesized greater puff volume, longer puff duration and puff interval, and higher puff velocity during tobacco smoking among (1) MJ-using teens; (2) teens whose onset of MJ smoking occurred before tobacco (MBT). One hundred and three tobacco-dependent adolescents presented for smoking cessation treatment (66.0% female, 71.0% European American, mean age 15.3+/−1.25 years) smoked one cigarette of their own brand in the laboratory prior to study entry. Topography and associated physiological measures among current recreational (<5 days in a 14-day period) MJ users (n=25), current heavy (≥5 days in a 14-day period) MJ users (n=22) and current non-MJ-smoking teens (n=56) were compared. There were no differences in tobacco smoking topography or physiological measures by recent MJ-smoking history or by order of substance initiation. Significantly more African American than European American adolescent smokers reported MJ use before tobacco. Our findings in adolescent smokers are consistent with results from adult studies in which history of MJ smoking was not associated with changes in tobacco smoking topography.

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