INTRODUCTION

Here is the latest summary of research abstracts. Note that several articles are from the Journal of Clinical Pharmacology volume 42(11 supp). CCIC members may also wish to take note of the fact that the 2003 meeting of the International Cannabinoid Research Society (ICRS) will take place in Cornwall, Ontario on June 25-28th 2003. The deadline for abstracts has not yet been posted but will likely be in March 2003. Further details are available at www.cannabinoidsociety.org or shortly on the CCIC website (www.ccicht.ca).

BASIC SCIENCE


We previously identified a novel common virus integration site, Evi11, by means of retroviral insertional mutagenesis. We demonstrated that the gene encoding the peripheral cannabinoid receptor (Cb2) is the potential target, suggesting that Cb2 is a proto-oncogene. To elucidate a role for this G protein-coupled receptor (GPCR) in leukemic transformation we generated a Cb2-EGFP cDNA construct that was introduced into 32D/G-CSF-R cells. These cells require IL-3 to proliferate in vitro, whereas in the presence of G-CSF they differentiate towards mature neutrophils. We demonstrate that 32D/G-CSF-R/Cb2-EGFP cells migrate in a transwell assay in response to the Cb2 ligand 2-arachidonoylglycerol (2-AG), indicating that the fusion protein was functional. When cultured in the presence of G-CSF neutrophilic differentiation of Cb2-EGFP expressing 32D/G-CSF-R cells was completely blocked. Moreover, a Cb2-specific antagonist fully recovered the G-CSF-induced neutrophilic differentiation of 32D/G-CSF-R/Cb2-EGFP cells. To investigate which signal transduction pathway(s) may be involved in the block of neutrophilic maturation, differentiation experiments were carried out using specific inhibitors of signaling routes. Interestingly, full rescue of G-CSF induced neutrophilic differentiation was observed when cells were cultured with the MEK inhibitors, PD98059 or U0126, and partial recovery was detected with the PI3-K inhibitor LY-294,002. These studies demonstrate that the Cb2 receptor is an onco-protein that blocks neutrophilic differentiation when overexpressed in myeloid precursor cells. Cb2 appears to mediate its activity through MEK/ERK and PI3-K pathways.


Cannabinoids act at receptors on peripheral and central neurons to modulate diverse physiological functions and produce analgesia. Corneal sensory nerves express the CB1 cannabinoid receptor and project to two spatially discrete regions of the lower brainstem, the trigeminal interpolaris/caudalis (Vii/Vc) transition and subnucleus caudalis/upper cervical cord (Vc/C1) junction region. The function of CB1 expression on corneal nerves is not known. To determine if cannabinoid receptors in the anterior eye affect the activity of trigeminal brainstem neurons at the Vii/Vc and Vc/C1 the CB1 agonist, WIN55,212-2 (WIN-2), was applied topically prior to chemical excitation of corneal afferent fibers. In the first series of experiments WIN-2 was applied topically prior to excitation of corneal nociceptors by mustard oil (MO). WIN-2 reduced significantly the number of Fos-like immunoreactive neuronal nuclei (Fos-LI) at the Vii/Vc
transition (-46.7+/−8.2%, P<0.05), while smaller non-significant reductions occurred at the Vc/C1 junction region (-20.3+/−7.6%). The selective CB1 antagonist, SR141716A (1mg/kg, i.v.), prevented WIN-2-evoked reduction in Fos-LI after MO. Systemic administration of WIN-2 (1 or 10mg/kg, i.p.) or SR141716A (1mg/kg, i.v.) or topical corneal application of morphine sulfate did not affect Fos-LI produced by MO. In parallel experiments, topical WIN-2 reduced the magnitude of single unit activity recorded at the Vi/Vc transition (-80+/−7%, P<0.025), but not at the Vc/C1 junction region (-34+/−30%) evoked by CO(2) pulses applied to the cornea. Topical morphine did not alter CO(2)-evoked unit activity at either recording location. These results indicated that cannabinoid receptor agonists acted, at least in part, at CB1 receptors in the anterior eye to reduce corneal stimulation-evoked trigeminal brainstem neural activity. Corneal nociceptor-evoked activity at the Vi/Vc transition was reduced significantly by topical WIN-2, while activity at the Vc/C1 junction region displayed only minor decreases. These findings were consistent with the hypothesis that CB1 receptors affect the activity of corneal-responsive neurons that preferentially contribute to homeostasis of the anterior eye and/or reflexive aspects of nociception rather than the sensory-discriminative aspects of corneal nociception.


Previous reports from our laboratory have demonstrated that ethanol- and cannabinoid-induced ataxia is modulated by cerebellar adenosine A(1) receptor because intracerebellar (i.c.b.) adenosine A(1) agonists potentiated and A(1) antagonist attenuated ataxia by these psychoactive drugs. In this study, the novel approach involving pretreatment with adenosine A(1) antisense oligodeoxynucleotide via multiple routes provided further direct evidence of mouse cerebellar A(1) modulation of ethanol- and cannabinoid-induced ataxia. Animal groups were pretreated with A(1) antisense and its mismatch by oral (p.o.) (3.12, 6.25, 12.5, 50 &mgr;g/12 h; total three treatments/each dose), intraperitoneal (i.p.) (3.12, 5, 10, 50 &mgr;g/12 h; total three treatments/each dose), and i.c.b. (2 &mgr;g/12 h; total three treatments) routes. Based on our standard rotorod test, marked antagonism to ethanol (2 g/kg; i.p.) and Delta(9)-THC (15 &mgr;g; i.c.b.)-induced ataxia was observed 12 h after the last antisense treatment. Pretreatment with A(1) receptor mismatch was without an effect. The antagonism following systemic (p.o.; i.p.) antisense pretreatment was dose-dependent. No change in the normal motor coordination was observed when the animals were pretreated with antisense or its mismatch followed by vehicle. Results of Western blotting using commercially available antibodies and cerebellar membranes from various animal groups which received antisense and its mismatch via three routes confirmed a significant decrease in the A(1) adenosine receptor protein. These results, for the first time, demonstrated an oral and systemic effectiveness of A(1) antisense towards adenosine receptors in the central nervous system.


The endogenous cannabinoid, anandamide, has been shown to attenuate naloxone-precipitated opiate withdrawal in rodents. Here we show that the spontaneous, but not the naloxone-precipitated withdrawal syndrome in morphine-dependent mice is attenuated by the inhibitor of carrier-mediated anandamide transport N-(4-hydroxyphenyl) arachidonylethanolamide (AM404) (2 and 10 mg/kg, i.p.). These results suggest that spontaneous but not opioid antagonist-precipitated withdrawal is associated with dynamic changes in endogenous cannabinoid signaling.


Recent studies demonstrate the possible existence of tonic modulatory control of nociceptive input mediated by spinal cannabinoid receptors (CB1). Accordingly, it is predicted that a reduction in the spinal CB1 receptors may enhance sensitivity to sensory stimuli and a decrease in spinal antinociceptive potency to cannabinoid agonists. An antisense oligodeoxynucleotide (ODN) specific to the CB1 receptor was used to 'knock-down' CB1
receptors in the lumbar spinal cord and dorsal root ganglia by the local, repeated intrathecal (i.th.) administration of the ODN. This treatment resulted in a decrease in lumbar spinal CB1 receptor expression accompanied by a decrease in the response thresholds to both innocuous tactile and noxious thermal stimuli. The antinociceptive action of the CB1 agonist, WIN 55,212-2, by i.th. administration was also significantly attenuated after treatment with the antisense ODN. Similar treatment using a mismatch control ODN had no effect on receptor protein or on sensory thresholds. The effects of the antisense ODN treatment on sensory thresholds were fully reversed after discontinuation of the ODN injection. The antisense ODN treated rats also showed a significant increase in lumbar spinal dynorphin A. Acute i.th. injection of MK-801 or an antidynorphin antiserum blocked the antisense ODN-induced tactile and thermal hypersensitivity. These data support the possibility of endogenous inhibitory cannabinoid tone to limit spinal afferent input of thermal and tactile stimuli. Lifting of this inhibitory tone through a 'knock-down' of spinal CB1 receptors apparently lowers the thresholds for sensory input, as reflected by the actions of MK-801 to block tonic and thermal hypersensitivity. The increased spinal dynorphin may act to further promote afferent outflow and abnormal pain because sequestration of spinal dynorphin with antiserum also reverses the manifestations of abnormal pain following knock-down of CB1 receptors.


Cannabinoids, the active components of marijuana and their endogenous counterparts, exert many of their actions in brain through the seven-transmembrane receptor CB(1). This receptor is coupled to the activation of the extracellular signal-regulated kinase (ERK) cascade. However, the precise molecular mechanism for CB(1)-mediated ERK activation is still unknown. Here, we show that in U373 MG human astrocytoma cells, CB(1) receptor activation with the cannabinoid agonist Delta(8)-tetrahydrocannabinol dimethyl heptyl (HU-210) was coupled to ERK activation and protection from ceramide-induced apoptosis. HU-210-induced ERK activation was inhibited by tyrphostin AG1478 and PP2, widely employed inhibitors of the epidermal growth factor receptor (EGF(R)) and the Src family of cytosolic tyrosine kinases, respectively. However, HU-210 stimulation resulted in neither EGF(R) phosphorylation, Src tyrosine phosphorylation, nor increased Src activity. In addition, dominant-negative forms of both proteins were unable to prevent cannabinoid-induced ERK activation, thus excluding the existence of CB(1)-mediated EGF(R) transactivation or Src activation. Wortmannin and 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294,002), inhibitors of the phosphatidylinositol 3-kinase (PI3K) signaling pathway, blocked cannabinoid-induced ERK activation. Likewise, HU-210 stimulated the PI3K downstream targets protein kinase B (PKB), as shown by its phosphorylation in Thr 308 and Ser 473 residues, and Raf-1. Moreover, betagamma subunit release mimicked ERK and PI3K/PKB activation, suggesting that activation of class IB PI3K mediates cannabinoid action. Pro-survival HU-210 action also required activation of both PI3K and ERK signaling pathways. In conclusion, CB(1)-induced ERK activation was mediated by PI3K(IB) and this effect may have important consequences in the control of cell death/survival decision.


Recent studies suggest that the endocannabinoid system modulates feeding. Despite the existence of central mechanisms for the regulation of food intake by endocannabinoids, evidence indicates that peripheral mechanisms may also exist. To test this hypothesis, we investigated (1) the effects of feeding on intestinal anandamide accumulation; (2) the effects of central (intracerebroventricular) and peripheral (intraperitoneal) administration of the endocannabinoid agonist anandamide, the synthetic cannabinoid agonist R-(+)-(2,3-dihydro-5-methyl-3-[(4-morpholiny1)methyl]pyrol[1,2,3-de]-1,4-b enzoazxin-6-yl)(1-naphthalenyl) methane monomethanesulfonate (WIN55,212-2), and the CB1-selective antagonist N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (SR141716A) on food intake in rats; and (3) the effects of sensory deafferentation on the modulation of feeding by cannabinoids. Food deprivation produced a sevenfold increase in anandamide content in the small intestine but not in the brain or stomach. Refeeding normalized intestinal anandamide
levels. Peripheral but not central administration of anandamide or WIN55,212-2 promoted hyperphagia in partially satiated rats. Similarly, peripheral but not central administration of SR141716A reduced food intake. Capsaicin deafferentation abolished the peripheral effects of both cannabinoid agonists and antagonists, suggesting that these agents modulate food intake by acting on CB1 receptors located on capsaicin-sensitive sensory terminals. Oleoylthanolamide, a noncannabinoid fatty ethanolamide that acts peripherally, prevented hyperphagia induced by the endogenous cannabinoid anandamide. Pretreatment with SR141716A enhanced the inhibition of feeding induced by intraperitoneal administration of oleoylthanolamide. The results reveal an unexpected role for peripheral CB1 receptors in the regulation of feeding.


Inhibition of prostaglandins synthesis does not completely explain non-steroidal anti-inflammatory drug-induced spinal antinociception. Among other mediators, endocannabinoids are involved in pain modulation. Indomethacin-induced antinociception, in the formalin test performed in spinally microdialysed mice, was reversed by co-administration of the cannabinoid 1 (CB(1)) antagonist, N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1-H-pyrazole-3-carboxamide (AM-251), but not by co-infusion of prostaglandin E(2). Indomethacin was ineffective in CB(1) knockout mice. AM-251 also reversed the indomethacin-induced antinociception in a test of inflammatory hyperalgesia to heat. Furthermore, during the formalin test, indomethacin lowered the levels of spinal nitric oxide (NO), which activates cellular reuptake and thus breakdown of endocannabinoids. The pronociceptive effect of an NO donor, 3-methyl-N-nitroso-sydnone-5-imine (RE-2047), was abolished by co-administration of the endocannabinoid transporter blocker N-(4-hydroxyphenyl) arachidonoyl amide (AM-404). Moreover, the antinociceptive activity of the NO synthase inhibitor, N-nitro-L-arginine methyl ester (L-NAME), was reversed by AM-251. Thus we propose that at the spinal level, indomethacin induces a shift of arachidonic acid metabolism towards endocannabinoids synthesis secondary to cyclooxygenase inhibition. In addition, it lowers NO levels with subsequent higher levels of endocannabinoids.


The aim of this study was to compare the effects of the genetic and pharmacological disruption of CB1 cannabinoid receptors on the elevated plus-maze test of anxiety. In the first experiment, the behaviour of CB1-knockout mice and wild-type mice was compared. In the second experiment, the cannabinoid antagonist SR141716A (0, 1, and 3 mg/kg) was administered to both CB1-knockout and wild type mice. Untreated CB1-knockout mice showed a reduced exploration of the open arms of the plus-maze apparatus, thus appearing more anxious than the wild-type animals, however no changes in locomotion were noticed. The vehicle-injected CB1-knockout mice from the second experiment also showed increased anxiety as compared with wild types. Surprisingly, the cannabinoid antagonist SR141716A reduced anxiety in both wild type and CB1 knockout mice. Locomotor behaviour was only marginally affected. Recent evidence suggests the existence of a novel cannabinoid receptor in the brain. It has also been shown that SR141716A binds to both the CB1 and the putative novel receptor. The data presented here supports these findings, as the cannabinoid receptor antagonist affected anxiety in both wild type and CB1-knockout mice. Tentatively, it may be suggested that the discrepancy between the effects of the genetic and pharmacological blockade of the CB1 receptor suggests that the novel receptor plays a role in anxiety.

a selective CB1 receptor antagonist, on licking microstructure in rats ingesting a palatable sucrose solution. METHODS. Microstructural analyses of licking for a 10% sucrose solution was performed over a range of agonist and antagonist doses administered to non-deprived, male Lister hooded rats. RESULTS. Delta(9)-tetrahydrocannabinol (0.5, 1 and 3 mg/kg) and anandamide (1 mg/kg and 3 mg/kg) significantly increased total number of licks. This was primarily due to an increase in bout duration rather than bout number. There was a non-significant increase in total licks following administration of 2-arachidonoyl glycerol (0.2, 1.0 and 2.0 mg/kg), whereas administration of the CB1 antagonist SR141716 (1 mg/kg and 3 mg/kg) significantly decreased total licks. All drugs, with the exception of anandamide, significantly decreased the intra-bout lick rate. An exponential function fitted to the cumulative lick rate curves for each drug revealed that all compounds altered the asymptote of this function without having any marked effects on the exponent. CONCLUSIONS. These data are consistent with endocannabinoid involvement in the mediation of food palatability.


Cannabinoid receptors were named because they have affinity for the agonist delta9-tetrahydrocannabinol (delta9-THC), a ligand found in organic extracts from Cannabis sativa. The two types of cannabinoid receptors, CB1 and CB2, are G protein coupled receptors that are coupled through the Gi/o family of proteins to signal transduction mechanisms that include inhibition of adenyl cyclase, activation of mitogen-activated protein kinase, regulation of calcium and potassium channels (CB1 only), and other signal transduction pathways. A class of the eicosanoid ligands are relevant to lipid-mediated cellular signaling because they serve as endogenous agonists for cannabinoid receptors, and are thus referred to as endocannabinoids. Those compounds identified to date include the eicosanoids arachidonoylthanolamide (anandamide), 2-arachidonoylglycerol and 2-arachidonylglycerol ether (noladin ether). Several excellent reviews on endocannabinoids and their synthesis, metabolism and function have appeared in recent years. This paper will describe the biological activities, pharmacology, and signal transduction mechanisms for the cannabinoid receptors, with particular emphasis on the responses to the eicosanoid ligands.


In superior cervical ganglion neurons, N-(piperidiny-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (SR141716A) competitively antagonizes the Ca(2+) current effect of the cannabinoid (CB) agonist (R)-(+-)[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone (WIN55212-2), and behaves as an inverse agonist by producing opposite current effects when applied alone. In contrast, in neurons expressing CB1 with a K -->A mutation at residue 3.28(192) (i.e., K3.28A), SR141716A competitively antagonizes the effects of WIN55212-2, but behaves as a neutral antagonist by producing no current effects itself. Receptor modeling studies suggested that in the CB1 inactive (R) state, SR141716A stabilizes transmembrane helix 6 in its inactive conformation via aromatic stacking with F3.36/W6.48. In this binding site, SR141716A would exhibit higher affinity for CB1 R due to a hydrogen bond between the SR141716A C3 substituent and K3.28(192), a residue available to SR141716A only in R. To test this hypothesis, a "mutant thermodynamic cycle" was constructed that combined the evaluation of SR141716A affinity at WT CB1 and K3.28A with an evaluation of the wild-type CB1 and K3.28A affinities of an SR141716A analog, 5-(4-chlorophenyl)-3-[(E)-2-cyclohexylethenyl]-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole (VCHSR), that lacks hydrogen bonding potential at C3. Binding affinities suggested that K3.28 is involved in a strong interaction with SR141716A in WT CB1, but does not interact with VCHSR. Thermodynamic cycle calculations indicated that a direct interaction occurs between the C3 substituent of SR141716A and K3.28 in WT CB1. Consistent with these results, VCHSR acted as a neutral antagonist at WT CB1. These results support the hypothesis that
hydrogen bonding of the SR141716A C3 substituent with K3.28 is responsible for its higher affinity for the inactive R state, leading to its inverse agonism.


In canine renal tubular cells, effect of olvanil, a presumed cannabinoid and vanilloid receptor modulator, on intracellular Ca(2+) concentration ([Ca(2+)](i)) was measured by using fura-2. Olvanil (5-100 &micro;M) caused a rapid and sustained [Ca(2+)](i) rise in a concentration-dependent manner. Olvanil-induced [Ca(2+)](i) rise was prevented by 70 and 90% by removal of extracellular Ca(2+) and La(3+), respectively, but was not changed by dihydropyridines, verapamil and diltiazem. In Ca(2+)-free medium, thapsigargin, an inhibitor of the endoplasmic reticulum Ca(2+)-ATPase, caused a monophasic [Ca(2+)](i) rise, after which the increasing effect of olvanil on [Ca(2+)](i) was abolished; also, pretreatment with olvanil partly reduced thapsigargin-induced [Ca(2+)](i) rise. U73122, an inhibitor of phospholipase C, abrogated ATP-, but partly inhibited olvanil-, induced [Ca(2+)](i) rise. Two cannabinoid receptor antagonists (AM251 and AM281; 5 &micro;M) and a vanilloid receptor antagonist (capsazepine; 100 &micro;M) did not alter olvanil (50 &micro;M)-induced [Ca(2+)](i) rise. These results suggest that olvanil rapidly increases [Ca(2+)](i) in renal tubular cells, by stimulating both extracellular Ca(2+) influx and intracellular Ca(2+) release via mechanism(s) independent of stimulation of cannabinoid and vanilloid receptors.


BACKGROUND: Anandamide, an endogenous lipid, activates both cannabinoid (CB(1)) and vanilloid (VR1) receptors, both of which are co-expressed in rat dorsal root ganglion (DRG) cells. Activation of either receptor results in analgesia but the relative contribution of CB(1) and VR1 in anandamide-induced analgesia remains controversial. Here we compare the in vitro pharmacology of recombinant and endogenous VR1 receptors using calcium imaging, in clonal and DRG cells, respectively. We also consider the contribution of CB(1) and VR1 receptors to anandamide-induced analgesia. METHODS: Using a Flurometric Imaging Plate Reader (FLIPR(TM)), calcium imaging has been used to study the effects of several vanilloid and cannabinoid ligands in rat VR1-transfected HEK293 (rVR1-HEK) cells and in DRG cells. The effect of pre-exposure of several vanilloid and cannabinoids has also been compared in DRG cells. RESULTS: The VR1 agonists capsaicin, olvanil, (N-(4-hydroxyphenyl-arachinoylamide) (AM404) and anandamide caused a concentration-dependent increase in intracellular calcium concentration ([Ca(2+)](i)), with similar temporal profiles in both rVR1-HEK and DRG cells, and potency (pEC(50)) values of 8.25 (SEM 0.11), 8.37 (0.04), 6.96 (0.06), 5.85 (0.01) and 7.45 (0.10), 7.55 (0.07), 6.10 (0.13), approximately 5.5, respectively. These responses were inhibited by the VR1 antagonist capsazepine (1 micro M). In contrast, application of synthetic cannabinoid antagonists failed to inhibit the anandamide-induced increase in [Ca(2+)](i). Reapplication of VR1 agonists significantly inhibited a subsequent challenge to either capsaicin or anandamide in either cell type, whilst pre-exposure to cannabinoid agonists were without effect. CONCLUSION: Here we provide evidence that the pharmacology of recombinant rVR1 receptors is similar to those endogenously expressed in DRG cells. Moreover, we have shown that VR1, but not CB(1), receptors are involved in anandamide-induced responses in dorsal root primary neurones in vitro. Therefore, the analgesic properties of anandamide are likely to be mediated, at least in part, by VR1 activation in DRG cells in vivo.


1 Endogenous neuronal lipid mediator anandamide, which can be synthesized in the lung, is a ligand of both cannabinoid (CB) and vanilloid receptors (VR). The tussigenic effect of anandamide has not been studied. The current study was designed to test the direct tussigenic effect of anandamide in conscious guinea-pigs, and its effect on VR1 receptor function in isolated primary guinea-pig nodose ganglia neurons. 2 Anandamide (0.3-3 mg.ml(-1)), when given by aerosol, induced cough in conscious guinea-pigs in a concentration dependent manner. When
guinea-pigs were pretreated with capsazepine, a VR1 antagonist, the anandamide-induced cough was significantly inhibited. Pretreatment with CB1 (SR 141716A) and CB2 (SR 144528) antagonists had no effect on anandamide-induced cough. These results indicate that anandamide-induced cough is mediated through the activation of VR1 receptors.

Anandamide (10-100 micro M) increased intracellular Ca(2+) concentration estimated by Fluo-4 fluorescence change in isolated guinea-pig nodose ganglia cells. The anandamide-induced Ca(2+) response was inhibited by two different VR1 antagonists: capsazepine (1 micro M) and iodo-resiniferatoxin (I-RTX, 0.1 micro M), indicating that anandamide-induced Ca(2+) response was through VR1 channel activation. In contrast, the CB1 (SR 141716A, 1 micro M) and CB2 (SR 144528, 0.1 micro M) receptor antagonists had no effect on Ca(2+) response to anandamide.

In conclusion, these results provide evidence that anandamide activates native vanilloid receptors in isolated guinea-pig nodose ganglia cells and induces cough through activation of VR1 receptors. British Journal of Pharmacology (2002) 137, 831-836. doi:10.1038/sj.bjp.0704950


Structure-activity relationships (SAR) studies were performed for a series of heterocyclic cannabinoids by using the Electronic-Topological Method (ETM). Biological activities of the compounds possessing different skeletons were measured on cannabinoid receptor binding affinity. Molecular fragments being specific for active compounds only ('activity features') were revealed. In a similar way, "breaks of activity" (i.e. molecular fragments that are typical of inactive compounds and cannot be a part of an active compound) were calculated by applying the ETM. Requirements necessary for a compound to be active were formulated; they resulted from detailed analysis of all compounds under study. For better understanding, appropriate examples of the requirements violation that cause a decrease or loss of the activity in view were found.


CB1 receptors have been localized to primary afferent neurons, but little is known about the direct effect of cannabinoids on these neurons. The depolarization-evoked increase in the concentration of free intracellular calcium ([Ca(2+)](i)), measured by microfluorimetry, was used as a bioassay for the effect of cannabinoids on isolated, adult rat primary afferent neurons 20-28 h after dissociation of dorsal root ganglia. Cannabinoid agonists CP 55,940 (100 nM) and WIN 55,212-2 (1 &mgr;mM) had no effect on the mean K(+)-evoked increase in [Ca(2+)](i) in neurons with a somal area<800 &mgr;m(2), but the ligands attenuated the evoked increase in [Ca(2+)](i) by 35% in neurons defined as intermediate in size (800-1500 &mgr;m(2)). The effects of CP 55,940 and WIN 55,212-2 were mediated by the CB1 receptor on the basis of relative effective concentrations, blockade by the CB1 receptor antagonist SR141716A and lack of effect of WIN 55,212-3. Intermediate-size neurons rarely responded to capsaicin (100 nM). Although cannabinoid agonists generally did not inhibit depolarization-evoked increases in [Ca(2+)](i) in small neurons, immunocytochemical studies indicated that CB1 receptor-immunoreactivity occurred in this population. CB1 receptor-immunoreactive neurons ranged in size from 227 to 2995 &mgr;m(2) (mean somal area of 1044 &mgr;m(2)). In double labeling studies, CB1 receptor-immunoreactivity co-localized with labeling for calcitonin gene-related peptide and RT97, a marker for myelination, in some primary afferent neurons. The decrease in evoked Ca(2+) influx indicates that cannabinoids decrease conductance through voltage-dependent calcium channels in a subpopulation of primary afferent neurons. Modulation of calcium channels is one mechanism by which cannabinoids may decrease transmitter release from primary afferent neurons. An effect on voltage-dependent calcium channels, however, represents only one possible effect of cannabinoids on primary afferent neurons. Identifying the mechanisms by which cannabinoids modulate nociceptive neurons will increase our understanding of how cannabinoids produce anti-nociception in normal animals and animals with tissue injury.

Endogenous cannabinoids (endocannabinoids) are endogenous compounds that resemble the active ingredient of marijuana and activate the cannabinoid receptor in the brain. They mediate retrograde signaling from principal cells to both inhibitory ("depolarization-induced suppression of inhibition" (DSI)) and excitatory ("depolarization-induced suppression of excitation") afferent fibers. Transient endocannabinoid release is triggered by voltage-dependent Ca(2+) influx and is upregulated by group I metabotropic glutamate receptor activation. Here we show that muscarinic acetylcholine receptor (mAChR) activation also enhances transient endocannabinoid release (DSI) and induces persistent release. Inhibitory synapses in the rat hippocampal CA1 region of acute slices were studied using whole-cell patch-clamp techniques. We found that low concentrations (0.2-0.5 microm) of carbachol (CCh) enhanced DSI without affecting basal evoked IPSCs (eIPSCs) by activating mAChRs on postsynaptic cells. Higher concentrations of CCh (> or =1 microm) enhanced DSI and also persistently depressed basal eIPSCs, mainly by releasing endocannabinoids. Persistent CCh-induced endocannabinoid release did not require an increase in [Ca2+] but was dependent on G-proteins. Although they were independent at the receptor level, muscarinic and glutamatergic mechanisms of endocannabinoid release shared intracellular machinery. Replication of the effects of CCh by blocking acetylcholinesterase with eserine suggests that mAChR-mediated endocannabinoid release is physiologically relevant. This study reveals a new role of the muscarinic cholinergic system in mammalian brain.


Stimulation of cannabinoid receptors with endogenous cannabinoid anandamide and its enzyme-resistant analogue R-(+)-methanandamide improved cardiac resistance to arrhythmias induced by coronary occlusion and reperfusion. This antiarrhythmic effect was not associated with activation of NO synthase, since pretreatment with NG-nitro-L-arginine methyl ester had no effect on the incidence of ischemia/reperfusion-induced arrhythmias. Blockade of ATP-dependent K+ channels with glibenclamide did not abolish the antiarrhythmic effect of R-(+)-methanandamide. Antiarrhythmic activity of endogenous cannabinoids is probably associated with their direct effects on the myocardium.


Although the proposition that repeated marijuana use can lead to marijuana dependence has long been accepted, only recently has evidence emerged suggesting that abstinence leads to clinically significant withdrawal symptoms. Converging evidence from human and animal studies has increased our understanding of cannabinoid dependence. One of the most powerful tools to advance this area of research is the CB1 cannabinoid receptor antagonist SR 141716A, which reliably precipitates withdrawal syndromes in mice, rats, and dogs that have been treated repeatedly with cannabinoids. In addition, the use of CB1 receptor knockout mice has revealed that not only cannabinoid dependence is mediated through a CB1 receptor mechanism of action, but CB1 receptors also modulate opioid dependence. Moreover, the results of other genetically altered mouse models suggest the existence of a reciprocal relationship between cannabinoid and opioid systems in drug dependence. Undoubtedly, these animal models will play pivotal roles in further characterizing cannabinoid dependence and elucidating the mechanisms of action, as well as developing potential pharmacotherapies for cannabinoid dependence.

effect on PPI on its own or following disruptions by psychotomimetic agents. In addition, we investigated the effects of SR 141716A on elevated levels of hyperactivity and stereotypy elicited by d-amphetamine. METHODS. These studies were conducted in rats using standard methodologies for determination of PPI following acoustic stimuli, and d-amphetamine-induced hyperactivity and stereotypies. RESULTS. Decreased startle responses to 120 dB stimuli were observed in rats treated with CP 55940 (0.1 mg/kg IP) in the absence and presence of a 73 dB pre-pulse. These effects were reversed by SR 141716A (5 and 10 mg/kg, respectively). SR 141716A (0.1, 5, 10 mg/kg) had no effect on PPI on its own or following disruptions by apomorphine, d-amphetamine or MK-801. Conversely, in separate experiments different antipsychotic agents reversed disruptions in PPI induced by d-amphetamine (haloperidol), apomorphine (haloperidol or clozapine) or MK-801 (clozapine or olanzapine). In addition, unlike haloperidol, SR 141716A (5 mg/kg) did not reverse d-amphetamine-mediated increases in hyperactivity or stereotypy. CONCLUSIONS. The CP 55940-mediated decreases in startle amplitude confound assessment of the effects of CB(1) receptor activation on PPI. The failure of SR 141716A to reverse disruptions in PPI, hyperactivity or stereotypy induced by non-cannabinoid psychotomimetic agents suggests that blockade of the CB(1) receptor on its own is not sufficient for antipsychotic therapy.


Over the past few years, considerable attention has focused on cannabidiol (CBD), a major nonpsychotropic constituent of cannabis. The authors present a review on the chemistry of CBD and discuss the anticonvulsive, antianxiety, antipsychotic, antinausea, and antiarthritis properties of CBD. CBD does not bind to the known cannabinoid receptors, and its mechanism of action is yet unknown. It is possible that, in part at least, its effects are due to its recently discovered inhibition of anandamide uptake and hydrolysis and to its antioxidative effect.


Cannabinoids exert pleiotropic actions in the CNS, including the inhibition of inflammatory responses and the enhancement of neuronal survival after injury. Although cannabinoid receptors are distributed widely in brain, their presence has not been investigated previously in oligodendrocytes. This study examined the expression of cannabinoid type 1 (CB1) receptors in rat oligodendrocytes in vivo and in culture and explored their biological function. Expression of CB1 receptors by oligodendrocytes was demonstrated immunocytochemically in postnatal and in adult white matter as well as in oligodendrocyte cultures. Reverse transcription-PCR and Western blotting further confirmed the presence of CB1 receptors. Oligodendrocyte progenitors undergo apoptosis with the withdrawal of trophic support, as determined by TUNEL assay and caspase-3 activation, and both the selective CB1 agonist arachidonyl-2'-chloroethylamide/(all Z)-N-(2-cycloethyl)-5,8,11,14-eicosatetraenamide (ACEA) and the nonselective cannabinoid agonists HU210 and (+)-Win-55212-2 enhanced cell survival. To investigate intracellular signaling involved in cannabinoid protection, we focused on the phosphatidylinositol-3 kinase (PI3K)/Akt pathway. HU210, (+)-Win-55212-2, and ACEA elicited a time-dependent phosphorylation of Akt. Pertussis toxin abolished Akt activation, indicating the involvement of G(i)/G(o)-protein-coupled receptors. The CB1 receptor antagonist SR141716A partially inhibited Akt phosphorylation in response to HU210 and (+)-Win-55212-2 and abolished the effects of ACEA. Trophic support deprivation downregulated Akt activity, and cannabinoids recovered phospho-Akt levels. Inhibition of PI3K abrogated the survival action and the recovery of Akt activity in response to cannabinoids. SR141716A prevented only the protection conferred by ACEA. Nevertheless, SR141716A and the selective CB2 receptor antagonist SR144528 in combination inhibited the prosurvival action of HU210, which is in accordance with the finding of CB2 receptor expression by oligodendroglial cells. These data identify oligodendrocytes as potential targets of cannabinoid action in the CNS.
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An earlier report described the pharmacokinetics of delta-9 THC and the resulting brain function responses. In the present studies the pharmacokinetics of THC in plasma, brain and testis were related to impairment of spermatogenesis. THC-containing preparations, whatever their route of administration, were associated with the induction of gametotoxicity in all species studied including man. The pharmacokinetics and molecular binding of THC is similar in all experimental models. Concentrations of THC in plasma, fat, testis, brain and spleen were measured following administration of tracer amounts of C(14) delta-8 THC labelled at the C(11) position. Rats were administered 2 &mgr;Ci of the tracer by i.m. injection, and killed at regular intervals after a single or multiple dose of the label. After a single dose, the maximal radioactivity was reached in brain after 2 and 4 h and amounted to 0.06% of the administered dose. In the testis, the concentration did not exceed 0.023% of the administered dose. In epididymal fat, the total radioactivity after 4 h was five times higher than in the brain and after 24 h it was eight times greater. After multiple injections of C(14) THC, concentrations of the drug remained low in the plasma, brain and testis not exceeding 2-7 ng/g, but the epididymal fat tracer concentration was 40-80 times higher. Plasma concentrations of C(14) THC were of the same magnitude as those measured by GCMS in the plasma of men exposed to marihuana smoke or THC, and in whom alterations of spermatogenesis were observed. In these studies, plasma THC ranged from 9.5x10(12) M to 2.4x10(14) M. These data illustrate the efficiency of the blood-brain barrier and blood-testicular barrier in limiting the storage of THC into brain and testis. During chronic exposure to THC the pharmacokinetic molecular mechanisms which limit the storage of THC in the brain and testis are not sufficient to prevent a persistent deregulation of membrane signalling and the induction of functional and morphological changes which reflect a premature apoptosis of spermatogenic cells. Long term, longitudinal epidemiological studies have reported decreased spermatogenesis in healthy, fertile adult males. But no study has been initiated to relate the oligospermia of this population to the consumption of widely used psychoactive drugs. Copyright 2002 John Wiley & Sons, Ltd.


1',1'-Cyclopropyl side chain substituents enhance the affinities of Delta(8)-tetrahydrocannabinol and respective cannabidiol analogues for the CB1 and CB2 cannabinoid receptors. The results support the hypothesis for a subsite within CB1 and CB2 binding domain at the level of the benzylic side chain carbon in the tetrahydrocannabinol and cannabidiol series. Efficient procedures for the synthesis of 1',1'-cyclopropyl analogues are described.


Endogenous cannabinoid signaling pathways have been implicated in protection of the brain from hypoxia, ischemia, and trauma, but the mechanism for these protective effects is uncertain. We found that in CB1 cannabinoid receptor knock-out mice, mortality from permanent focal cerebral ischemia was increased, infarct size and neurological deficits after transient focal cerebral ischemia were more severe, cerebral blood flow in the ischemic penumbra during reperfusion was reduced, and NMDA neurotoxicity was increased compared with wild-type littermates. These findings indicate that endogenous cannabinoid signaling pathways protect mice from ischemic stroke by a mechanism that involves CB1 receptors, and suggest that both blood vessels and neurons may be targets of this protective effect.


The nonpsychoactive plant cannabinoid, (-)-cannabidiol, modulates in vivo responses to Delta(9)-tetrahydrocannabinol. We have found that cannabidiol can also interact with cannabinoid CB(1) receptor agonists in the mouse vas deferens, a tissue in which prejunctional cannabinoid CB(1) receptors mediate inhibition of electrically evoked contractions by suppressing
noradrenaline and/or ATP release. Cannabidiol (0.316-10 &mgr;M) attenuated the ability of (R)-(+)
[2,3-dihydro-5-methyl-3-(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1-naphthalenylmethanone (R-(+)
WIN55212) to inhibit contractions in a concentration-related, surmountable manner with a K(B) value (120.3 nM) well below its reported cannabinoid receptor CB(1)/CB(2) K(i) values. Cannabidiol (10 &mgr;M) also antagonized (-)-cis-3-[2-hydroxy-4-(1,1-
dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol (CP55940; K(B)=34 nM) and [D-
Ala(2), NMePhe(4), Gly-ol]enkephalin (DAMGO; K(B)=5.6 &mgr;M) and attenuated contractile responses to noradrenaline, phenylephrine and methoxamine but not to beta, gamma-
methyleneadenosine 5'-triphosphate. At 3.16-10 &mgr;M, it increased the amplitude of evoked contractions, probably by enhancing contractile neurotransmitter release. We conclude that cannabidiol antagonizes R-(+)
WIN55212 and CP55940 by acting at prejunctional sites that are unlikely to be cannabinoid CB(1) or CB(2) receptors.


Previous studies have shown beneficial effects of the cannabinoid CB(1)/CB(2) receptor agonist (R)-4,5-dihydro-2-methyl-4-(4-morpholylmethyl)-1-(1-naphthalenylcarbonyl)-6H-pyrrolo
[3,2,1-ij]quinolinol-6-one mesylate (WIN 55,212-2) in dt(sz) mutant hamsters, a model of idiopathic paroxysmal dystonia (dyskinesia). To examine the pathophysiological significance of the cannabinergic system in the dystonic syndrome, the effect of the cannabinoid CB(1) receptor antagonist N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-
carboxamide (SR 141716A) on severity of dystonia was investigated in dt(sz) mutants which exhibit episodes of dystonic and choreoathetotic disturbances in response to mild stress. SR 141716A (5 and 10 mg/kg i.p.) failed to exert any effects on the severity of dystonia. While the antidystonic efficacy of WIN 55,212-2 (5 mg/kg i.p.) was confirmed; cannabidiol (which has low affinity to cannabinoid receptors) tended to delay the progression of dystonia only at a high dose (150 mg/kg i.p.). The antidystonic and cataleptic effects of WIN 55,212-2 (5 mg/kg i.p.) were completely antagonized by pretreatment with SR 141716A at doses of 2.5 mg/kg (catalepsy) and 10 mg/kg (antidystonic efficacy). These data indicate that the antidystonic efficacy of WIN 55,212-
2 is selectively mediated via CB(1) receptors. The lack of prodystonic effects of SR 141716A together with only moderate antidystonic effects of WIN 55,212-2 suggests that reduced activation of cannabinoid CB(1) receptors by endocannabinoids is not critically involved in the dystonic syndrome. In view of previous pathophysiological findings in mutant hamsters, the antidystonic efficacy of WIN 55,212-2 can be explained by modulation of different neurotransmitter systems within the basal ganglia.


A majority (84%) of G protein-coupled receptors have a proline (P5.50) in the middle of the fifth transmembrane domain. However, one of the unique structural features of cannabinoid receptors is the replacement of the conserved P5.50 by a leucine (L5.50). It has been shown that a conserved tyrosine (Y5.58), located at the cytoplasmic side of P5.50, is crucial for the signal transduction of several G protein-coupled receptors. We proposed that the replacement of P5.50 by L5.50 and the presence of the conserved Y5.58 in this context are important for the function of CB2. Mutating L5.50 to a proline abolished ligand binding, whereas mutating Y5.58 to an alanine resulted in a rightward shift of the competition binding curves. Both of these mutations led to a complete loss of the ability of cannabinoid agonists to inhibit forskolin-stimulated cAMP accumulation.


Capsaicin acting on the vanilloid type 1 receptor (VR1) excites a subset of primary sensory neurons. Systemic capsaicin treatment of adult or neonatal rats results in selective damage of the B-type neurons in the rat sensory ganglia by causing a long-lasting mitochondrial
lesion that has been described in detail in previous studies. The endocannabinoid, anandamide, exhibits an agonist effect on VR1 receptors. The physiological role of anandamide as a VR1 agonist is still uncertain. This study addresses whether high doses of anandamide induce similar ultrastructural changes to those described for capsaicin. The effect of neonatally administered anandamide (1 mg/kg) on neurons of the trigeminal ganglia and the hippocampal formation was examined in the light and electron microscope from the first day after injections to the 20th week after treatment. Anandamide was found to cause mitochondrial damage of the B-type neurons of trigeminal ganglia similar to what has been described for capsaicin. The time course of damage was also comparable. In addition to the cells of the trigeminal ganglia, B-type cells of dorsal root ganglia were also damaged. A-type neurons and satellite glial cells were not affected either in the trigeminal or in the dorsal root ganglia. In the hippocampal formation, where a subpopulation of local circuit neurons is known to contain cannabinoid type 1 (CB1) but not VR1 receptors, anandamide did not cause morphological changes of mitochondria either in the dentate gyrus or in Ammon's horn. At 3 weeks of age, all VR1-immunoreactive neurons in the trigeminal ganglia of animals treated neonatally with anandamide displayed swollen mitochondria. The results suggest that anandamide, at pharmacologically relevant doses, acts on the VR1 receptor and causes prolonged and selective mitochondrial damage of B-type sensory neurons, as has previously been described for capsaicin.


Hemp (Cannabis sativa L.) is a species considered as having one of the most complicated mechanisms of sex determination. Peroxidase and esterase isoenzymes in leaves of the two sexual phenotypes of hemp were studied. Significant differences in isoperoxidase and isoesterase patterns were found between male and female plants, both in the number and stain intensity of bands. For both esterase and peroxidase, the isoenzymatic spectrum is richer for staminate plants. Also, some differences are obvious between the two sexes concerning catalase and peroxidase activities, as well as the level of soluble protein. The quantitative analysis of flavones, polyholozides and polyphenols emphasized differences depending not only on sex, but also on tested organ.


Endocannabinoids (endogenous ligands of cannabinoid receptors) such as anandamide (N-arachidonylethanolamine) and 2-arachidonoylglycerol (2-AG) are inactivated upon enzymatic hydrolysis. Recent progress in the enzymological and molecular biological studies on the 'endocannabinoid hydrolases' is reviewed in this article. Anandamide is hydrolyzed to arachidonic acid and ethanolamine by a membrane-bound amidase generally referred to as fatty acid amide hydrolase (FAAH). This enzyme has a broad substrate specificity, hydrolyzing oleamide (an endogenous sleep-inducing factor) and 2-AG as well as anandamide. cDNA cloning revealed that FAAH is composed of 579 amino acids and belongs to the amidase signature family. A serine residue functioning as a catalytic nucleophile and several other catalytically important residues were identified in its primary structure. Furthermore, recent generation and analysis of the FAAH gene-deficient mice demonstrated the central role of this enzyme in the metabolism of anandamide. Alternatively, an amidase, which is distinct from FAAH but also hydrolyzing anandamide and other N-acyl ethanolamines at acidic pH, was identified in human megakaryoblastic cells and rat organs such as lung and spleen. As for the 2-AG hydrolysis, in addition to the known monoacylglycerol lipase, other esterases and FAAH may be involved.


We studied the possibility of decreasing the area of ischemic necrosis during myocardial infarction with HU-210, a selective cannabinoid receptor agonist. Activation of cannabinoid receptors with HU-210 had practically no effect on collateral blood flow in the myocardium, but considerably decreased the area of necrosis. There results indicate that cannabinoid receptor
agonist HU-210 possesses cardioprotective activity and delays the formation of necrotic zones during coronary occlusion and reperfusion.


The endocannabinoid system is a valuable target for drug discovery, because it is involved in the regulation of many cellular and physiological functions. The endocannabinoid system constitutes the endogenous lipids anandamide, 2-arachidonoylglycerol and noladin ether, and the cannabinoid CB1 and CB2 receptors as well as the proteins for their inactivation. It is thought that (endo)cannabinoid-based drugs may potentially be useful to reduce the effects of neurodegeneration. This paper reviews recent developments in the endocannabinoid system and its involvement in neuroprotection. Exogenous (endo)cannabinoids have been shown to exert neuroprotection in a variety of in vitro and in vivo models of neuronal injury via different mechanisms, such as prevention of excitotoxicity by CB1-mediated inhibition of glutamatergic transmission, reduction of calcium influx, and subsequent inhibition of deleterious cascades, TNF-alpha formation, and anti-oxidant activity. It has been suggested that the release of endogenous endocannabinoids during neuronal injury might be a protective response. However, several observations indicate that the role of the endocannabinoid system as a general endogenous protection system is questionable. The data are critically reviewed and possible explanations are given.


Human leukocytes express cannabinoid (CB) receptors, suggesting a role for both endogenous ligands and Delta(9)-tetrahydrocannabinol (THC) as immune modulators. To evaluate this, human T cells were stimulated with allogeneic dendritic cells (DC) in the presence or absence of THC (0.625-5 &mgr;g/ml). THC suppressed T cell proliferation, inhibited the production of interferon-gamma and shifted the balance of T helper 1 (Th1)/T helper 2 (Th2) cytokines. Intracellular cytokine staining demonstrated that THC reduced both the percentage and mean fluorescence intensity of activated T cells capable of producing interferon-gamma, with variable effects on the number of T cells capable of producing interleukin-4. Exposure to THC also decreased steady-state levels of mRNA encoding for Th1 cytokines, while increasing mRNA levels for Th2 cytokines. The CB2 receptor antagonist, SR144528, abrogated the majority of these effects. We conclude that cannabinoids have the potential to regulate the activation and balance of human Th1/Th2 cells by a CB2 receptor-dependent pathway.

CLINICAL SCIENCE


BACKGROUND: Although about 7 million people in the US population use marijuana at least weekly, there is a paucity of scientific data on persistent neurocognitive effects of marijuana use. OBJECTIVE: To determine if neurocognitive deficits persist in 28-day abstinent heavy marijuana users and if these deficits are dose-related to the number of marijuana joints smoked per week. METHODS: A battery of neurocognitive tests was given to 28-day abstinent heavy marijuana abusers. RESULTS: As joints smoked per week increased, performance decreased on tests measuring memory, executive functioning, psychomotor speed, and manual dexterity. When dividing the group into light, middle, and heavy user groups, the heavy group performed significantly below the light group on 5 of 35 measures and the size of the effect ranged from 3.00 to 4.20 SD units. Duration of use had little effect on neurocognitive performance. CONCLUSIONS: Very heavy use of marijuana is associated with persistent decrements in neurocognitive performance even after 28 days of abstinence. It is unclear if these decrements
will resolve with continued abstinence or become progressively worse with continued heavy marijuana use.


Cannabinoids, including smoked marijuana and delta9-tetrahydrocannabinol (THC) (dronabinol, Marinol), have been used to treat human immunodeficiency virus-1 (HIV)-associated anorexia and weight loss. Concerns have been raised, however, that these compounds might have adverse effects on the immune system of subjects with HIV infection. To determine whether such effects occur, the authors designed a randomized, prospective, controlled trial comparing the use of marijuana cigarettes (3.95% THC), dronabinol (2.5 mg), and oral placebo in HIV-infected adults taking protease inhibitor-containing highly active antiretroviral therapy (HAART). Assays of immune phenotype (including flow cytometric quantitation of T cell subpopulations, B cells, and natural killer [NK] cells) and immunefunction (including assays for induced cytokine production, NK cell function, and lymphoproliferation) were performed at baseline and weekly thereafter. On the basis of these measurements and during this short 21-day study period, few statistically significant effects were noted on immune system phenotypes orfunctions in this patient population.


BACKGROUND: The Children in the Community Study is a prospective longitudinal study investigating the association between early drug use (childhood, adolescence, and early 20s) and later psychiatric disorders (in the late 20s). METHODS: Using data from a community-based sample of 736 adults (50% female) from upstate New York, the subjects were interviewed at the mean ages of 14, 16, 22, and 27 years. Psychiatric disorders, measured by age-appropriate versions of the University of Michigan Composite International Diagnostic Interview, and participant's drug use were assessed. RESULTS: Adolescent and young adult tobacco use was significantly associated with an increased risk of alcohol dependence and substance use disorders at a mean age of 27 years, but not with new episodes of major depressive disorder. Earlier alcohol use significantly predicted later major depressive disorder, alcohol dependence, and substance use disorders in the late 20s, as did early marijuana use and other illicit drug use. Except for the effect of tobacco use on major depressive disorder, early drug use was significantly related to later psychiatric disorders, even after statistically controlling for age, sex, parental educational level, family income, and prior episodes of major depressive disorder and substance use disorders. CONCLUSIONS: Our results suggest that early drug use is associated with and predicts later psychiatric disorders. Preventive implications stem from the importance of studying a range of psychiatric disorders in the context of substance use assessed over a wide age range.


In the 35 years since the active compound of marijuana, delta9-tetrahydrocannabinol, was isolated, the psychological and physiological impact of marijuana use has been actively investigated. Animal models have demonstrated that cannabinoid administration acutely alters multiple hormonal systems, including the suppression of the gonadal steroids, growth hormone, prolactin, and thyroid hormone and the activation of the hypothalamic-pituitary-adrenal axis. These effects are mediated by binding to the endogenous cannabinoid receptor in or near the hypothalamus. Despite these findings in animals, the effects in humans have been inconsistent, and discrepancies are likely due in part to the development of tolerance. The long-term consequences of marijuana use in humans on endocrine systems remain unclear.


The past 10 to 15 years of clinical and basic research have produced strong evidence demonstrating that cannabis can and does produce dependence. Clinical and epidemiological studies indicate that cannabis dependence is a relatively common phenomenon associated with
significant psychosocial impairment. Basic research has identified a neurobiological system specific to the actions of cannabinoids. Human and nonhuman studies have demonstrated a valid withdrawal syndrome that is relatively common among heavy marijuana users. Last, clinical trials evaluating treatments for cannabis dependence suggest that this disorder, like other substance dependence disorders, is responsive to intervention, yet the majority of patients have difficulty achieving and maintaining abstinence. Of concern, treatment seeking for marijuana dependence has increased almost twofold over the past 10 years. This report briefly reviews selected research literature relevant to our current understanding of cannabis dependence, its associated consequences, and treatment efficacy.


Drug testing in substance abuse treatment programs is focused on urine analysis of parent drugs and major metabolites. Huestis reported that serial monitoring of the major urinary cannabinoid metabolite (Delta-THC-COOH)-to-creatinine ratios in paired urine specimens (collected at least 24 hours apart) could differentiate new marijuana or hashish use from residual cannabinoid metabolite excretion in urine after previous drug use. Subjects with a history of chronic marijuana use were screened for cannabinoids in urine over several months by an enzyme immunoassay (EMIT) with a cut-off value of 50 ng/mL. Presumptive positive specimens were confirmed by gas chromatography-mass spectrometry (GC-MS) for Delta-THC-COOH with a cut-off value of 15 ng/mL. The objective of this study was to determine whether a semiquantitative cannabinoids immunoassay (corrected for creatinine concentration) could differentiate new marijuana use from residual cannabinoid excretion in chronic users of marijuana or hashish compared with GC-MS. The criterion for new marijuana use was a cannabinoid-to-creatinine ratio ≥ 0.5 (dividing the immunoassay quantitative result to creatinine ratio of specimen 2 by the specimen 1 ratio, specimen 3 by the specimen 2 ratio, etc.). Urine specimens were analyzed by fluorescence-polarization immunoassay (FPIA) on an Abbott TD FL analyzer after analysis by GC-MS. In 90 urine specimens (group A) with Delta-THC-COOH values determined by GC-MS, the mean Delta-THC-COOH concentration was 44.4 ng/mL (range, 16-100), and the mean FPIA total cannabinoids value was 91.7 ng/mL (range, 21-204 ng/mL) with a correlation coefficient of 0.993 (group A). In 111 specimens (group B), the mean Delta-THC-COOH concentration was 361 ng/mL (range, 101-960 ng/mL). The mean FPIA value was 657 ng/mL (range, 211-1,270 ng/mL), and the correlation coefficient of the B series was 0.975. Percent cross-reactivity for Delta-THC-COOH standards prepared in drug-free urine by FPIA was 82% at 25 ng/mL, 45% at 50 ng/mL, and 50% at 100 ng/mL. Overall, there was 89% agreement (132 of 148 specimens) between FPIA and GC-MS. In 16 of 148 specimens, however, the FPIA and GC-MS paired urine data did not agree. The sensitivity of the FPIA assay was 95.3%, and the specificity was 44.4%. The authors conclude that FPIA cannabinoid analysis should be further evaluated as an alternative to GC-MS quantitation to help distinguish new marijuana use from residual marijuana metabolite excretion in clinical drug treatment programs.


For the purposes of this review, the impact of prenatal exposure to marijuana in adolescent offspring is discussed in the context that the effects may be apparent only when the multifaceted nature of complex behaviors is examined and that such exposure can be distinguished from those of prenatal exposure to cigarettes. The data are derived from adolescents participating in an on-going longitudinal study for whom prenatal marijuana and cigarette exposure had been ascertained with the low-risk, predominantly middle-class sample that had been assessed since birth. In this report, cognitive functioning and visual perceptual performance in 9- to 12-year-olds and facets of attention in 13- to 16-year-olds are examined. These three areas of behavior all appear to be affected differentially by maternal use of marijuana or cigarettes. Prenatal cigarette exposure was associated with lowered IQ, poorer impulse control, and poorer performance on tests requiring fundamental aspects of visuoperceptual
performance. In contrast, prenatal marijuana did not have a negative impact on IQ or on basic visuoperceptual skills. Rather, in utero exposure to marijuana had an impact on the application of these skills in tasks in problem-solving situations requiring visual integration and analytical skills as well as sustained attention. These differential findings are discussed in terms of cigarette exposure having a "bottom-up" impact and marijuana exposure having a "top-down" impact. The latter is also discussed in terms of prenatal marijuana's negative association with aspects of executive function.


Because there is a possibility that cannabis or cannabis-like molecules might be used as treatments for certain conditions in the future, it becomes important to consider the possible adverse effects of these compounds. In this paper, the authors review the evidence for persisting effects of nonacute cannabis use on the central nervous system, as reflected by alteration in neuropsychological performance. From the 40 articles that met criteria for inclusion in this review, the authors could not detect consistent evidence for persisting neuropsychological deficits in cannabis users; however, 22 of the 40 studies reported at least some subtle impairments. The inability to reach a firm conclusion results largely from methodological limitations inherent in most studies. These are considered in detail to inform future studies on (nonacute) consequences of cannabis consumption on cognitive abilities.


This article presents data from two avenues of marijuana research. First, the author shows that daily marijuana smoking in healthy individuals produces dependence, as demonstrated by withdrawal symptoms such as increased irritability and depression and decreased food intake. In addition, two antidepressant medications were evaluated to assess their potential effectiveness in the treatment of marijuana withdrawal symptoms: (1) sustained-release bupropion (0, 300 mg/day) and (2) nefazodone (0, 450 mg/day). Research participants were regular marijuana smokers who lived in a residential laboratory in groups of two to four. While inpatients, participants smoked active marijuana (2.8%-3.1% THC) repeatedly for 4 days, followed by 8 to 12 days of placebo marijuana (0.0% THC). Results show that during marijuana abstinence, (1) bupropion increased ratings of irritability, depression, and stomach pain and decreased food intake and sleep quality compared to placebo maintenance, and (2) nefazodone decreased anxiety during marijuana withdrawal but did not alter ratings of irritability and misery. Thus, neither medication showed promise as potential treatments for symptoms of marijuana withdrawal. The second avenue of research focused on the effect of cannabinoids in individuals with muscle mass loss, an indicator of wasting in HIV illness. Given that there are little scientific data contributing to the debates concerning medical marijuana, this study directly compared the effects of oral delta9-THC (0, 10, 20, 30 mg PO) to smoked marijuana (0.0%, 1.8%, 2.8%, 3.9% THC) in HIV + marijuana smokers with muscle mass loss (< 90% body cell mass/height). Multiple dimensions of human behavior were measured, including food intake, mood, and cognitive performance. Drugs were administered using a within-subject, double-blind, staggered, double-dummy design. Participants were free to self-select from a variety of foods throughout most of the session. Preliminary data (n = 9) suggest that oral THC was more effective at increasing food intake, but the volunteers "liked" the effects of smoked marijuana more than the effects of oral THC.


AbstractRATIONALE. Symptoms of marijuana withdrawal include increased irritability, depression and anxiety, and decreased sleep quality. Nefazodone, which is an antidepressant with sedative properties, may attenuate symptoms of marijuana withdrawal.OBJECTIVE. The present within-subject, placebo-controlled study investigated the effects of nefazodone during marijuana withdrawal.METHODS. Marijuana smokers [ n=7; averaging 6.0 (+/-1.3) marijuana
cigarettes/day, 6.4 (+/-0.4) days/week], not seeking treatment for marijuana use, were maintained on two doses of nefazodone (0, 450 mg/day) for 26 days each. Each maintenance condition began with an outpatient phase (9 days) and continued with an inpatient phase (17 days) in a residential laboratory. Marijuana was smoked 5 times per inpatient day at 1000, 1300, 1600, 1900 and 2200 hours. On days 1-4 (baseline), the first four marijuana cigarettes were placebo (0.00% THC), while the final marijuana cigarette was active (3.04% THC). On inpatient days 5-8, only active marijuana was smoked, while on days 9-16, only placebo marijuana was smoked. Mood, psychomotor task performance, food intake and sleep were measured daily. The order of maintenance dose was counterbalanced between groups.

RESULTS. Nefazodone maintenance did not alter the acute effects of active marijuana as compared to placebo nefazodone maintenance. During marijuana withdrawal, nefazodone decreased ratings of "Anxious", and "Muscle Pain", while having no effect on the marked increase in ratings of "Irritable", "Miserable" or decreased sleep quality.

CONCLUSIONS. Nefazodone decreased certain marijuana withdrawal symptoms, but participants still reported substantial discomfort. These data provide further evidence of marijuana withdrawal, and highlight the need for more marijuana treatment options.


The cognitive effects of long-term cannabis use are insufficiently understood. Most studies concur that cognitive deficits persist at least several days after stopping heavy cannabis use. But studies differ on whether such deficits persist long term or whether they are correlated with increasing duration of lifetime cannabis use. The authors administered neuropsychological tests to 77 current heavy cannabis users who had smoked cannabis at least 5000 times in their lives, and to 87 control subjects who had smoked no more than 50 times in their lives. The heavy smokers showed deficits on memory of word lists on Days 0, 1, and 7 of a supervised abstinence period. By Day 28, however, few significant differences were found between users and controls on the test measures, and there were few significant associations between total lifetime cannabis consumption and test performance. Although these findings may be affected by residual confounding, as in all retrospective studies, they suggest that cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use.


Marijuana and delta9-tetrahydrocannabinol (THC) increase heart rate, slightly increase supine blood pressure, and on occasion produce marked orthostatic hypotension. Cardiovascular effects in animals are different, with bradycardia and hypotension the most typical response. Cardiac output increases, and peripheral vascular resistance and maximum exercise performance decrease. Tolerance to most of the initial cardiovascular effects appears rapidly. With repeated exposure, supine blood pressure decreases slightly, orthostatic hypotension disappears, blood volume increases, heart rate slows, and circulatory responses to exercise and Valsalva maneuver are diminished, consistent with centrally mediated, reduced sympathetic, and enhanced parasympathetic activity. Receptor-mediated and probably nonneuronal sites of action account for cannabinoid effects. The endocannabinoid system appears important in the modulation of many vascular functions. Marijuana's cardiovascular effects are not associated with serious health problems for most young, healthy users, although occasional myocardial infarction, stroke, and other adverse cardiovascular events are reported. Marijuana smoking by people with cardiovascular disease poses health risks because of the consequences of the resulting increased cardiac work, increased catecholamine levels, carboxyhemoglobin, and postural hypotension.


As documented in national surveys, for the past several years, marijuana has been the most commonly abused drug in the United States, with approximately 6% of the population 12 years and older having used the drug in the month prior to interview. The use of marijuana is not
without significant health hazards. Marijuana is associated with effects on almost every organ system in the body, ranging from the central nervous system to the cardiovascular, endocrine, respiratory/pulmonary, and immune systems. Research presented in this special supplement will show that in addition to marijuana abuse/dependence, marijuana use is associated in some studies with impairment of cognitive function in the young and old, fetal and developmental consequences, cardiovascular effects (heart rate and blood pressure changes), respiratory/pulmonary complications such as chronic cough and emphysema, impaired immune function leading to vulnerability to and increased infections, and the risk of developing head, neck, and/or lung cancer. In general, acute effects are better studied than those of chronic use, and more studies are needed that focus on disentangling effects of marijuana from those of other drugs and adverse environmental conditions.


OBJECTIVE: To determine whether cannabis use in adolescence predisposes to higher rates of depression and anxiety in young adulthood. DESIGN: Seven wave cohort study over six years. SETTING: 44 schools in the Australian state of Victoria. PARTICIPANTS: A statewide secondary school sample of 1601 students aged 14-15 followed for seven years. MAIN OUTCOME MEASURE: Interview measure of depression and anxiety (revised clinical interview schedule) at wave 7. RESULTS: Some 60% of participants had used cannabis by the age of 20; 7% were daily users at that point. Daily use in young women was associated with an over fivefold increase in the odds of reporting a state of depression and anxiety after adjustment for intercurrent use of other substances (odds ratio 5.6, 95% confidence interval 2.6 to 12). Weekly or more frequent cannabis use in teenagers predicted an approximately twofold increase in risk for later depression and anxiety (1.9, 1.1 to 3.3) after adjustment for potential baseline confounders. In contrast, depression and anxiety in teenagers predicted neither later weekly nor daily cannabis use. CONCLUSIONS: Frequent cannabis use in teenage girls predicts later depression and anxiety, with daily users carrying the highest risk. Given recent increasing levels of cannabis use, measures to reduce frequent and heavy recreational use seem warranted.


Bleach, nitrite, chromate, and hydrogen peroxide-peroxidase are effective urine adulterants used by the illicit drug users to conceal marijuana-positive results. Methods for detecting nitrite and chromate are available. Effects of other oxidizing agents that could possibly be used as adulterants and are difficult to detect or measure are presented in this report. Urine samples containing 40 ng/mL of 11-nor-delta9-THC-9-carboxylic acid (THC-acid) were treated with 10 mmol/L of commonly available oxidizing agents. Effects of horseradish peroxidase of activity 10 unit/mL and extracts from 2.5 g of red radish (Raphanus sativus, Radicula group), horseradish (Armoracia rusticana), Japanese radish (Raphanus sativus, Daikon group), and black mustard seeds (Brassica nigra), all with 10 mmol/L of hydrogen peroxide, were also examined. After 5 min, 16 h and 48 h of exposure at room temperature (23 degrees C) the specimens were tested by a gas chromatographic-mass spectrometric method for THC-acid. A control group treated with sodium hydrosulfite to reduce the oxidants, was also tested to investigate the effect of oxidizing agents on THC-acid in the extraction method. THC-acid was lost completely in the extraction method when treated with chromate, nitrite, oxone, and hydrogen peroxide/ferrous ammonium sulfate (Fenton's reagent). Some losses were also observed with persulfate and periodate (up to 25%). These oxidants, and other oxidizing agents like permanganate, periodate, peroxidase, and extracts from red radish, horseradish, Japanese radish and black mustard seeds destroyed most of the THC-acid (> 94%) within 48 h of exposure. Chlorate, perchlorate, iodate, and oxychloride under these conditions showed little or no effect. Complete loss was observed when THC-acid was exposed to 50 mmol/L of oxychloride for 48 h. Several oxidizing adulterants that are difficult to test by the present urine adulterant testing methods showed considerable effects on the destruction of THC-acid. The time and temperature for these effects were similar to those used by most laboratories to collect and test specimens. In several cases, the loss of THC-acid was > 94%.

Background: The association between cannabis use and the development of a first psychotic episode was studied in a group of 100 young people identified as being at very high risk for the onset of psychosis. Method: The 'ultra' high risk cohort was identified by the presence of subthreshold psychotic symptoms, or a combination of first-degree relative with a psychotic disorder and recent functional decline. Thirty-two per cent of the cohort developed an acute psychotic episode over the 12-month period after recruitment. As a component of a larger research study, the level of cannabis use by participants in the year prior to enrolment in the study was assessed at intake. Results: Cannabis use or dependence in the year prior to recruitment to this study was not associated with a heightened risk of developing psychosis over the following 12-month period and therefore did not appear to contribute to the onset of a psychotic disorder. Conclusion: The results of this study suggest that cannabis use may not play an integral role in the development of psychosis in a high-risk group. While this study does not support a role for cannabis in the development of first-episode psychosis, we cannot conclude that cannabis use should be completely ignored as a candidate risk factor for onset of psychosis. A number of weaknesses of the study (the low level of cannabis use in the current sample, the lack of monitoring of cannabis use after intake) suggest that it may be premature to dismiss cannabis use as a risk factor for the development of psychosis and further research is urged in this area.


This review describes what is known about effects of marijuana and cannabinoids in relation to human physiological and disease outcomes. The acute physiological effects of marijuana include a substantial dose-dependent increase in heart rate, generally associated with a mild increase in blood pressure. Orthostatic hypotension may occur acutely as a result of decreased vascular resistance. Smoking marijuana decreases exercise test duration in maximal exercise tests, increases the heart rate at submaximal levels of exercise. Tolerance develops to the acute effects of marijuana smoking and delta9-tetrahydrocannibol (THC) over several days to a few weeks. The cardiovascular responses that occur in response to THC are mediated by the autonomic nervous system, with recent findings also demonstrating that the human cannabinoid receptor system plays a role in regulating the cardiovascular response. Although several mechanisms exist by which marijuana use might contribute to the development of chronic cardiovascular conditions or acutely trigger cardiovascular events, there are few data regarding marijuana/THC use and cardiovascular disease outcomes. A large cohort study showed no association of marijuana use with cardiovascular disease hospitalization or mortality. However, acute effects of marijuana use include a decrease of the time until the onset of chest pain in patients with angina pectoris; one study has shown that marijuana may trigger the onset of myocardial infarction. Patients who have coronary heart disease or are at high risk for the development of CHD should be cautioned about the potential hazards of marijuana use as a precipitant for clinical events. Research directions might include more studies of cardiovascular disease outcomes and relationships of marijuana with cardiovascular risk factors, studies of metabolic and physiologic effects of chronic marijuana use that may affect cardiovascular disease risk, increased understanding of the role of the cannabinoid receptor system in cardiovascular regulation, and studies to determine if there is a therapeutic role for cannabinoids in blood pressure control or for neuroprotection after stroke.


Habitual smoking of marijuana has a number of effects on the respiratory and immune systems that may be clinically relevant. These include alterations in lung function ranging from no to mild airflow obstruction without evidence of diffusion impairment, an increased prevalence of
acute and chronic bronchitis, striking endoscopic findings of airway injury (erythema, edema, and increased secretions) that correlate with histopathological alterations in bronchial biopsies, and dysregulated growth of the bronchial epithelium associated with altered expression of nuclear and cytoplasmic proteins involved in the pathogenesis of bronchogenic carcinoma. Other consequences of regular marijuana use include ultrastructural abnormalities in human alveolar macrophages along with impairment of their cytokine production, antimicrobial activity, and tumoricidal function. Cannabinoid receptor expression is altered in leukocytes collected from the blood of chronic smokers, and experimental models support a role for delta9-tetrahydrocannabinol in suppressing T cell function and cell-mediated immunity. The potential for marijuana smoking to predispose to the development of respiratory malignancy is suggested by several lines of evidence, including the presence of potent carcinogens in marijuana smoke and their resulting deposition in the lung, the occurrence of premalignant changes in bronchial biopsies obtained from smokers of marijuana in the absence of tobacco, impairment of antitumor immune defenses by delta9-tetrahydrocannabinol, and several clinical case series in which marijuana smokers were disproportionately over represented among young individuals who developed upper or lower respiratory tract cancer. Additional well designed epidemiological and immune monitoring studies are required to determine the potential causal relationship between marijuana use and the development of respiratory infection and/or cancer.


OBJECTIVES: An association between use of cannabis in adolescence and subsequent risk of schizophrenia was previously reported in a follow up of Swedish conscripts. Arguments were raised that this association may be due to use of drugs other than cannabis and that personality traits may have confounded results. We performed a further analysis of this cohort to address these uncertainties while extending the follow up period to identify additional cases.

DESIGN: Historical cohort study.

SETTING: 1969-70 survey of Swedish conscripts (>97% of the country's male population aged 18-20).

PARTICIPANTS: 50 087 subjects: data were available on self reported use of cannabis and other drugs, and on several social and psychological characteristics.

MAIN OUTCOME MEASURES: Admissions to hospital for ICD-8/9 schizophrenia and other psychoses, as determined by record linkage.

RESULTS: Cannabis was associated with an increased risk of developing schizophrenia in a dose dependent fashion both for subjects who had ever used cannabis (adjusted odds ratio for linear trend of increasing frequency 1.2, 95% confidence interval 1.1 to 1.4, P<0.001), and for subjects who had used only cannabis and no other drugs (adjusted odds ratio for linear trend 1.3, 1.1 to 1.5, P<0.015). The adjusted odds ratio for using cannabis >50 times was 6.7 (2.1 to 21.7) in the cannabis only group. Similar results were obtained when analysis was restricted to subjects developing schizophrenia after five years after conscription, to exclude prodromal cases.

CONCLUSIONS: Cannabis use is associated with an increased risk of developing schizophrenia, consistent with a causal relation. This association is not explained by use of other psychoactive drugs or personality traits relating to social integration.

BEHAVIOURAL SCIENCE


In order to place the issues of drug abuse in a proper perspective and to allow rational, evidence-based decision-making, an analysis of the international data on the use of illicit drugs and the misuse of legally prescribed psychotropic drugs was undertaken. The data show that by far the most widely abused drug is cannabis, followed, according to region, by amphetamine-type stimulants or cocaine. While opiate abuse is far less widespread, it accounts for a disproportionately large proportion of medical and social problems. The illicit use of licit medicines
is a very small, and declining, problem. The implications of these data for physicians, politicians, regulators and administrators are discussed.


Background The links between drug use and psychosis are of major aetiological and prognostic significance. Psychosis and drug dependence frequently co-occur within the prison population, providing the opportunity to study this link more closely. Aims To explore the relationship between psychosis and drug dependence in a sample of prisoners. Method A total of 3142 prisoners were surveyed nationally, and structured clinical data were obtained from a subsample of 503 respondents. Psychiatric assessment was based on the Schedules for Clinical Assessment in Neuropsychiatry (version 1.0). Measures of amphetamine, cannabis, cocaine and heroin use and dependence were obtained through self-report. Results Logistic regression analyses indicated that first use of amphetamines or cocaine before the age of 16 years and severe cannabis or cocaine dependence were related to an increased risk of psychosis. In contrast, severe dependence on heroin was associated with a reduced risk of this classification. Conclusions Severe dependence on cannabis and psychostimulants is associated with a higher risk of psychosis and is in contrast to severe dependence on heroin, which has a negative relationship with psychosis.

Jones, B. C., B. T. Jones, et al. (2002). "Social users of alcohol and cannabis who detect substance-related changes in a change blindness paradigm report higher levels of use than those detecting substance-neutral changes." Psychopharmacology (Berl).

RATIONALE. Understanding the cognitions underpinning substance use has stalled using the Stroop paradigm. OBJECTIVE. To employ a novel version of the flicker paradigm for induced change blindness to independently compare information processing biases in social users of alcohol and cannabis. METHOD. Alcohol and cannabis experiments were independently run. In both, participants were asked to view successively and repeatedly on a monitor two versions of a visual scene (an original and a slightly changed version) until the change was detected. In fact, in both experiments two simultaneous changes competed for detection: a substance-neutral and a substance-related change. RESULTS. In both the alcohol and the cannabis experiments, participants detecting the substance-related change reported higher levels of use than those detecting the substance-neutral change. CONCLUSION. A substance-related processing bias was independently revealed for both substances. The utility of the flicker paradigm for substance use research is demonstrated as sensitive and quick to administer (taking only 1 min).


OBJECTIVE To examine the relationship among nicotine, alcohol, and marijuana use; level of sensation seeking (SS); and pubertal development.METHOD Subjects were early and middle adolescent males and females recruited from a psychiatric clinic ( = 77) and two general pediatric clinics ( = 131). SS was measured by using the Sensation Seeking Scale for Children. Pubertal development was measured with a modified Pubertal Development Scale that was completed by the adolescent and his/her parent about the adolescent. Adolescent self-reports of nicotine, alcohol, and marijuana use were also obtained using questionnaires.RESULTS SS was higher in males and females who reported nicotine and alcohol use and in males who reported marijuana use. SS was positively associated with pubertal development in males and females, even when controlling for age. Furthermore, SS mediated the relationship of pubertal development and drug use in males and females.CONCLUSIONS The observation that SS mediates the relationship between pubertal development and drug use in males and females may contribute to understanding changes in drug use that are seen during adolescence. In addition, SS is associated with drug use and is easily measured in a variety of clinical settings.

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