INTRODUCTION

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BASIC SCIENCE


Oral administration of the opioid antagonist nalmefene alone (up to 20 mg/kg) failed to show a significant effect on acute food intake in mice. However, combined oral dosing of nalmefene and subthreshold doses of AM251, a cannabinoid CB1 receptor inverse agonist, led to a significant reduction in food intake in both lean and diet-induced obese (DIO) mice. Furthermore, the anorectic effect of a high dose of AM251 was further enhanced when co-administered with nalmefene. The results support a synergistic interaction between opioid and cannabinoid systems in regulating feeding behavior.


Cannabidiol, the major non-psychoactive component of marijuana, has various pharmacological actions of clinical interest. It is reportedly effective as an anti-inflammatory and anti-arthritic in murine collagen-induced arthritis. The present study examined the anti-inflammatory and anti-hyperalgesic effects of cannabidiol, administered orally (5-40 mg/kg) once a day for 3 days after the onset of acute inflammation induced by intraplantar injection of 0.1 ml carrageenan (1% w/v in saline) in the rat. At the end of the treatment prostaglandin E2 (PGE2) was assayed in the plasma, and cyclooxygenase (COX) activity, production of nitric oxide (NO; nitrite/nitrate content), and of other oxygen-derived free radicals (malondialdehyde) in inflamed paw tissues. All these markers were significantly increased following carrageenan. Thermal hyperalgesia, induced by carrageenan and assessed by the plantar test, lasted 7 h. Cannabidiol had a time- and dose-dependent anti-hyperalgesic effect after a single injection. Edema following carrageenan peaked at 3 h and lasted 72 h; a single dose of cannabidiol reduced edema in a dose-dependent fashion and subsequent daily doses caused further time- and dose-related reductions. There were decreases in PGE2 plasma levels, tissue COX activity, production of oxygen-derived free radicals, and NO after three doses of cannabidiol. The effect on NO seemed to depend on a lower expression of the endothelial isoform of NO synthase. In conclusion, oral cannabidiol has a beneficial action on two symptoms of established inflammation: edema and hyperalgesia.


OBJECTIVE: The aim of this study was to investigate the expression of cannabinoid receptors in human uterine smooth muscle during pregnancy and to evaluate the effects of
endogenous and exogenous cannabinoids on myometrial contractility in vitro. Study design Human myometrial biopsy specimens were obtained at elective cesarean delivery and snap frozen or mounted for isometric recording under physiologic conditions. Cumulative doses of the endogenous cannabinoid anandamide or the exogenous cannabinoid Delta(9) (indicates a double bond between carbons 9 and 10) tetrahydrocannabinol were added in the range 1 nmol/L to 100 micromol/L. Selectivity of the cannabinoid receptor agonists was investigated with specific antagonists for the CB(1) and the CB(2) receptors. Reverse transcription-polymerase chain reaction with primers for the CB(1) and CB(2) receptors was performed on messenger RNA that was isolated from human pregnant myometrium. RESULTS: Both anandamide and Delta(9)-tetrahydrocannabinol exerted a direct relaxant effect on human pregnant myometrium in vitro, which was of equal potency for both compounds. This relaxant effect was antagonized by the specific CB(1) receptor antagonist, SR 141716, but not by the specific CB(2) receptor antagonist, SR 144528 (n=6 specimens, P<.01). Both the CB(1) and CB(2) receptors are expressed in human myometrium. CONCLUSIONS: Both endogenous and exogenous cannabinoids exert a potent and direct relaxant effect on human pregnant myometrium, which is mediated through the CB(1) receptor. This highlights a possible role for endogenous cannabinoids during human parturition and pregnancy. These results also support the view that the use of exogenous cannabinoids during pregnancy is not linked independently with preterm labor.
increase is almost entirely eliminated by the cannabinoid agonist CP55,940. These data suggest that cannabinoids affect MHC class II expression through actions on CIITA at the transcripational level.


Endocannabinoids may serve as retrograde messengers to inhibit neurotransmitter release during depolarization-induced suppression of inhibition (DSI) or excitation (DSE). We therefore tested whether endocannabinoids inhibit N-type voltage-dependent Ca(2+) channels by activating G(1/o)-protein-coupled CB1 cannabinoid receptors (CB1R)-a possible mechanism underlying DSI/DSE. Three putative endocannabinoids [2-arachidonoylglycerol (2-AG), 2-arachidonyl glycerol ether (2-AGE), and anandamide (AEA)] and the cannabimimetic aminoalkylindole WIN 55,212-2 (WIN) inhibited whole-cell Ca(2+) currents in rat sympathetic neurons previously injected with cDNA encoding a human CB1R. Agonist-mediated Ca(2+) current inhibition was blocked by a selective CB1R antagonist [SR141716A, N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboximide hydrochloride] and pertussis toxin (PTX) pretreatment. The rank order of potency was WIN (IC(50) = 2 nM) > 2-AGE (350 nM) > 2-AG (480 nM) > AEA (approximately 3 microM), with each agonist displaying similar efficacy (approximately 50% maximal inhibition). Increasing CB1R expression level significantly enhanced AEA potency. AEA (10 microM) also inhibited Ca(2+) channels in a voltage-independent, CB1R-independent, and PTX-insensitive manner, whereas 2-AG and 2-AGE were devoid of this activity. All three endocannabinoids activated G-protein-coupled inwardly rectifying potassium (GIRK) channels, GIRK1/4, heterologously expressed in sympathetic neurons. These results suggest a mechanism by which endocannabinoids might influence presynaptic function.


Endogenous and exogenous cannabinoids (CBs) acting through the CB(1) receptors have been implicated in the regulation of several behavioral and neuroendocrine functions. Modulation of endocannabinoidergic system by ethanol in mouse brain, and the association of suicide and mood disorders with alcoholism suggest possible involvement of the cannabinoidergic system in the pathophysiology of depression and suicide. Therefore, the present study was undertaken to examine the levels of CB(1) receptors and mediated signaling in the dorsolateral prefrontal cortex (DLPFC) of subjects with major depression who had died by suicides (depressed suicides, DS). [(3)H]CP-55,940 and CB(1) receptor-stimulated [(35)S]GTPgammaS binding sites were analyzed in membranes obtained from DLPFC of DS (10) and matched normal controls (10). Upregulation (24%, P<0.0001) of CB(1) receptor density (B(max)) was observed in DS (644.6+/-48.8 fmol/mg protein) compared with matched controls (493.3+/-52.7 fmol/mg protein). However, there was no significant alteration in the affinity of receptor (DS; 1.14+/-0.08 vs control; 1.12+/-0.10 nM). Higher density of CB(1) receptors in DS (38%, P<0.001) was also demonstrated by Western blot analysis. The CB(1) receptor-stimulated [(35)S]GTPgammaS binding was significantly greater (45%, P<0.001) in the DLPFC of DS compared with matched controls. The observed upregulation of CB(1) receptors with concomitant increase in the CB(1) receptor-mediated [(35)S]GTPgammaS binding suggests a role for enhanced cannabinoidergic signaling in the prefrontal cortex of DS. The cannabinoidergic system may be a novel therapeutic target in the treatment of depression and/or suicidal behavior. Molecular Psychiatry (2004) 9, 184-190. doi:10.1038/sj.mp.4001376


The last decade has witnessed a rapid expansion in our understanding of the mammalian endogenous cannabinoid system. In just a few short years since the discovery of endogenous lipids that serve as cannabinoids in vivo, these molecules have been shown to participate in a
broad array of physiological and pathological processes. Consequently, attention has been directed at defining the proteins responsible for endocannabinoid synthesis, transport, and metabolism. Recently, multiple fatty acid oxygenases including, most notably, cyclooxygenase-2 (COX-2), have been implicated in endocannabinoid metabolism. This review will highlight connections between COX-2 and the endogenous cannabinoid system. The available biochemical evidence supporting a role for COX-2 in endocannabinoid metabolism will be presented. Finally, the potential biological consequences of COX-2-mediated endocannabinoid oxygenation will be discussed.


The cannabinoid 1 receptor antagonist AM 251 is known to block the inhibitory effects of endocannabinoids and synthetic cannabinoid agonists on transmitter release through an action at presynaptic cannabinoid 1 receptors in brain. We examined the ability of AM 251 to inhibit sodium channel-dependent functions and the binding of [3H]batrachotoxinin A 20-alpha-benzoate to sodium channels in mouse brain synaptic preparations. Depolarization of synaptoneurosomes by the sodium channel site 2-specific neurotoxin veratridine, which is abolished by tetrodotoxin, was found to be inhibited in a concentration-dependent fashion by AM 251 (IC50=8.9 microM). Veratridine-dependent (tetrodotoxin suppressible) release, of L-glutamic acid and GABA from synaptosomes was also reduced by AM 251 [IC50s=8.5 microM (L-glutamic acid), 9.2 microM (GABA)]. The binding of the radioligand [3H]batrachotoxinin A 20-alpha-benzoate to site 2 on sodium channels was displaced by AM 251 (IC50=11.2 microM). Scatchard analysis of binding showed that at its IC50, AM 251 increased (by 2.3 times) the KD of radioligand without altering Bmax, suggesting a competitive mechanism of inhibition by AM 251. Kinetic experiments indicated that AM 251 inhibits equilibrium binding by allosterically accelerating the dissociation of the [3H]-batrachotoxinin A 20-alpha-benzoate:sodium channel complex. Our data suggest that micromolar concentrations of AM 251 are capable of reducing neuronal excitability and inhibiting release of excitatory and inhibitory transmitters through blockade of voltage-sensitive sodium channels in brain.


Changes in vascular responsiveness are proposed as the basis for some of the cardiovascular complications in cholestasis. Cholestasis is also associated with accumulation of endogenous opioid peptides and evidence of nitric oxide (NO) overproduction. On the other hand, it is well known that anandamide, an endogenous cannabinoid ligand, causes hypotension and a decrease in systemic vascular resistance. In the present study, the possible role of the cannabinoid system in cholestasis-induced mesenteric vascular bed responsiveness was investigated. Mesenteric arteries of bile duct-ligated and sham-operated rats receiving daily administrations of saline were used for evaluating phenylephrine or anandamide dose-response, acute effects of N(G)-nitro-L-arginine methyl ester (L-NAME, 100 microM), a non-selective inhibitor of NO synthase (NOS), or naltrexone, an opioid receptors antagonist (1 microM). The other groups of bile duct-ligated and sham-operated rats received daily intraperitoneal administration of L-NAME (20 mg/kg/day), amino guanidine, a selective inducible NOS (iNOS) inhibitor (150 mg/kg/day) or naltrexone (10 mg/kg/day). After 7 days, the superior mesenteric artery was cannulated and the mesenteric vascular bed was perfused according to the McGregor method. Anandamide-induced relaxation was significantly potentiated in mesenteric vascular beds of bile duct-ligated rats. Chronic treatment of bile duct-ligated animals with L-NAME and aminoguanidine blocked this hyperresponsiveness while the hyperresponsiveness was potentiated at large doses of anandamide on chronic treatment of these animals with naltrexone. Although acute L-NAME treatment of mesenteric beds completely blocked the anandamide-induced vasorelaxation in sham-operated rats, this vasorelaxation still was present in bile duct-ligated animals. Anandamide-induced vasorelaxation remained unaffected after acute naltrexone treatment of mesenteric beds in both bile duct-ligated and sham-operated rats. Our results indicate that (1) there is enhanced anandamide-induced vasorelaxation in cholestatic rats,
probably due to a defect in cannabinoid or vanilloid receptors and (2) NO overproduction may be involved in cholestasis-induced vascular hyperresponsiveness.


**STUDY OBJECTIVES:** The principal component of marijuana, delta-9-tetrahydrocannabinol increases sleep in humans. Endogenous cannabinoids, such as N-arachidonylethanolamine (anandamide), also increase sleep. However, the mechanism by which these molecules promote sleep is not known but might involve a sleep-inducing molecule such as adenosine. Microdialysis samples were collected from the basal forebrain in order to detect levels of adenosine before and after injection of anandamide. **DESIGN:** Rats were implanted for sleep studies, and a cannula was placed in the basal forebrain to collect microdialysis samples. Samples were analyzed using high-performance liquid chromatography. **SETTINGS:** Basic neuroscience research laboratory. **PARTICIPANTS AND INTERVENTIONS:** Three-month-old male F344 rats. At the start of the lights-on period, animals received systemic injections of dimethyl sulfoxide (vehicle), anandamide, SR141716A (cannabinoid receptor 1 [CB1] antagonist), or SR141716A and anandamide. One hour after injections, microdialysis samples were collected (5 microL) from the basal forebrain every hour over a 20-minute period for 5 hours. The samples were immediately analyzed via high-performance liquid chromatography for adenosine levels. Sleep was also recorded continuously over the same period. **MEASUREMENTS AND RESULTS:** Anandamide increased adenosine levels compared to vehicle controls with the peak levels being reached during the third hour after drug injection. There was a significant increase in slow-wave sleep during the third hour. The induction in sleep and the rise in adenosine were blocked by the CB1-receptor antagonist, SR141716A. **CONCLUSIONS:** Anandamide increased adenosine levels in the basal forebrain and also increased sleep. The soporific effects of anandamide were mediated by the CB1 receptor, since the effects were blocked by the CB1-receptor antagonist. These findings identify a potential therapeutic use of endocannabinoids to induce sleep in conditions where sleep may be severely attenuated.


We have investigated the vascular effects of N-arachidonoyl-dopamine (NADA), a novel endocannabinoid/vanilloid. NADA caused vasorelaxant effects comparable to those of anandamide in small mesenteric vessels (G3), the superior mesenteric artery (G0) and in the aorta. In G3, addition of N(G)-nitro-L-arginine methyl ester (300 micro M) or the dopamine (D1) receptor antagonist (SCH23390, 1 micro M) did not affect responses to NADA. In the presence of 60 mM KCl, after de-endothelialisation, or after K(+) channel inhibition with charybdotoxin (100 nM) and apamin (500 nM), relaxant responses to NADA were inhibited. In G3, pretreatment with the vanilloid receptor (VR) agonist capsaicin (10 micro M) or the VR antagonist capsazepine (10 micro M) reduced vasorelaxation to NADA. In G3, application of the CB1 antagonist SR141716A at 1 micro M but not 100 nM reduced the potency of NADA. Another CB1 antagonist, AM251 (100 nM and 1 micro M), did not affect vasorelaxation to NADA. After endothelial denudation, SR141716A (1 micro M) did not reduce the responses further. A combination of capsaicin and SR141716A (1 micro M) reduced vasorelaxation to NADA further than with capsaicin pretreatment alone. The novel endothelial cannabinoid (CB) receptor antagonist O-1918 opposed vasorelaxation to NADA in G3. In the superior mesenteric artery (G0), vasorelaxation to NADA was not dependent on an intact endothelium and was not sensitive to O-1918, but was sensitive to capsaicin and SR141716A or AM251 (both 100 nM). The results of the present study demonstrate for the first time that NADA is a potent vasorelaxant. In G3, the effects of NADA are mediated by stimulation of the VR and the novel endothelial CB receptor, while in G0, vasorelaxation is mediated through VR1 and CB1 receptors.

Cannabinoids exhibit broad, immune, modulating activity by targeting many cell types within the immune system, including T cells, which exhibit sensitivity, as evidenced by altered activation, proliferation, and cytokine expression. As a result of the critical role calcium plays in T cell function coupled with previous findings demonstrating disruption of the calcium-regulated transcription factor, nuclear factor of activated T cells, by cannabinoid treatment, the objective of the present investigation was to perform an initial characterization of the role of the cannabinoid receptors in the regulation of the intracellular calcium concentration ([Ca(2+)]i) by Delta(9)-tetrahydrocannabinol (Delta(9)-THC) in T lymphocytes. Here, we demonstrate that Delta(9)-THC robustly elevates [Ca(2+)]i in purified, murine, splenic T cells and in the human peripheral blood acute lymphoid leukemia (HPB-ALL) human T cell line but only minimally elevates [Ca(2+)]i in Jurkat E6-1 (dysfunctional cannabinoid receptor 2-expressing) human T cells. Removal of extracellular calcium severely attenuated the Delta(9)-THC-mediated rise in [Ca(2+)]i in murine, splenic T cells and HPB-ALL cells. Pretreatment with cannabinoid receptor antagonists, SR144528 and/or SR141716A, led to an attenuation of Delta(9)-THC-mediated elevation in [Ca(2+)]i in splenic T cells and HPB-ALL cells but not in Jurkat E6-1 cells. Furthermore, pretreatment of HPB-ALL cells with SR144528 antagonized the small rise in [Ca(2+)]i elicited by Delta(9)-THC in the absence of extracellular calcium. These findings suggest that Delta(9)-THC induces an influx of extracellular calcium in T cells in a cannabinoid receptor-dependent manner.


OBJECTIVE:: There is growing evidence for an implication of the CB1 receptor subtype of the endocannabinoid system in the regulation of eating and fat deposition. To further define the physiological role of these receptors in the control of energy balance, we characterized the phenotype of CB1 receptor knockout (CB1(-/-)) mice maintained on an obesity-prone regimen or on a standard chow. DESIGN:: CB1 (+/+) male mice were compared to wild-type animals (CB1 (+/+) male mice) in two feeding paradigms: (1) with a standard laboratory regimen (3.5 kcal/g, 14.5% of energy as fat) and (2) on a free-choice paradigm consisting of offering both the standard laboratory chow and a high-fat diet (HFD) (4.9 kcal/g, 49% of energy as fat). RESULTS:: When maintained on the standard diet, CB1 (-/-) mice are lean. At the age of 20 weeks, their body weight and adiposity are, respectively, 24 and 60% lower than that of CB1 (+/+) mice. They are slightly hypophagic, but when expressed as percent of body weight, their relative energy intake is similar to that of the wild-type animals. Furthermore, inactivation of CB1 receptors reduces plasma insulin and leptin levels, and enhances the response to intracerebroventricular leptin injection. The free-choice paradigm shows that the preference for a high-fat highly palatable chow is slightly delayed in onset but maintained in CB1 (-/-) mice. However, loading CB1 (-/-) mice with this obesity-prone diet does not result in development of obesity. Knockout mice do not display hyperphagia or reduction of their relative energy intake in contrast to CB1 (+/+) mice, and their feeding efficiency remains low. These data suggest an improved energetic metabolism with the high-fat regimen. Furthermore, the insulin resistance normally occurring in HFD-fed mice is not present in CB1 (-/-) mice. CONCLUSION:: These results provide evidence that the stimulation of CB1 receptors is a key component in the development of diet-induced obesity, and that these receptors and their endogenous ligands are implicated not only in feeding control but also in peripheral metabolic regulations. The lack of effect of SR141716, a selective CB1 receptor antagonist, in CB1 (-/-) mice further supports this hypothesis, as this compound was previously shown to display potent anti-obesity properties in diet-induced obese C57BL/6 mice. International Journal of Obesity advance online publication, 10 February 2004; doi:10.1038/sj.ijo.0802583


Using two distinct anti-CB2 receptor Abs, we investigated the expression patterns of the peripheral cannabinoid receptor CB2 in human secondary lymphoid organs. Immunohistochemical analysis using an N-terminal specific anti-CB2 Ab revealed high protein expression in the germinal centers (GCs) of secondary follicles. A C-terminal specific anti-CB2 Ab, which only recognizes a nonphosphorylated inactive receptor, showed positivity in the mantle
zones (MZs) and marginal zones (MGZs) of the secondary follicles where resting cells reside, and in the primary follicles. In contrast, no positivity was observed in GCs using the C-terminal Ab, suggesting that active CB2 receptors are mainly present on cells in the GCs. Dual immunohistochemical analysis revealed that B lymphocytes express the CB2 protein abundantly. In contrast to B cells in the MZ or MGZ, CB2-expressing cells in the GCs coexpress the costimulatory membrane protein CD40, which is mainly expressed in the GCs and at very low levels in the MZs and MGZs and the proliferation marker Ki-67. Using the human Raji B cell line as a model, we demonstrate in a transwell assay that moderate migration occurs upon stimulation of the CB2 receptor with the endocannabinoid 2-arachidonoylglycerol, which is enhanced by CD40 costimulation. Our findings, that GC-related cells express active CB2 and that CB2-dependent migration requires CD40 costimulation, suggest that CB2 is involved in B cell activation.


Activation of the CB1 cannabinoid receptor inhibits neurotransmission at numerous synapses in the brain. Indeed, CB1 is essential for certain types of both short- and long-term synaptic depression. It was demonstrated recently that CB1 is critical for activity-dependent long-term depression (LTD) at glutamatergic corticostriatal synapses in acute brain slice preparations. Here, we show that CB1 activation is necessary, but not solely sufficient, for induction of LTD and that the requisite signaling by endocannabinoids (eCBs) occurs during a time window limited to the first few minutes after high-frequency stimulation delivery. In addition, we have applied intracellularly anandamide membrane transporter inhibitors to provide novel evidence that postsynaptic transport mechanisms are responsible for the release of eCBs from striatal medium spiny neurons. These findings shed new light on the mechanisms by which transient eCB formation participates in the induction of long-lasting changes in synaptic efficacy that could contribute to brain information storage.


BOLD-contrast functional magnetic resonance imaging (fMRI) was used to investigate the effects of the synthetic cannabinoid agonist HU210 on the rat brain in order to determine potential CNS sites of action for the functional effects of cannabinoids. After obtaining basal data, rats (n = 8) were given the cannabinoid agonist HU210 (10 microg/kg i.v) and volume data sets collected for 85 mins. Significant increases in functional BOLD activity were observed in specific brain regions including those important in pain (PAG), reward (VTA and accumbens) and motor function (striatum). In order to confirm cannabinoid receptor involvement in the HU210 evoked functional BOLD activity, rats (n = 8) were pre-treated with the CB(1) cannabinoid receptor antagonist SR141716A (100 microg/kg i.v) prior to HU210. Pretreatment with SR141716A abolished all significant evoked HU210 functional BOLD activity. To exclude the involvement of potential systemic effects induced by the cannabinoid agonist administration on the observed evoked functional BOLD activity a separate experiment investigated the effect of HU210 (10 microg/kg i.v) on mean arterial pressure and showed that HU210 had no significant effect on pressure under chloral hydrate anaesthesia. In summary, this study demonstrates that the cannabinoid agonist HU210 evokes a significant increase in BOLD functional activity in specific regions and that this was cannabinoid receptor mediated. Furthermore the study indicates the potential value of fMRI in rodents to delineate pharmacologically induced changes in regional brain function.


Anorexia nervosa (AN) is a severe and disabling psychiatric disorder, characterized by profound weight loss and body image disturbance. Family and twin studies indicate a significant
The genetic contribution to this disorder although no genetic mutation has yet been identified. The endocannabinoid system has recently been implicated in many physiological functions including appetite regulation. We, therefore, undertook a family based study to test the hypothesis whether a polymorphism of the CNR1 gene, which encodes human CB1 receptor, a subclass of the central cannabinoid receptor, contributes to the susceptibility to AN. Fifty two families (parents with one or two affected siblings) were genotyped for the (AAT) trinucleotide repeat of CNR1 gene. Using the haplotype relative risk (HRR) method, the distribution of alleles transmitted to the patients was not found to be significantly different from the non-transmitted parental alleles. However, upon dividing the samples to restricting and binging/purging subtypes of AN, the extended transmission disequilibrium test (ETDT) revealed that there is preferential transmission of different alleles in each of the subtypes. The 14 repeat allele was preferentially transmitted in the binging/purging AN group (P = 0.05) but not in the restricting AN group, whereas the 13 repeat allele was preferentially transmitted in the restricting AN group (almost significant, P = 0.07) but not in the binging/purging AN group. Our study suggests that restricting AN and binging/purging AN may be associated with different alleles of the CNR1 gene.


Marijuana produces a number of characteristic behaviors in humans and animals, including memory impairment, antinociception, and locomotor and psychoactive effects. However, tolerance and dependence to cannabinoids develops after chronic use, as demonstrated both clinically and in animal models. The potential therapeutic benefits of certain cannabinoid-mediated effects, as well as the use of marijuana for its psychoactive properties, has raised interest in understanding the cellular adaptations produced by chronic administration of this class of drugs. The primary active constituent of marijuana, delta9-tetrahydrohydrocannabinol (THC), binds to specific G-protein-coupled receptors. The central nervous system (CNS) effects of THC are mediated by CB1 receptors, which couple primarily to inhibitory G-proteins. High levels of CB1 receptors are found in the basal ganglia, hippocampus, cortex, and cerebellum, consistent with the profile of behavioral effects. Studies over the past decade have determined that CB1 receptors undergo downregulation and desensitization following chronic administration of THC or synthetic cannabinoid agonists. In general, these adaptations are regionally widespread and of considerable magnitude, and are thought to contribute to tolerance to cannabinoid-mediated behavioral effects. Adaptation at the effector level has been more difficult to characterize, although it appears that alterations in cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activity may be particularly important in cannabinoid dependence. A striking characteristic of CB1 receptor adaptation is the region dependence of the magnitude and rate of development of downregulation and desensitization. These regional differences may provide interesting insights into the mechanisms of CB1 receptors receptor signaling in different brain regions. Moreover, region-specific adaptations in CB1 receptors following chronic cannabinoid administration may produce differential adaptations at the in vivo level.


The major psychoactive component of cannabis derivatives, delta9-THC, activates two G-protein coupled receptors: CB1 and CB2. Soon after the discovery of these receptors, their endogenous ligands were identified: lipid metabolites of arachidonic acid, named endocannabinoids. The two major main and most studied endocannabinoids are anandamide and 2-arachidonyl-glycerol. The CB1 receptor is massively expressed through-out the central nervous system whereas CB2 expression seems restricted to immune cells. Following endocannabinoid binding, CB1 receptors modulate second messenger cascades (inhibition of adenylate cyclase, activation of mitogen-activated protein kinases and of focal-adhesion kinases) as well as ionic conductances (inhibition of voltage-dependent calcium channels, activation of several potassium channels). Endocannabinoids transiently silence synapses by decreasing neurotransmitter release, play major parts in various forms of synaptic plasticity because of their ability to behave as retrograde messengers and activate non-cannabinoid receptors (such as vanilloid receptor type-1), illustrating the complexity of the endocannabinoid system. The diverse cellular targets of
endocannabinoids are at the origin of the promising therapeutic potentials of the endocannabinoid system.


Growing evidence suggests that a major physiological function of the cannabinoid signaling system is to modulate neuroinflammation. This review discusses the anti-inflammatory properties of cannabinoid compounds at molecular, cellular and whole animal levels, first by examining the evidence for anti-inflammatory effects of cannabinoids obtained using in vivo animal models of clinical neuroinflammatory conditions, specifically rodent models of multiple sclerosis, and second by describing the endogenous cannabinoid (endocannabinoid) system components in immune cells. Our aim is to identify immune functions modulated by cannabinoids that could account for their anti-inflammatory effects in these animal models.


Endogenous cannabinoid ligands (endocannabinoids) produced by neurons, astrocytes, and microglial cells activate cannabinoid receptors, the molecular target for marijuana's bioactive ingredient Delta(9)-tetrahydrocannabinol. The molecular mechanism underlying the production of the most abundant endocannabinoid, 2-arachidonoylglycerol (2-AG), is unclear. A prevalent hypothesis proposes that activation of metabotropic receptors coupled to the phosphatidylinositol-specific phospholipase C and diacylglycerol (DG) lipase pathway will systematically lead to increases in 2-AG production. Here, we show that ATP increases 2-AG production by cultured microglial cells in a phosphatidylinositol-specific phospholipase C and DG lipase-dependent manner. However, efficacious activation of metabotropic P2Y purinergic receptors coupled to phosphatidylinositol-specific phospholipase C does not increase 2-AG production. This suggests that ionotropic, and not metabotropic, purinergic receptors control 2-AG production at an unexpected enzymatic step of its metabolic pathway. We show that activation of P2X7 ionotropic receptors, which are highly permeable to calcium, is necessary and sufficient to increase 2-AG production in microglial cells. We also show that the sustained rise in intracellular calcium induced by activation of P2X7 receptors directly increases DG lipase activity while inhibiting the activity of monoacylglycerol lipase, the enzyme that degrades 2-AG. This inverse sensitivity of DG lipase and monoacylglycerol lipase to calcium constitutes an original and efficient modality for sustained accumulation of 2-AG. Because prolonged increases in 2-AG amounts in brain parenchyma are thought to orchestrate neuroinflammation, the enzymatic steps involved in 2-AG synthesis and degradation by microglial cells constitute appealing targets for therapy aimed at controlling exacerbated neuroinflammation.


Previous studies suggest that long-term cannabis use causes cognitive impairment, including lack of motivation and impaired attention, conditions that also resemble core negative symptoms of schizophrenia. The anterior cingulate cortex (ACC) plays an important role in normal cognition, particularly in relation to motivation and attention. This could suggest that changes in the cannabinoid (CB) system might be present in the ACC of patients suffering schizophrenia. The present study examined the distribution and density of CB1 cannabinoid receptors in the left ACC taken postmortem from patients with schizophrenia (n=10) and matched control subjects (n=9). Radioligand binding of [3H]SR141716A, an antagonist that specifically targets CB1 receptors of the endogenous cannabinoid system, was examined on ACC sections using quantitative autoradiography. CB1 receptors had a homogenous distribution among the layers of ACC. A significant 64% increase in [3H]SR141716A specific binding to CB1 receptors was found in the schizophrenia group as compared to the control group (mean+/-.S.E.M.: 46.15+/-.6.22 versus 28.02+/-.2.40 fmol/mg estimated tissue equivalents; p=0.03). The present results support the suggestion that changes in the endogenous cannabinoid system in the ACC may be involved in the pathology of schizophrenia particularly in relation to negative symptoms.
CLINICAL SCIENCE


BACKGROUND: Controversy remains as to whether cannabis acts as a causal risk factor for schizophrenia or other functional psychotic illnesses. Aims To examine critically the evidence that cannabis causes psychosis using established criteria of causality. METHOD: We identified five studies that included a well-defined sample drawn from population-based registers or cohorts and used prospective measures of cannabis use and adult psychosis. RESULTS: On an individual level, cannabis use confers an overall twofold increase in the relative risk for later schizophrenia. At the population level, elimination of cannabis use would reduce the incidence of schizophrenia by approximately 8%, assuming a causal relationship. Cannabis use appears to be neither a sufficient nor a necessary cause for psychosis. It is a component cause, part of a complex constellation of factors leading to psychosis. CONCLUSIONS: Cases of psychotic disorder could be prevented by discouraging cannabis use among vulnerable youths. Research is needed to understand the mechanisms by which cannabis causes psychosis.


Objective. To report popliteal artery entrapment in a patient with distal necrosis and cannabis-related arteritis, two rare or exceptional disorders never described in association. To conduct a targeted review and especially to seek information on the clinical presentation with characteristics specific to each disorder so as to hasten the diagnosis and choose appropriate management. Material and methods. A 19-year-old man who presented with plantar claudication associated with necrosis in a toe underwent diagnostic arteriography and surgery for popliteal artery entrapment type III. Results. Surgical clearance resolved the popliteal artery entrapment but left the clinical symptoms unchanged. Closer questioning disclosed a history of cannabis consumption and intravenous vasodilatory therapy was started. After the 21-day course of vasodilator agents the pain disappeared and the toe necrosis regressed. The patient stopped taking cannabis and had no signs of recurrence. Conclusion. Whereas a popliteal artery entrapment, albeit a rare event, is well described and responds to standardized treatment, popliteal artery entrapment associated with cannabis-induced arteritis is an exceptional event that could confuse management. Because young people-the age group mainly at risk for popliteal artery entrapment-increasingly use cannabis, cannabis arteritis could become a more frequent event associated with other arterial disorders that may confuse the diagnosis and complicate management. Our experience in a young patient suggests that coexisting popliteal artery entrapment and distal necrosis in a young patient should raise a strong suspicion of an associated vascular disorder possibly related to cannabis consumption. Intravenous vasodilatation treatment is successful provided that cannabis use is discontinued.


Marijuana (Cannabis sativa) is a commonly used recreational drug among humans; animals may be exposed following ingestion or accidental inhalation of smoke. From January 1998 to January 2002, 213 incidences were recorded of dogs that developed clinical signs following oral exposure to marijuana, with 99% having neurologic signs, and 30% exhibiting gastrointestinal signs. The marijuana ingested ranged from 1/2 to 90 g. The lowest dose at which signs occurred was 84.7 mg/kg and the highest reported dose was 26.8 g/kg. Onset of signs ranged from 5 min to 96 h, with most signs occurring within 1 to 3 h after ingestion. The signs lasted from 30 min to 96 h. Management consisted of decontamination, sedation (with diazepam as drug of choice), fluid therapy, thermoregulation and general supportive care. All followed animals made full recoveries.
Long-term cannabis abuse may increase the risk of schizophrenia. Nerve growth factor (NGF) is a pleiotropic neurotrophic protein that is implicated in development, protection and regeneration of NGF-sensitive neurones. We tested the hypothesis that damage to neuronal cells in schizophrenia is precipitated by the consumption of cannabis and other neurotoxic substances, resulting in raised NGF serum concentrations and a younger age for disease onset. The NGF serum levels of 109 consecutive drug-naive schizophrenic patients were measured and compared with those of healthy controls. The results were correlated with the long-term intake of cannabis and other illegal drugs. Mean (+/- SD) NGF serum levels of 61 control persons (33.1 +/- 31.0 pg/ml) and 76 schizophrenics who did not consume illegal drugs (26.3 +/- 19.5 pg/ml) did not differ significantly. Schizophrenic patients with regular cannabis intake (> 0.5 g on average per day for at least 2 years) had significantly raised NGF serum levels of 412.9 +/- 288.4 pg/ml (n = 21) compared to controls and schizophrenic patients not consuming cannabis (p < 0.001). In schizophrenic patients who abused not only cannabis, but also additional substances, NGF concentrations were as high as 2336.2 +/- 1711.4 pg/ml (n = 12). On average, heavy cannabis consumers suffered their first episode of schizophrenia 3.5 years (n = 21) earlier than schizophrenic patients who abstained from cannabis. These results indicate that cannabis is a possible risk factor for the development of schizophrenia. This might be reflected in the raised NGF-serum concentrations when both schizophrenia and long-term cannabis abuse prevail.


There is a noticeable lack of targeted treatment options for marijuana dependence, in particular pharmacologic approaches. This is the first study evaluating a targeted pharmacologic approach for marijuana dependence. The goals of the study were to determine if such patients would seek pharmacologic treatment, whether these patients could be retained in treatment using a design previously developed for cocaine-dependent patients, and especially whether valproex sodium showed promise as a treatment agent for marijuana dependence. We found that marijuana-dependent patients will seek treatment, and such patients can be adequately maintained in a pharmacologic trial. Regardless of treatment group, patients reported a significant reduction in their frequency and amount of marijuana use as well as a reduction in irritability. Given the lack of proven effective treatments for marijuana dependence, pharmacotherapies should be sought. The design of a preliminary clinical trial should include a psychosocial/behavioral intervention emphasizing motivation and medication compliance and a placebo control group. (Am J Addict 2004;13:21-32)


The incidence of oral cancer amongst young adults is increasing in many European and high incidence countries. The aim of this study was to evaluate the major risk factors for oral cancer in young adults using a case-control design. A sample of 116 patients aged 45 years and younger, diagnosed with squamous cell carcinoma of the oral cavity between 1990 and 1997 from the south east of England were included. Two-hundred and seven controls who had never had cancer, matched for age, sex and area of residence, were recruited. The self-completed questionnaire contained items about exposure to the following risk factors: tobacco products, cannabis, alcohol and diet. Conditional logistic analyses were conducted adjusting for social class, ethnicity, tobacco and alcohol habits. All tests for statistical significance were two-sided. The majority of oral cancer patients reported exposure to the major risk factors of tobacco and alcohol even at this younger age. The estimated risks associated with tobacco or alcohol use were low (OR range: 0.6-2.5) among both males and females. Only smoking for 21 years or more produced significantly elevated odds ratios (OR=2.1; 95% CI: 1.1-4.0). Exposure associated with other major risk factors did not produce significant risks in this sample. Long term consumption of fresh fruits and vegetables in the diet appeared to be protective for both males and females. The results suggest that although this younger sample exhibit similar behavioural risk factors to older
oral cancer patients, the low odds produced in addition to the relatively short duration of exposure, suggest that factors other than tobacco and alcohol may be implicated in the development of oral cancer in these younger patients.


BEHAVIOURAL SCIENCE

Adolescent marijuana use has tripled recently, and the once-noted race gap between African American and Caucasian adolescents in marijuana use appears to have disappeared. Yet, relatively little research has examined marijuana use among African American adolescents. In this study, we examined developmental trajectories of marijuana use among Caucasian and African American adolescents to identify whether and when differences in marijuana use appear and whether the precursors and outcomes associated with these developmental trajectories differ by race. Findings indicate that both the developmental patterns and outcomes associated with marijuana use are different for African American and Caucasian adolescents. Early-onset Caucasian and mid-onset African American adolescents experienced the greatest number of negative outcomes later in life associated with their marijuana use, suggesting that groups to target for intervention may vary by race.


School-based drug prevention is a central component of drug control strategies. This paper assesses quantitatively its contributions in the United States from a social policy perspective. The social benefits per participant stemming from reduced drug use (approximately $840 from tobacco, alcohol, cocaine and marijuana) appear to exceed the economic costs of running the programs (approximately $150 per participant); while the benefits associated with reduced cocaine use alone (approximately $300) exceed the costs, the corresponding figure for marijuana (approximately $20) is small. Even if prevention reduced the use of other illicit drugs (e.g. heroin) by as much as it reduced use of cocaine, the majority of benefits would still stem from reductions in use of tobacco and alcohol, which has implications for how school-based drug prevention is funded and whether it is perceived more as a weapon in the war on illicit drugs or as a public health measure. Specific numeric results are subject to considerable uncertainty, but the basic character of the conclusions appears to be robust with respect to parameter uncertainty. The greatest uncertainties concern the permanence of prevention's effects and how to value instances of initiation being deferred but not completely prevented. [Caulkins JP, Pacula RL, Paddock S, Chiesa J. What we can--and cannot--expect from school-based drug prevention. Drug Alcohol Rev 2004;23:79-87]


The aim of this study was to make a first comparative approach to teenagers'consumption of psychoactive substances within samples drawn in France and in Brazzaville the Congo. The samples consisted of 1637 French high-school students and 155 Congolese students. An anonymous questionnaire with 13 closed items was completed. Whilst 82.1% of the male and 74.5% of the female French students had already consumed some alcoholic drinks, only 42.4% of the male and 44.0% of female Congolese students had consumed alcohol. French high school students were more affected by tobacco addiction: 22.2% (male) and 22.9% (female) of the French students smoked daily; only 3.0% (male) and 1.9% (female) Congolese students were smokers. The consumption of psychotropic medicines (sedatives, anxiolytics or hypnotics) appeared overall to be less among French high school students than the
Congolesse, particularly in boys (11.9% versus 17.2%). This consumption was mainly from medicine taken without medical prescription or misused. The use of cannabis appeared overall to be higher among French high school students (45.9% of males and 31.6% of females) than the Congolese (12.5% of males and 7.4% of females).


AIMS: To assess the utility of biological testing in a general population survey for estimating prevalence and evaluating self-report data quality. DESIGN: An audio computer-assisted interview was administered to subjects from June 2001 to January 2002. Immediately following the interview, subjects were requested to participate in hair, oral fluid and urine testing. SETTING: Subjects were from randomly selected households in the City of Chicago using multi-stage sampling methods. Interviews were conducted in subjects' homes. PARTICIPANTS: The data represent 627 randomly selected adult participants, ages 18-40 years. MEASUREMENTS: Prevalence, kappa, conditioned kappa, sensitivity, specificity, under-reporting, 'mixed model' and logistic regression. FINDINGS: Higher rates of marijuana use were generated from survey reports than from drug testing. Drug testing generated higher prevalence rates than survey reports for recent use of cocaine and heroin. Under-reporting of recent drug use was apparent for all three substances. Sensitivity was particularly low for cocaine and heroin. Race was related to under-reporting, with African Americans less likely to report marijuana use despite a positive test result. CONCLUSIONS: The utility of drug testing for surveys depends on the type of substance examined as well as on the type of test employed. Multiple tests have more utility than a single test. Drug testing is useful for identifying the levels and sources of under-reporting in a survey and provides a basis for adjusting prevalence estimates based on self-reports.


Aim. To examine the prevalence and possible interconnections among the frequencies of consuming various psychoactive substances in Zagreb adolescents. Also, to assess risk factors associated with the use of tobacco, alcohol, and marijuana. Method. We applied an anonymous, multi-dimensional, self-reporting questionnaire on a representative sample of 2,404 elementary and high school students (total age range, 13-23 years) from Zagreb, Croatia. The questionnaire was designed to explore the extent to which examinees consumed various psychoactive substances, as well as to assess their attitudes and knowledge about the substances. The sociodemographic data were collected on all examinees, their hierarchy of values, family relations, adjustment to school, relationships with peers, and high-risk and delinquent behavior. We analyzed the interconnections among the frequencies of consuming various psychoactive substances, and assessed the factors possibly predictive of substance use. Results. Almost 90% of all examinees experimented with alcohol at least once, 80% with tobacco, 39% with marijuana, and 9% with Ecstasy. Thirty-six percent consumed alcohol and 11% marijuana several times a month, whereas 28% smoked tobacco daily. Although there was no statistically significant difference according to sex in experimenting with psychoactive substances, day-to-day abuse was significantly more frequent among young men than women. About 43% of our examinees believed consuming marijuana should become legally permitted, 37% were against this policy, and 21% were undecided on this issue. Our results showed a high degree of interconnection among the frequencies of consuming tobacco, alcohol, and marijuana. We also found that the best predictive factors for consummation of these three substances were a history of high-risk and delinquent behavior, troubled adjustment to school, domination of hedonistic values, and poor family relations. Regression analysis and pondering for ratios of particular predictors of psychoactive substances use gave values for coefficients of multiple regression as follows: R=0.548 (R(2)=0.300; p<0.001) for tobacco, R=0.575 (R(2)=0.330; p<0.001) for alcohol, and R=0.608 (R(2)=0.370; p<0.001) for marijuana. Knowledge about the consequences of consuming psychoactive substances positively correlated with the frequency of consuming tobacco (r=0.213, p<0.001), alcohol (r=0.226, p<0.001), and marijuana (r=0.320, p<0.001). Conclusion. Most adolescents had personal experience with psychoactive substance abuse, mostly alcohol, tobacco, and marijuana, but only a smaller proportion became regular consumers. The frequency
of substance consumption implied a generalized tendency towards substance abuse among Zagreb adolescents. Our findings could serve as an empirical basis for the re-evaluation of the current drug prevention programs and programs aimed at preventing other forms of risk behavior among children and adolescents.


Chronic administration of 3,4-methylenedioxymethamphetamine (MDMA) is associated with long-term depletion of serotonin (5-HT) and loss of 5-HT axons in the brains of rodents and nonhuman primates. Despite the broad database concerning the selective serotonergic neurotoxicity of recreational MDMA consumption by humans, controversy still exists with respect to the question of whether the well-known functional consequences of these neurotoxic effects, such as memory impairment, were caused by chronic 5-HT deficiency. Habituation and prepulse inhibition (PPI) of the acoustic startle response (ASR) can be used as a marker of central serotonergic functioning in rodents and humans. Thus, we investigated the functional status of the central serotonergic system in chronic but abstinent MDMA users by measuring PPI and habituation of ASR. PPI and habituation of ASR were measured in three groups. The first group (MDMA group) included 20 male drug-free chronic users of MDMA; the second group (cannabis group) consisted of 20 male drug-free chronic users of cannabis; and the third group (healthy controls) comprised 20 male participants with no history of illicit drug use. Analysis revealed significantly increased PPI of MDMA users compared to those of cannabis users and healthy controls. Cannabis users and healthy controls showed comparable patterns of PPI. There were no differences in habituation among the three groups. These results suggest that the functional consequences of chronic MDMA use may be explained by 5-HT receptor changes rather than by a chronic 5-HT deficiency condition. Use of cannabis does not lead to alterations of amplitude, habituation, or PPI of ASR. Neuropsychopharmacology advance online publication, 18 February 2004; doi:10.1038/sj.npp.1300396


PURPOSE: To investigate the influence of two potentially protective factors, Health-as-a-Value and spirituality, on monthly alcohol, cigarette, and marijuana use in two multiethnic groups of adolescents varying in risk. METHODS: Three-hundred-eighty-two students from continuation/alternative high school, a population considered at risk for drug use, participated in the study. The other sample of 260 students was drawn from a medical magnet high school, and is considered to be at lower risk. Similar surveys containing measures of spirituality, "Health-as-a-Value," and monthly substance use, were distributed. Logistic regression analyses were performed. RESULTS: The analyses revealed that spirituality was protective against monthly alcohol use and marijuana use in the lower risk sample. In the higher risk sample, spirituality was protective against all monthly use. "Health-as-a-Value" (HAV) was protective against monthly alcohol use in the low risk sample, and protective against all monthly use in the higher risk sample. Importantly, when both constructs were entered into the same model, spirituality and HAV were independently protective of all monthly use for the higher risk sample and of monthly alcohol use in the lower risk sample. CONCLUSIONS: These findings extend earlier work on protective factors. "Health-as-a-Value" and spirituality may be protective against substance use in environments with different levels of use. Future studies should explore these findings in longitudinal analyses.


PURPOSE: To evaluate the association of body piercing with sociodemographic factors, peer substance use, and high-risk behaviors. METHODS: Cross-sectional analysis using Wave II of the National Longitudinal Study of Adolescent Health (Add Health) Public Use Dataset, a nationally representative, school-based sample of 4337 adolescents, aged 13-18 years, surveyed
in 1996. The major predictor variable was body piercing at locations other than the ears. The outcome variables were selected from five areas of high-risk behaviors including sexual intercourse, substance use (problem drinking, smoking, and marijuana use), violent behavior (fighting and inflicting injuries), antisocial behavior (truancy, shoplifting, and running away), and mood problems (depression, suicidal ideation and suicide attempts). The association between body piercing and peer substance use was also examined. RESULTS: Females (7.2% vs. 1.5%) and older adolescents were more likely to report piercing (all p's <0.01) in linear regression analysis, controlling for sociodemographic factors, body piercing was significantly associated with higher levels of peer substance use (beta = 1.40 [99% CI.57-2.23]). In logistic regression analyses, controlling for sociodemographic factors, piercing was associated with sexual intercourse (OR = 4.5 [99% CI 2.1-10.0]), smoking (3.1 [1.6-5.9]), marijuana use (3.0 [1.6-5.9]), truancy (2.6 [1.3-5.3]), running away from home (3.0 [1.2-7.2]), suicidal ideation (2.5 [1.2-4.9]), and suicide attempts (3.0 [1.2-7.5]). CONCLUSIONS: Clinically, body piercing may serve as a marker for higher levels of peer substance use and potential problem behavior.


The 'Prevention Paradox' applies when low-risk individuals in a population contribute the most cases of a condition or problem behaviour by virtue of their being in the majority, thereby recommending a universal or whole of population approach to prevention. The applicability of a universal as opposed to a targeted high-risk approach to the prevention of youth substance use was examined in two studies of children and adolescents conducted in Victoria, Australia. These studies were reanalysed by recombining developmental, social and individual measures to form cumulative risk indices for substance use. In Study 1, a cross-sectional survey of students, most regular tobacco, alcohol and cannabis use by 15/16-year-olds occurred in the moderate and low-risk groups, recommending a universal prevention strategy. However, the majority of illicit drug use occurred in the highest-risk group (top 15%). Furthermore, in younger age groups both legal and illegal drug use was concentrated mainly in the highest risk group. Study 2 used data from a major longitudinal study where risk factors at around age 11/12 years were used to predict substance use at age 17/18 years. Most students who admitted involvement in frequent smoking, heavy drinking and, although to a lesser degree, cannabis were classified as low or average risk. It is concluded that universal prevention strategies are needed for late adolescent alcohol, tobacco and cannabis use and more targeted strategies for addressing harm related to early age drug use, frequent cannabis use and illegal drug use. [Stockwell T, Toumbourou JW, Letcher P, Sanson A, Bond L. Risk and protection factors for different intensities of adolescent substance use: when does the prevention paradox apply? Drug Alcohol Rev 2004;23:67 - 77]


This study of a dually diagnosed population in Colorado estimated the prevalence of hepatitis C to be 29.7%, or sixteen times higher than that in the general population. In attempts to determine possible risk factors, a surprisingly high correlation was found between the use of tobacco and HCV infection. This appears to be beyond the risk factor conveyed by IV drug use. Of the patients whose primary diagnoses were cocaine, opiate, amphetamine, or poly-substance dependence (drugs often used intravenously), 42% of the tobacco users were HCV positive, while only 20% of the non-tobacco using patients with similar primary diagnoses were HCV positive. The association of tobacco use with HCV was found to be even more striking for females with alcohol, sedative/hypnotic, inhalant, or cannabis dependence, as none of the seventeen non-tobacco using female patients with these diagnoses were HCV positive, while fourteen of the 45 (31%) tobacco-using females with these diagnoses did test positive for HCV. Results of this study suggest that tobacco use may in some way influence the susceptibility to infection with hepatitis C virus. (Am J Addict 2004;13:46-52)

We compared reports of increased substance use in Manhattan 1 and 6 months after the September 11, 2001, terrorist attacks. Data from 2 random-digit-dial surveys conducted 1 and 6 months after September 11 showed that 30.8% and 27.3% of respondents, respectively, reported increased use of cigarettes, alcohol, or marijuana. These sustained increases in substance use following the September 11 terrorist attacks suggest potential long-term health consequences as a result of disasters.