INTRODUCTION
There were 56 references this month. Feedback on the layout has been positive so it will be retained. A large number of abstracts come from a single issue of Prostaglandins Leukot Essent Fatty Acids vol 66(2-3).

BASIC SCIENCE

The current review evaluates the evidence that some of the pharmacological and behavioral effects of ethanol (EtOH), including EtOH-prefering behavior, may be mediated through the endocannabinoid signaling system. The recent advances in the understanding of the neurobiological basis of alcoholism suggest that the pharmacological and behavioral effects of EtOH are mediated through its action on neuronal signal transduction pathways and ligand-gated ion channels, receptor systems, and receptors that are coupled to G-proteins. The identification of a G-protein-coupled receptor, namely, the cannabinoid receptor (CB1 receptor) that was activated by Delta(9)-tetrahydrocannabinol (Delta(9)-THC), the major psychoactive component of marijuana, led to the discovery of endogenous cannabinoid agonists. To date, two fatty acid derivatives identified to be arachidonylethanolamide (AEA) and 2-arachidonylglycerol (2-AG) have been isolated from both nervous and peripheral tissues. Both these compounds have been shown to mimic the pharmacological and behavioral effects of Delta(9)-THC. The involvement of the endocannabinoid signaling system in the development of tolerance to the drugs of abuse including EtOH has not been known until recently. Recent studies from our laboratory have demonstrated for the first time the down-regulation of CB1 receptor function and its signal transduction by chronic EtOH. The observed down-regulation of CB1 receptor binding and its signal transduction results from the persistent stimulation of the receptors by the endogenous CB1 receptor agonists, AEA and 2-AG, the synthesis of which has been found to be increased by chronic EtOH treatment. This enhanced formation of endocannabinoids may subsequently influence the release of neurotransmitters. It was found that the DBA/2 mice, known to avoid EtOH intake, have significantly reduced brain-CB1-receptor function consistent with other studies, where the CB1 receptor antagonist SR141716A has been shown to block voluntary EtOH intake in rodents. Similarly, activation of the CB1 receptor system promoted alcohol craving, suggesting a role for the CB1 receptor gene in excessive EtOH drinking behavior and development of alcoholism. Ongoing investigations may lead to the development of potential therapeutic strategies for the treatment of alcoholism.


Exogenous cannabinoids disrupt behavioral learning and impede induction of long-term potentiation (LTP) in the hippocampus, yet endogenous cannabinoids (endocannabinoids) transiently suppress inhibitory post-synaptic currents (IPSCs) by activating cannabinoid CB1 receptors on GABAergic interneurons. We found that release of endocannabinoids by a rat CA1 pyramidal cell during this depolarization-induced suppression of inhibition (DSI) enabled a normally ineffective train of excitatory post-synaptic currents (EPSCs) to induce LTP in that cell,
but not in neighboring cells. By showing that endocannabinoids facilitate LTP induction and help target LTP to single cells, these data shed new light on the physiological roles of endocannabinoids and may lead to a greater understanding of their effects on behavior and potential clinical use.


Marijuana is a complex substance containing over 60 different forms of cannabinoids, the active ingredients. Cannabinoids are now known to have the capacity for neuromodulation, via direct, receptor-based mechanisms at numerous levels within the nervous system. These have therapeutic properties that may be applicable to the treatment of neurological disorders; including anti-oxidative, neuroprotective, analgesic and anti-inflammatory actions; immunomodulation, modulation of glial cells and tumor growth regulation. This article reviews the emerging research on the physiological mechanisms of endogenous and exogenous cannabinoids in the context of neurological disease.


The fatty acid amide hydrolase (FAAH), is the enzyme responsible for the hydrolysis of anandamide, an endocannabinoid. The FAAH knockout, the assays for FAAH, the activity of its substrates, its reversibility and its cloning from rat, mouse, human, and pig are covered in this review. The conserved regions of FAAH are described in terms of sequence and function, including the domains that contains the serine catalytic nucleophile, the hydrophobic domain important for self-association, the proline rich domain region which may be important for subcellular localization and the fatty acid chain binding domain. The FAAH mouse promoter region was characterized in terms of its transcription start site and its activity in different cell types. The distribution of FAAH in the major organs in the body is described as well as regional distribution in the brain and its correlation with cannabinoid receptors. Since FAAH is recognized as a drug target, a large number of inhibitors have been synthesized and tested since 1994 and these are reviewed in terms of reversibility, potency, and specificity for FAAH.


The newly reported benzoflavone moiety from the plant Passiflora incarnata Linneaus has been evaluated in light of traditional reports on the use of P. incarnata in breaking down cannabis addiction. In the modern or allopathic system of therapeutics, there has been no suitable remedy to combat the severe withdrawal effects of various cannabis products, including marihuana, marijuana, bhang, hashish, ganja, etc., the world-wide consumption of which has attained alarming proportions especially among the younger generation. Mice were given a 10-mg-kg(-1) twice-daily dose of delta9-tetrahydrocannabinol (delta9-THC) by mouth for six days to make them dependent upon cannabinoids. Concurrently, other groups of mice were administered delta9-THC along with a 10- or 20-mg-kg(-1) twice-daily dose of the benzoflavone moiety from P. incarnata orally for 6 days. Upon measuring locomotor activity during the treatment regimen, it was noticed that the mice receiving the P. incarnata extract and delta9-THC together developed significantly less tolerance and dependence, relative to the mice receiving delta9-THC alone. Upon administration of SR-141716A, a selective cannabinoid-receptor antagonist (10 mg kg(-1), p.o.) to all the groups of mice on the 7th day, an artificial withdrawal was produced due to an abrupt decline of delta9-THC levels in mouse brain. However, the typical withdrawal effects like paw tremors and head shakes were significantly less in the mice given delta9-THC+P. incarnata benzoflavone moiety for 6 days. Upon administration of 20 mg kg(-1) of the P. incarnata benzoflavone moiety to mice showing severe symptoms of withdrawal due to administration of SR-141716A, there was a marked attenuation of withdrawal effects, thereby suggesting the usefulness of the benzoflavone moiety in delta9-THC withdrawal. Thus, the benzoflavone moiety of P. incarnata, when administered concurrently with delta9-THC, prevented the development of tolerance and dependence of cannabinoids in mice. Even an acute administration of the
benzoflavone moiety (20 mg kg\(^{-1}\), p.o.) significantly blocked the expression of withdrawal effects in delta9-THC-dependent mice.


Anandamide (N -arachidonoyl-ethanolamine, AEA) was the first endogenous ligand of cannabinoid receptors to be discovered. Yet, since early studies, AEA appeared to exhibit also some effects that were not mediated by cannabinoid CB(1) or CB(2) receptors. Indeed, AEA exerts some behavioral actions also in mice with genetically disrupted CB(1) receptors, whereas in vitro it is usually a partial agonist at these receptors and a weak activator of CB(2) receptors. Nevertheless, several pharmacological effects of AEA are mediated by CB(1) receptors, which, by being coupled to G-proteins, can be seen as AEA 'metabotropic' receptors. Furthermore, at least two different, and as yet uncharacterized, G-protein-coupled AEA receptors have been suggested to exist in the brain and vascular endothelium, respectively. AEA is also capable of directly inhibiting ion currents mediated by L-type Ca(2+) channels and TASK-1 K(+) channels. However, to date the only reasonably well characterized, non-cannabinoid site of action for AEA is the vanilloid receptor type 1 (VR1), a non-selective cation channel gated also by capsaicin, protons and heat. VR1 might be considered as an AEA 'ionotropic' receptor and, under certain conditions, mediates effects ranging from vasodilation, broncho-constriction, smooth muscle tone modulation and nociception to stimulation of hippocampal pair-pulse depression, inhibition of tumor cell growth and induction of apoptosis.


Sensory neural dysfunction is common in patients with peripheral neuropathy, a major complication of diabetes mellitus. In animal models of inflammatory and neuropathic pain cannabinoids potently attenuate pain behaviour, cannabinoid (CB) receptors located on nociceptive primary afferent neurones being important in their anti-hyperalgesic actions. A key measure of sensory neurone function is stimulus-evoked neuropeptide release. We investigated the effect of cannabinoid on capsaicin-evoked release of calcitonin gene-related peptide (CGRP) from the rat paw skin in vitro, comparing non-diabetic and streptozotocin-induced diabetic animals. Diabetes caused a greater than two-fold increase in basal and capsaicin-evoked CGRP release. The synthetic CB(1)/CB(2) receptor agonist, CP55940 (100 nM), inhibited capsaicin-evoked CGRP release in both non-diabetic (30.92±7.69%, P<0.05) and diabetic animals (37.82±9.85%, P<0.05). The CB(1) receptor antagonist SR141716A (100 nM), but not the CB(2) receptor antagonist SR144528 (100 nM), significantly attenuated the inhibitory action of CP55940. The endogenous cannabinoid, anandamide (100 nM) inhibited capsaicin-evoked CGRP release in non-diabetic animals (28.88±7.12%, P<0.05) but neither the CB(1) nor the CB(2) receptor antagonist attenuated this action of anandamide. Anandamide (100 nM) did not significantly inhibit capsaicin-evoked CGRP release from the paw skin of diabetic animals, but it did produce a small stimulation of CGRP release at high concentrations (10 μM). These data suggest that peripheral CB(1) receptors mediate inhibition of capsaicin-evoked neuropeptide release from the paw skin of both non-diabetic and diabetic animals. However, pathological changes in the diabetic animals appear to preclude the non-CB(1) receptor mediated inhibitory action of the endogenous cannabinoid, anandamide.


In recent years, our knowledge on the cannabinoid pharmacology has shown a significant rise in terms of both quantity (more compounds and more targets) and quality (more selective compounds). This allows to consider cannabinoids and related compounds as a promising new line of research for therapeutic treatment of a variety of conditions, such as brain injury, chronic pain, glaucoma, asthma, cancer and AIDS-associated effects and other pathologies. Motor disorders are another promising field for the therapeutic application of cannabinoid-related compounds, since the control of movement is one of the more relevant physiological roles of the
endocannabinoid transmission in the brain. There are two pathologies, Parkinson's disease and Huntington's chorea, which are particularly interesting from a clinical point of view due to the direct relationship of endocannabinoids and their receptors with neurons that degenerate in those disorders. However, other neurological pathologies, such as Alzheimer's disease or multiple sclerosis, which are not motor disorders in origin, but present a strong alteration in the control of movement, have also been a subject of interesting research for a cannabinoid therapy. This review will summarize our current knowledge on the role of these endogenous substances in the control of movement and, in particular, on the possible therapeutic usefulness of these compounds in the treatment of motor pathologies.


The endogenous cannabinoid anandamide (AEA) is transported into cells by a temperature-sensitive process of facilitated diffusion. This uptake process has been characterised both biochemically and pharmacologically, and shown to be regulated at least in part by the intracellular metabolism of the accumulated AEA by fatty acid amide hydrolase. In this review, the properties of this transport process are briefly reviewed together with the corresponding transport mechanisms for the related endogenous compounds 2-arachidonoylglycerol and palmitoylethanolamide. In addition, the possibility that these transport mechanisms can be targets for therapeutic strategies aimed at prolonging the effects of the endocannabinoids is discussed.


Analogues of the biaryl pyrazole N-(piperidinyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (SR141716; 5) were synthesized to investigate the structure-activity relationship (SAR) of the aminopiperidine region. The structural modifications include the substitution of alkyl hydrazines, amines, and hydroxyalkylamines of varying lengths for the aminopiperidinyl moiety. Proximity and steric requirements at the aminopiperidine region were probed by the synthesis of analogues that substitute alkyl hydrazines of increasing chain length and branching. The corresponding amide analogues were compared to the hydrazides to determine the effect of the second nitrogen on receptor binding affinity. The N-cyclohexyl amide 14 represents a direct methine for nitrogen substitution for 5, reducing the potential for heteroatom interaction, while the morpholino analogue 15 adds the potential for an additional heteroatom interaction. The series of hydroxyalkyl amides of increasing chain length was synthesized to investigate the existence of additional receptor hydrogen binding sites. In displacement assays using the cannabinoid agonist [(3)H]1R,3R,4R)-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol (CP 55 940; 2) or the antagonist [(3)H]5, 14 exhibited the highest CB(1) affinity. In general, increasing the length and bulk of the substituent was associated with increased receptor affinity and efficacy (as measured in a guanosine 5'-triphosphate-gamma-[35S] assay). However, in most instances, receptor affinity and efficacy increases were no longer observed after a certain chain length was reached. A quantitative SAR study was carried out to characterize the pharmacophoric requirements of the aminopiperidine region. This model indicates that ligands that exceed 3 A in length would have reduced potency and affinity with respect to 5 and that substituents with a positive charge density in the aminopiperidine region would be predicted to possess increased pharmacological activity.


Many aspects of the physiology and pharmacology of anandamide (arachidonoyl ethanol amide), the first endogenous cannabinoid ligand ('endocannabinoid') isolated from pig brain, have been studied since its discovery in 1992. Ethanol amides from other fatty acids have also been identified as endocannabinoids with similar in vivo and in vitro pharmacological properties. 2-Arachidonoylglycerol and noladin ether (2-arachidonyl glyceryl ether), isolated in 1995 and 2001,
respectively, so far, display pharmacological properties in the central nervous system, similar to those of anandamide. The endocannabinoids are widely distributed in brain, they are synthesized and released upon neuronal stimulation, undergo reuptake and are hydrolyzed intracellularly by fatty acid amide hydrolase (FAAH). For therapeutic purposes, inhibitors of FAAH may provide more specific cannabinoid activities than direct agonists, and several such molecules have already been developed. Pharmacological effects of the endocannabinoids are very similar, yet not identical, to those of the plant-derived and synthetic cannabinoid receptor ligands. In addition to pharmacokinetic explanations, direct or indirect interactions with other receptors have been considered to explain some of these differences, including activities at serotonin and GABA receptors. Binding affinities for other receptors such as the vanilloid receptor, have to be taken into account in order to fully understand endocannabinoid physiology. Moreover, possible interactions with receptors for the lysophosphatidic acids deserve attention in future studies. Endocannabinoids have been implicated in a variety of physiological functions. The areas of central activities include pain reduction, motor regulation, learning/memory, and reward. Finally, the role of the endocannabinoid system in appetite stimulation in the adult organism, and perhaps more importantly, its critical involvement in milk ingestion and survival of the newborn, may not only further our understanding of the physiology of food intake and growth, but may also find therapeutic applications in wasting disease and infant's 'failure to thrive'.


In conscious, freely-moving, male, Sprague-Dawley rats, the regional haemodynamic responses to the synthetic cannabinoids, WIN-55212-2 and HU 210, were compared. The possible involvement of cannabinoid, CB(1)-receptors, or beta(2)-adrenoceptors in the responses to WIN-55212-2 and HU 210 were investigated using the CB(1)-receptor antagonist, AM 251, or the beta(2)-adrenoceptor antagonist, ICI 118551, respectively. Both WIN-55212-2 (150 &mgr;g kg(-1)) and HU 210 (100 &mgr;g kg(-1)) had pressor, renal, and mesenteric vasoconstrictor and hindquarters vasodilator actions, although the effects of HU 210 were much more sustained than those of WIN-55212-2. Lower doses of the cannabinoids (WIN-55212-2, 50 &mgr;g kg(-1), HU 210, 10 &mgr;g kg(-1)) had less consistent actions. All the significant cardiovascular effects of WIN-55212-2 and HU 210 were antagonized by pretreatment with AM 251 (3 mg kg(-1)). Furthermore, pretreatment with the beta(2)-adrenoceptor antagonist, ICI 118551, inhibited the hindquarters vasodilator effects of WIN-55212-2 and of HU 210. On the basis of the present findings, and our earlier work, it is suggested that, in conscious rats, the pressor and vasoconstrictor effects of HU 210 and WIN-55212-2 involve cannabinoid-receptor-mediated increases in sympathetic activity. The accompanying hindquarters vasodilator actions of these agonists are cannabinoid receptor-mediated and appear to involve beta(2)-adrenoceptors.


The fatty acid amide anandamide produces hypotension and a decrease in systemic vascular resistance in vivo. A drop in blood pressure is also seen with synthetic cannabinoid (CB) receptor agonists. The hypotensive responses to anandamide and synthetic cannabinoids are absent in CB1 receptor gene knockout mice. In isolated arteries and perfused vascular beds, anandamide induces vasodilator responses, which cannot be mimicked by synthetic cannabinoids. Instead, vanilloid receptors on perivascular sensory nerves play a key role in these effects of anandamide. Activation of vanilloid receptors by anandamide triggers the release of sensory neuropeptides such as the vasodilator calcitonin gene-related peptide (CGRP). Anandamide is detected in blood and in many cells of the cardiovascular system, and macrophage-derived anandamide may be involved in several hypotensive clinical conditions. Interestingly, cannabinoid and vanilloid receptors display an overlap in ligand recognition properties, and the frequently used CB1 receptor antagonist SR141716A also inhibits vanilloid receptor-mediated responses. The presence of anandamide in endothelial cells, neurones and activated macrophages (monocytes), and its ability to activate CB and vanilloid receptors make this lipid a potential bioregulator in the cardiovascular system.
Two types of cannabinoid receptor have been discovered so far, CB(1) (2:1: CBD:1:CB1:), cloned in 1990, and CB(2) (2:1: CBD:2:CB2:), cloned in 1993. Distinction between these receptors is based on differences in their predicted amino acid sequence, signaling mechanisms, tissue distribution, and sensitivity to certain potent agonists and antagonists that show marked selectivity for one or the other receptor type. Cannabinoid receptors CB(1) and CB(2) exhibit 48% amino acid sequence identity. Both receptor types are coupled through G proteins to adenylyl cyclase and mitogen-activated protein kinase. CB(1) receptors are also coupled through G proteins to several types of calcium and potassium channels. These receptors exist primarily on central and peripheral neurons, one of their functions being to inhibit neurotransmitter release. Indeed, endogenous CB(1) agonists probably serve as retrograde synaptic messengers. CB(2) receptors are present mainly on immune cells. Such cells also express CB(1) receptors, albeit to a lesser extent, with both receptor types exerting a broad spectrum of immune effects that includes modulation of cytokine release. Of several endogenous agonists for cannabinoid receptors identified thus far, the most notable are arachidonylethanolamide, 2-arachidonoylglycerol, and 2-arachidonylglycerol ether. It is unclear whether these eicosanoid molecules are the only, or primary, endogenous agonists. Hence, we consider it premature to rename cannabinoid receptors after an endogenous agonist as is recommended by the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. Although pharmacological evidence for the existence of additional types of cannabinoid receptor is emerging, other kinds of supporting evidence are still lacking.


The effect of 2-arachidonoylglycerol, a cannabimimetic eicosanoid, was studied on mucosa-free longitudinal muscle strips isolated from the guinea-pig distal colon. In the presence of indomethacin (3 &mgr;M) and N(G)-nitro-L-arginine (100 &mgr;M), 2-arachidonoylglycerol (10 nM-10 &mgr;M) produced concentration-dependent and tetrodotoxin (1 &mgr;M)-sensitive contractions of the longitudinal muscle strips. The contractions were markedly attenuated in the presence of atropine (0.2 &mgr;M), and partially by hexamethonium (100 &mgr;M) pretreatment. The response to 2-arachidonoylglycerol was mimicked with N-arachidonoylethanolamine (anandamide, 0.1-30 &mgr;M), another cannabimimetic eicosanoid, but the cannabinoid CB(1)/CB(2) receptor agonist, R-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benz oxazin-6-yl]-1-naphthalenylmethanone (WIN55,212-2) (0.1-10 &mgr;M), and the vanilloid receptor agonist, (all Z)-(4-hydroxyphenyl)-5,8,11,14-eicosatetraenamide (AM 404) (10-30 &mgr;M), were without effect. The cannabinoid CB(1) receptor antagonist, N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole -carboxamide (SR141716A) (1 &mgr;M), the cannabinoid CB(2) receptor antagonist, [N-[1S]-endo-1,3,3-trimethyl bicyclo [2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-car boxamide (SR144528) (1 &mgr;M), and the vanilloid receptor antagonist, capsazepine (10 &mgr;M), did not shift the concentration-response curve for 2-arachidonoylglycerol to the right. The contractile action of 2-arachidonoylglycerol was also partially attenuated in the presence of nordihydroguaiaretic acid (10 &mgr;M), a lipoxygenase inhibitor. These results indicate that 2-arachidonoylglycerol produces contraction of longitudinal muscle of the guinea-pig distal colon via mainly stimulation of myenteric cholinergic neurones, and that neither cannabinoid CB(1)/CB(2) receptors nor vanilloid receptors contributed to the response. The present results suggest the possibility that lipoxygenase metabolites may also contribute, at least in part, to the contractile action of 2-arachidonoylglycerol.


There is increasing evidence that endocannabinoids play roles in a number of physiological and pathophysiological processes ranging from the regulation of food intake to the
inhibition of cancer cell proliferation. Consequently, multiple investigations into endocannabinoid metabolic disposition have been initiated. Such studies have begun to shed light on the mechanisms that regulate the endogenous cannabinoid system. In addition, they have identified a number of novel, endocannabinoid-derived lipids. In the future, these studies may form the foundation of efforts designed to subtly manipulate endocannabinoid tone in vivo to achieve therapeutic benefits without the profound side-effects observed with synthetic cannabinoid treatment. In addition to the well-studied hydrolytic mode of endocannabinoid metabolism, accumulating data suggest that these lipids are also susceptible to oxidative metabolism by a number of fatty acid oxygenases. These include the cyclooxygenases, lipoxygenases, and cytochrome P450s known to be involved in eicosanoid production from arachidonic acid. The available evidence concerning endocannabinoid oxidation is reviewed and the potential biological significance of this mode of metabolism is considered.


Endocannabinoids serve as retrograde messengers in many brain regions. These diffusible lipophilic molecules are released by postsynaptic cells and regulate presynaptic neurotransmitter release. Here we describe an additional mechanism that mediates the spread of endocannabinoid signaling to distant inhibitory synapses. Depolarization of cerebellar Purkinje cells reduced the firing rate of nearby interneurons, and this reduction in firing was blocked by the cannabinoid receptor antagonist AM251. The cannabinoid receptor agonist WIN55,212-2 also reduced firing rates in interneurons, and this inhibition arose from the activation of a small potassium conductance. Thus, endocannabinoids released from the dendrites of depolarized neurons can lead to inhibition of firing in nearby cells. Because interneurons can project over several hundred micrometers, this inhibition of firing allows cells to regulate synaptic inputs at distances well beyond the limits of endocannabinoid diffusion.


Cannabis use is associated with a wide range of pharmacological effects, some of which have potential therapeutic benefit while others result in negative outcomes. Acute cannabinoid intoxication has been well documented to produce deficits in cognitive functioning with concomitant changes in glutamatergic, GABAergic, and cholinergic neurochemical systems in the hippocampus, each of which has been implicated in memory. Additionally, cannabis-dependent individuals abstaining from this drug can undergo a constellation of mild withdrawal effects. The use of the CB(1) cannabinoid receptor antagonist SR141716A and transgenic mice lacking the CB(1) receptor are critical tools for investigating the role of the endocannabinoid system in cognition, drug dependence, and other physiological processes. Converging evidence in which performance in a variety of memory tasks is enhanced following either SR141716A treatment or in CB(1) receptor knockout mice indicates that this system may play an important role in modulating cognition. There are also indications that this system may function to modulate opioid dependence. The purpose of this review is to describe recent advances that have furthered our understanding of the roles that the endocannabinoid system play on both cognition and drug dependence.


Fatty acid amides (FAAs) represent a class of neuromodulatory lipids that includes the endocannabinoid anandamide and the sleep-inducing substance oleamide. Both anandamide and oleamide produce behavioral effects indicative of cannabinoid activity, but only anandamide binds the cannabinoid (CB1) receptor in vitro. Accordingly, oleamide has been proposed to induce its behavioral effects by serving as a competitive substrate for the brain enzyme fatty acid amide hydrolase (FAAH) and inhibiting the degradation of endogenous anandamide. To test the role that FAAH plays as a mediator of oleamide activity in vivo, we have compared the behavioral effects of this FAA in FAAH(+/+) and (-/-) mice. In both genotypes, oleamide produced...
hypomotility, hypothermia, and ptosis, all of which were enhanced in FAAH(-/-) mice, were unaffected by the CB1 antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-di-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716A) and occurred in CB1(-/-) mice. Additionally, oleamide displayed negligible binding to the CB1 receptor in brain extracts from either FAAH(+/+) or (-/-) mice. In contrast, anandamide exhibited a 15-fold increase in apparent affinity for the CB1 receptor in brains from FAAH(-/-) mice, consistent with its pronounced CB1-dependent behavioral effects in these animals. Contrary to both oleamide and anandamide, monoacylglycerol lipids exhibited equivalent hydrolytic stability and pharmacological activity in FAAH(+/+) and (-/-) mice. Collectively, these results indicate that FAAH is a key regulator, but not mediator of FAA activity in vivo. More generally, these findings suggest that FAAs represent a family of signaling lipids that, despite sharing similar chemical structures and a common pathway for catabolism, produce their behavioral effects through distinct receptor systems in vivo.


Despite important advances in pharmacotherapeutic options for the prevention and treatment of nausea and vomiting during the 1990s, a significant proportion of patients still suffer debilitating nausea and vomiting symptoms. The most problematic areas are chemotherapy-induced nausea and vomiting particularly delayed emesis, postoperative nausea and vomiting, opioid-induced nausea and vomiting and motion sickness. The most vigorous research into new anti-emetics has focused on the neurokinin-1 (substance P) antagonists. Clinical trials conducted to date indicate that these agents have similar efficacy to 5-HT(3) antagonists in acute chemotherapy-induced nausea and vomiting, superior efficacy to available agents in delayed emesis, possibly superior efficacy against emesis in postoperative nausea and vomiting and no evidence of efficacy versus opioid or motion-induced nausea and vomiting. Other pharmacological strategies in development include agonising CB1 (cannabinoid) receptors, "broad spectrum" receptor antagonists and 5-HT(1A) receptor agonists, although clinical trials of these types of agents are not yet available. The neurokinin-1 antagonists appear to be promising agents for some nausea and vomiting states, although further clarification of their role is required.


During the last decade, research on the molecular biology and genetics of cannabinoid receptors has led to a remarkable progress in understanding of the endogenous cannabinoid system, which functions in a plethora of physiological processes in the animal. At present, two types of cannabinoid receptors have been cloned from many vertebrates, and three endogenous ligands (the endocannabinoids arachidonoyl ethanolamide, 2-arachidonoyl glycerol and 2-arachidonoyl-glycerol ether) have been characterized. Cannabinoid receptor type 1 (CB(1)) is expressed predominantly in the central and peripheral nervous system, while cannabinoid receptor type 2 (CB(2)) is present almost exclusively in immune cells. Cannabinoid receptors have not yet been cloned from invertebrates, but binding proteins for endocannabinoids, endocannabinoids and metabolic enzyme activity have been described in a variety of invertebrates except for molting invertebrates such as Caenorhabditis elegans and Drosophila. In the central nervous system of mammals, there is strong evidence emerging that the CB(1) and its ligands comprise a neuromodulatory system functionally interacting with other neurotransmitter systems. Furthermore, the presynaptic localization of CB(1) together with the results obtained from electrophysiological experiments strengthen the notion that in cerebellum and hippocampus and possibly in other regions of the central nervous system, endocannabinoids may act as retrograde messengers to suppress neurotransmitter release at the presynaptic site. Many recent studies using genetically modified mouse lines which lack CB(1) and/or CB(2) finally could show the importance of cannabinoid receptors in animal physiology and will contribute to unravel the full complexity of the cannabinoid system.


Anandamide (N-arachidonylethanolamine, AEA) is a major endocannabinoid, shown to impair mouse pregnancy and embryo development and to induce apoptosis in blastocysts. Here,
we review the roles of AEA, of the AEA-binding cannabinoid (CB) receptors, of the selective AEA membrane transporter (AMT), and of the AEA-hydrolyzing enzyme fatty acid amide hydrolase (FAAH), in human gestation. In particular, we discuss the interplay between the endocannabinoid system and the hormone-cytokine array involved in the control of human pregnancy, showing that the endocannabinoids take part in the immunological adaptation occurring during early pregnancy. In this line, we discuss the critical role of FAAH in human peripheral lymphocytes, showing that the expression of this enzyme is regulated by progesterone, Th1 and Th2 cytokines, which also regulate fertility. Moreover, we show that AEA and the other endocannabinoid, 2-arachidonoylglycerol, inhibit the release of the fertility-promoting cytokine leukemia inhibitory factor from human lymphocytes. Taken together, low FAAH and consistently high blood levels of AEA, but not CB receptors or AMT, can be early (<8 weeks of gestation) markers of spontaneous abortion, potentially useful as diagnostic tools for large-scale, routine monitoring of gestation in humans.


**BACKGROUND & AIMS:** The notion that specific receptors account for the ability of natural and synthetic cannabinoids to alter physiological functions, prompted this study aimed at assessing their functional presence in the human gut. **METHODS:** The effects have been studied of cannabinoids and selective antagonists of their receptors on chemically or electrically evoked contractions in preparations of human intestinal smooth muscle in vitro. **RESULTS:** Atropine prevented the contractions of longitudinal and circular muscle strips of ileum and colon induced by carbachol or electrical field stimulation; tetrodotoxin abolished only the latter which suggests they do involve activation of cholinergic neurons. The synthetic cannabinoid (+)-WIN 55,212-2 had no effect on carbachol contractions, but in a concentration-dependent fashion prevented those elicited by electrical field stimulation - which were insensitive to the putative endogenous cannabinoid anandamide - more potently in longitudinal than in circular strips. The selective CB1 receptor antagonist SR141716, which had no effect in the absence of (+)-WIN 55,212-2, competitively antagonised its inhibition of electrical field stimulation contractions, unlike the selective CB2 antagonist SR144528. **CONCLUSIONS:** Cannabinoid CB1 receptors are functionally present in the human ileum and colon; their pharmacological activation apparently results in inhibition of excitatory cholinergic pathways subserving smooth muscle contraction.


The effects of cannabinoid drugs on cAMP production were examined in mammalian brain. The cannabinoid receptor agonist (R)-(+-)[2,3-dihydro-5-methyl-3-[4-morpholiny lmethyl]pyrrolo[1,2,3-c,d]-1,4-benzoxazin-6-yl]-(1-naphthalenyl) methanone (WIN55,212-2) decreased forskolin-induced cAMP accumulation in a concentration-dependent manner (10(-8)-10(-5) M) in membranes from several rat and human brain regions, this effect being antagonized by 10(-5) M N-(piperidin-1-y l)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-p yrazole-3-carboxamide (SR141716A). Furthermore, high micromolar concentrations of SR141716A evoked a dose-dependent increase in basal cAMP in rat cerebellum and cortex, as well as in human frontal cortex. This effect was antagonized by WIN55,212-2 and abolished by N-ethylmaleimide, consistent with the involvement of cannabinoid CB(1) receptors through the activation of Gi/o proteins. These results suggest a ligand-independent activity for cannabinoid CB(1) receptor signaling cascade in mammalian brain.


(R)-(R)-3-(2-Hydroxymethylindanyl-4-oxy)phenyl-4,4,4-trifluoro-1-sulfonate (BAY 38-7271) is a new high-affinity cannabinoid receptor subtype 1 (CB1 receptor) ligand (K(i) = 0.46-1.85 nM; rat brain, human cortex, or recombinant human CB1 receptor), structurally unrelated to any
cannabinoid receptor ligand known so far. BAY 38-7271 was characterized as a CB1 receptor agonist in 5-[gamma(35)S]-thiophosphate triethylammonium salt binding assays using rat or human CB1 receptors. In the rat hypothermia assay, BAY 38-7271 induced a dose-dependent reduction in body temperature (minimal effective dose = 6 microg/kg, i.v.); whereas in rats trained to discriminate the CB1/CB2 receptor agonist (-)-cis-3-[2-hydroxy-4(1,1-dimethyl-heptyl)phenyl]-trans-4-(3-hydroxypropyl) cyclohexanol (CP 55,940; 0.03 mg/kg, i.p.) from vehicle, BAY 38-7271 induced complete generalization (3 microg/kg, i.v.). In both in vivo models, a specific CB1 receptor-mediated mechanism was confirmed by demonstrating that the effects of CP 55,940 and BAY 38-7271 were blocked by pretreatment with the selective CB1 receptor antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamidehydrochloride. In the rat traumatic brain injury model, BAY 38-7271 demonstrated highly potent and efficient neuroprotective properties when administered as a 4-h infusion immediately after induction of subdural hematoma (70% infarct volume reduction at 100 ng/kg/h). Even when applied with a 3-h delay, a significant neuroprotective efficacy could be observed (59% infarct volume reduction at 300 ng/kg/h). The neuroprotective potential of BAY 38-7271 was confirmed in a rat model of focal cerebral ischemia induced by permanent occlusion of the middle cerebral artery. It is concluded that the CB1/CB2 receptor agonist BAY 38-7271 shows pronounced neuroprotective properties that do not result from drug-induced hypothermia and that occur in a dose range devoid of typical cannabinoid-like side effects.


The discovery that the major psychoactive component of marijuana activated two G-protein coupled receptors prompted the search for the endogenous cannabinoid ligands now termed endocannabinoids. To date three putative ligands have been isolated, all consisting of arachidonic acid linked to a polar head group. Both synthetic and endogenous cannabinoids have been the focus of extensive study over the past few years. The signalling events produced by endocannabinoids as compared with Delta(9)-THC and synthetic cannabinoids contain many similarities. However, as research focuses more on endogenous ligands the divergence between these classes of compounds grows. This review focuses upon the developments in endocannabinoid signal transduction from receptor-mediated activation of common G-protein linked effector pathways through downstream regulation of gene transcription.


A short history of the discovery of the main plant cannabinoid, Delta(9)-tetrahydrocannabinol and of the endogenous cannabinoids anandamide, 2-arachidonoyl glycerol and 2-arachidonyl glyceryl ether (noladin ether) is presented. The role of the cannabinoids in neuroprotection, with emphasis on the endocannabinoids, is described. The unexpected production of aggression by Cannabis and cannabinoids under stressful conditions, published mainly in the past, is summarized.


A substantial amount of lysophosphatidic acid (LPA) (15.66 nmol/g tissue) was found to occur in the brain isolated from rats killed in liquid nitrogen. We found that a significant portion of brain LPA was accounted for by the arachidonic acid-containing species (5.4%). We obtained evidence that both 2-arachidonoyl species and 1-arachidonoyl species of LPA are present. The occurrence of 2-arachidonoyl LPA in the brain (0.53 nmol/g tissue) is a notable observation, because of its structural resemblance to 2-arachidonoyl-sn-glycerol (2-AG), an endogenous cannabinoid receptor ligand. We then examined the biological activity of 2-arachidonoyl LPA and compared it with that of 2-AG using neuroblastoma x glioma hybrid NG108-15 cells which express both the LPA receptor and cannabinoid CB1 receptor. We found that 2-arachidonoyl LPA interacts with the LPA receptor(s) to elicit the elevation of intracellular free Ca(2+) concentrations,
whereas 2-AG interacts exclusively with the cannabinoid CB1 receptor. Next, we examined the possible metabolic relationship between 2-arachidonoyl LPA and 2-AG and obtained clear evidence that rapid enzymatic conversion of 2-arachidonoyl LPA to 2-AG took place in the brain homogenate. It is noteworthy that two types of endogenous ligands, that interact with different types of receptors, are closely related metabolically and rapidly interconvert. (c) 2002 Elsevier Science (USA).


We studied, using RT-PCR, the relative expression of cannabinoid receptor (CBR) mRNA in peripheral blood mononuclear cells (PBMC) from different donor groups. Cells from normal donors expressed a CB2 mRNA level threefold higher than CB1 across all age, gender or ethnicity groups, and amplicons were of the same size in all donors. However, cells from marijuana users expressed higher levels of CBR mRNA, but with a preserved CB1/CB2 ratio of 1:3. CBR gene products were also studied following short-term mitogen activation in vitro. CB1 expression decreased following mitogen stimulation when compared to the time-matched medium only cells while the expression of CB2 mRNA remained unchanged. These studies suggest that marijuana smoking and immune activation can alter the basal levels of CB1 and CB2 in PBMCs.


The present review focuses on the role of the endogenous cannabinoid system in the modulation of immune response and control of cancer cell proliferation. The involvement of cannabinoid receptors, endogenous ligands and enzymes for their biosynthesis and degradation, as well as of cannabinoid receptor-independent events is discussed. The picture arising from the recent literature appears very complex, indicating that the effects elicited by the stimulation of the endocannabinoid system are strictly dependent on the specific compounds and cell types considered. Both the endocannabinoid anandamide and its congener palmitoylethanolamide, exert a negative action in the onset of a variety of parameters of the immune response. However, 2-arachidonoylglycerol appears to be the true endogenous ligand for peripheral cannabinoid receptors, although its action as an immunomodulatory molecule requires further characterization. Modulation of the endocannabinoid system interferes with cancer cell proliferation either by inhibiting mitogenic autocrine/paracrine loops or by directly inducing apoptosis; however, the proapoptotic effect of anandamide is not shared by other endocannabinoids and suggests the involvement of non-cannabinoid receptors, namely the VR1 class of vanilloid receptors. In conclusion, further investigations are needed to elucidate the function of endocannabinoids as immunosuppressant and antiproliferative/cytotoxic agents. The experimental evidence reviewed in this article argues in favor of the therapeutic potential of these compounds in immune disorders and cancer.


There are at least two types of cannabinoid receptors, CB(1) and CB(2), both coupled to G proteins. CB(1) receptors exist primarily on central and peripheral neurons, one of their functions being to modulate neurotransmitter release. CB(2) receptors are present mainly on immune cells. Their roles are proving more difficult to establish but seem to include the modulation of cytokine release. Endogenous agonists for cannabinoid receptors (endocannabinoids) have also been discovered, the most important being arachidonoyl ethanolamide (anandamide), 2-arachidonoyl glycerol and 2-arachidonyl glyceryl ether. Other endocannabinoids and cannabinoid receptor types may also exist. Although anandamide can act through CB(1) and CB(2) receptors, it is also a vanilloid receptor agonist and some of its metabolites may possess yet other important modes of action. The discovery of the system of cannabinoid receptors and endocannabinoids that constitutes the 'endocannabinoid system' has prompted the development of CB(1)- and CB(2)-selective agonists and antagonists/inverse agonists. CB(1)/CB(2) agonists are already used clinically, as anti-emetics or to stimulate appetite. Potential therapeutic uses of cannabinoid receptor agonists include the management of
multiple sclerosis/spinal cord injury, pain, inflammatory disorders, glaucoma, bronchial asthma, vasodilation that accompanies advanced cirrhosis, and cancer. Following their release onto cannabinoid receptors, endocannabinoids are removed from the extracellular space by membrane transport and then degraded by intracellular enzymic hydrolysis. Inhibitors of both these processes have been developed. Such inhibitors have therapeutic potential as animal data suggest that released endocannabinoids mediate reductions both in inflammatory pain and in the spasticity and tremor of multiple sclerosis. So too have CB(1) receptor antagonists, for example for the suppression of appetite and the management of cognitive dysfunction or schizophrenia.


Feeding induced in rats by cerebroventricular (i.c.v.) injection of orphanin FQ was potently and dose-dependently reversed by peripheral injection of either the opioid antagonist naloxone or the cannabinoid CB(1) receptor antagonist SR 141716\{N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-p yrazole-carboxamine}. The combination of these two agents inhibited food intake in a manner suggestive of additivity or supra-additivity.


The nucleus accumbens (NAc) represents a critical site for the rewarding properties of diverse classes of drugs of abuse. Glutamatergic afferents to the NAc are involved in the actions of psychostimulants and opioids, while the potentiation of dopaminergic neurotransmission in the NAc is a common feature of abused drugs, including cannabinoids. Cannabinoid receptors (CB1) are densely expressed in regions that provide excitatory innervation to the NAc, such as the amygdala, the cortex and the hippocampus. Recent in vitro evidence suggests that indeed cannabinoids modulate glutamatergic synapses in the NAc. In this study we recorded extracellularly from neurons in the shell of the NAc which responded to the stimulation of the baso-lateral amygdala (BLA) or the medial prefrontal cortex (PFC) in urethane anaesthetized rats. BLA or PFC stimulation induced generation of action potentials in NAc neurons. This excitatory effect was strongly inhibited by the synthetic cannabinoid agonists WIN 55212.2 (0.062-0.25 mg/kg, i.v.) and HU-210 (0.125-0.25 mg/kg, i.v.) or the psychoactive principle of Cannabis delta(9)-tetrahydrocannabinol (1.0 mg/kg, i.v.). Neither the D1 or D2 dopamine receptor antagonists (SCH23390 0.5-1.0 mg/kg, sulpiride 5-10 mg/kg, i.v.) or the opioid antagonist naloxone (1.0 mg/kg, i.v.) were able to reverse the action of cannabinoids, while the selective CB1 receptor antagonist/reverse agonist SR141716A (0.5 mg/kg, i.v.) fully suppressed the action of cannabinoid agonists, whereas per se had no significant effect. These results provide evidence that cannabinoids, in common with other drugs of abuse, in vivo strongly inhibit the excitability of neurons in the shell of the NAc.


The effects of cannabinoids on sympathetic neurotransmission in the rat isolated perfused mesenteric arterial bed, were investigated. Electrically evoked sympathetic neurogenic vasoconstriction was inhibited by the cannabinoid receptor agonists 11-hydroxy-dimethylheptyl-Delta(8)-tetrahydrocannabinol (HU210), (-)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]trans-4-(3-hydroxypropyl )-cyclohexanol (CP55,940) and methanandamide, and by (+)-11-hydroxy-Delta(8)-tetrahydrocannabinol (HU211), a (+)-stereoisomer of HU210. The inhibition was unaffected by cannabinoid CB(1) and CB(2) receptor antagonists. Electrically evoked release of endogenous noradrenaline from sympathetic nerves was inhibited by HU210, but not by HU211. Inhibition was blocked by a cannabinoid CB(1), but not a CB(2), receptor antagonist. HU210 attenuated contractions to noradrenaline, and all of the cannabinoids blocked contractions to KCl. Capsaicin pre-treatment had no significant effect on HU210- and CP55,940-mediated inhibition of sympathetic neurogenic contraction, but partly blocked inhibition mediated by methanandamide. These data show that cannabinoids can inhibit, by distinct pre- and postjunctional actions, sympathetic neurotransmission in the rat mesenteric arterial bed. The pre-junctional action is...
mediated by a cannabinoid CB(1)-like receptor, but the postjunctional action does not appear to involve either cannabinoid CB(1) or CB(2) receptors.


Anandamide (N-arachidonoylethanolamine) was the first ligand to be identified as an endogenous ligand of the G-protein coupled cannabinoid CB1 receptor. Subsequently, two other fatty acid ethanolamides, N-homo-gamma-linolenylethanolamine and N-7,10,13,16-docosatetraenylethanolamine were identified as endogenous cannabinoid ligands. A fatty acid ester, 2-arachidonoylglycerol (2-AG), and a fatty acid ether, 2-arachidonylglycerol ether also have been isolated and shown to be endogenous cannabinoid ligands. Recent studies have postulated the existence of carrier-mediated anandamide transport that is essential for termination of the biological effects of anandamide. A membrane bound amidohydrolase (fatty acid amide hydrolase, FAAH), located intracellularly, hydrolyzes and inactivates anandamide and other endogenous cannabinoids such as 2-AG. 2-AG has also been proposed to be an endogenous CB2 ligand. Structure-activity relationships (SARs) for endocannabinoid interaction with the CB receptors are currently emerging in the literature. This review considers cannabinoid receptor SAR developed to date for the endocannabinoids with emphasis upon the conformational implications for endocannabinoid recognition at the cannabinoid receptors.


Analgesia is an important physiological function of the endocannabinoid system and one of significant clinical relevance. This review discusses the analgesic effects of endocannabinoids at spinal and peripheral levels, firstly by describing the physiological framework for analgesia and secondly by reviewing the evidence for analgesic effects of endocannabinoids obtained using animal models of clinical pain conditions. In the spinal cord, CB(1) receptors have been demonstrated in laminae of the dorsal horn intimately concerned with the processing of nociceptive information and the modulation thereof. Similarly, CB(1) receptors have been demonstrated on the cell bodies of primary afferent neurones; however, the exact phenotype of cells which express this receptor requires further elucidation. Local administration, peptide release and electrophysiological studies support the concept of spinally mediated endocannabinoid-induced analgesia. Whilst a proportion of the peripheral analgesic effect of endocannabinoids can be attributed to a neuronal mechanism acting through CB(1) receptors expressed by primary afferent neurones, the antiinflammatory actions of endocannabinoids, mediated through CB(2) receptors, also appears to contribute to local analgesic effects. Possible mechanisms of this CB(2)-mediated effect include the attenuation of NGF-induced mast cell degranulation and of neutrophil accumulation, both of which are processes known to contribute to the generation of inflammatory hyperalgesia. The analgesic effects of cannabinoids have been demonstrated in models of somatic and visceral inflammatory pain and of neuropathic pain, the latter being an important area of therapeutic need. Analgesia is one of the principal therapeutic targets of cannabinoids. This review will discuss the analgesic effects of endocannabinoids in relation to two areas of therapeutic need, persistent inflammation and neuropathic pain. The more general aspects of the role of cannabinoids, endogenous and exogenous, in analgesia have been recently reviewed elsewhere (Rice, Curr Opin Invest Drugs 2001; 2: 399-414; Pertwee, Prog Neurobiol 2001; 63: 569-611; Rice, Mackie, In: Evers A. S, ed. Anesthetic Pharmacology: Physiologic Principles and Clinical Practice. St. Louis: Harcourt Health Sciences, 2002). Since a major goal in the development of cannabinoid-based analgesics is to divorce the antinociceptive effects from the psychotrophic effects, the discussion will focus on the antinociceptive effects produced at the spinal cord and/peripheral level as these areas are the most attractive targets in this regard. A mechanistic discussion of the 'framework' for analgesia will be followed by a description of studies examining the role of endocannabinoids in relieving pain; since the elucidation of these effects was undertaken using synthetic cannabinoids, reference will also be made to such studies, in the context of endocannabinoids.

Do endocannabinoids (eCBs) participate in long-term synaptic plasticity in the brain? Using pharmacological approaches and genetically altered mice, we show that stimulation of prelimbic cortex afferents at naturally occurring frequencies causes a long-term depression of nucleus accumbens glutamatergic synapses mediated by eCB release and presynaptic CB1 receptors. Translation of glutamate synaptic transmission into eCB retrograde signaling involved metabotropic glutamate receptors and postsynaptic intracellular Ca(2+) stores. These findings unveil the role of the eCB system in activity-dependent long-term synaptic plasticity and identify a mechanism by which marijuana can alter synaptic functions in the endogenous brain reward system.


What is the role of the cannabinoid system in invertebrates and can it tell us something about the human system? We discuss in this review the possible presence of the cannabinoid system in invertebrates. Endocannabinoid processes, i.e., enzymatic hydrolysis, as well as cannabinoid receptors and endocannabinoids, have been identified in various species of invertebrates. These signal molecules appear to have multiple roles in invertebrates; diminishing sensory input, control of reproduction, feeding behavior, neurotransmission and antiinflammatory actions. We propose that since this system worked so well, it was retained during evolution, and that invertebrates can serve as a model to study endogenous cannabinoid signaling.


Although it is now generally accepted that long-chain N-acylethanolamines and their precursors, N-acylethanolamine phospholipids, exist as trace constituents in virtually all vertebrate cells and tissues, their possible biological functions are just emerging. While anandamide (N-arachidonoylethanolamine) has received much attention due to its ability to bind to and activate cannabinoid receptors, the saturated and monounsaturated N-acylethanolamines, which usually represent the vast majority, are cannabinoid receptor-inactive but appear to interact with endocannabinoids and to have other signaling functions as well. Also, primary fatty acid amides, including the amide of oleic acid, which acts as a sleep-inducing agent, do not interact with cannabinoid receptors but are catabolically related to endocannabinoids. Here we review published information on the occurrence, metabolism, and possible signaling functions of the cannabinoid receptor-inactive N-acylethanolamines and primary fatty acid amides.


The present study investigated the effect of the cannabinoid CB(1) receptor antagonist, SR 141716 (N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazol e-carboxamide), on alcohol deprivation effect (i.e. the temporary increase in alcohol intake after a period of alcohol withdrawal) in Sardinian alcohol-preferring (sP) rats. As expected, alcohol-deprived rats virtually doubled voluntary alcohol intake during the first hour of re-access. Acute administration of SR 141716 (0, 0.3, 1 and 3 mg/kg, i.p.) completely abolished the alcohol deprivation effect. These results suggest that the cannabinoid CB(1) receptor is part of the neural substrate mediating the alcohol deprivation effect and that SR 141716 may possess anti-relapse properties.


Problem drug use and dependence are neurobehavioral disorders of complex origin. Although environmental factors contribute to drug abuse and addiction, genetic factors also play a significant role estimated at 40-60% of the total risk. Nonetheless, the precise identities of human genes that confer vulnerability to problem drug use remain mostly unknown. Here, we describe a
natural single nucleotide polymorphism in the human gene that encodes the principal endocannabinoid-inactivating enzyme, fatty acid amide hydrolase (FAAH), that in homozygous form is strongly associated with both street drug use and problem drug/alcohol use. This single nucleotide polymorphism results in a missense mutation (385C-->A) that converts a conserved proline residue to threonine (Pro129-->Thr), producing a FAAH variant that displays normal catalytic properties but an enhanced sensitivity to proteolytic degradation. Collectively, these results suggest that genetic mutations in FAAH may constitute important risk factors for problem drug use and support a potential link between functional abnormalities in the endogenous cannabinoid system and drug abuse and dependence.


N-arachidonoyl ethanolamine (anandamide) was the first endogenous cannabinoid receptor ligand to be discovered. Dual synthetic pathways for anandamide have been proposed. One is the formation from free arachidonic acid and ethanolamine, and the other is the formation from N-arachidonoyl phosphatidylethanolamine (PE) through the action of a phosphodiesterase. These pathways, however, do not appear to be able to generate a large amount of anandamide, at least under physiological conditions. The generation of anandamide from free arachidonic acid and ethanolamine is catalyzed by a degrading enzyme anandamide amidohydrolase/fatty acid amide hydrolase operating in reverse and requires large amounts of substrates. As for the second pathway, arachidonic acids esterified at the 1-position of glycerophospholipids, which are mostly esterified at the 2-position, are utilized for the formation of N-arachidonoyl PE, a stored precursor form of anandamide. In fact, the actual levels of anandamide in various tissues are generally low except in a few cases. 2-Arachidonoylglycerol (2-AG) was the second endogenous cannabinoid receptor ligand to be discovered. 2-AG is a degradation product of arachidonic acid-containing glycerophospholipids such as inositol phospholipids. Several investigators have demonstrated that 2-AG is produced in a variety of tissues and cells upon stimulation. 2-AG acts as a full agonist at the cannabinoid receptors (CB1 and CB2). Evidence is gradually accumulating and indicates that 2-AG is the most efficacious endogenous natural ligand for the cannabinoid receptors. In this review, we summarize the tissue levels, biosynthesis, degradation and possible physiological significance of two endogenous cannabimimetic molecules, anandamide and 2-AG.


The present study investigated the effect of the cannabinoid CB(1) receptor antagonist, SR 141716 (N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide), on the ability of low and high doses of morphine to, respectively, augment and suppress voluntary alcohol intake in selectively bred Sardinian alcohol-prefering rats. Acute administration of a low dose of morphine (1 mg/kg, s.c.) produced a specific and marked increase in alcohol intake, which correlated with an increase in blood alcohol levels and was prevented by either SR 141716 (0.3 mg/kg, i.p.) or naloxone (0.1 mg/kg, i.p.). A higher dose (10 mg/kg, s.c.) of morphine reduced both alcohol and food intakes and produced sedation and hypomotility. The suppressant effect of morphine on alcohol intake was blocked by naloxone (0.1 mg/kg, i.p.) but not by SR 141716 (0.3 mg/kg, i.p.). These results are in agreement with those showing the ability of SR 141716 to antagonize the appetitive and positive reinforcing properties of morphine and add further support to the hypothesis of the existence of a functional link between the action of opioids and of cannabinoids.


Five major approaches have been employed to determine the role of endocannabinoids in pain modulation: (1) studies of various markers of endocannabinoid action aimed at determining whether the necessary cannabinoid biochemical machinery is present in those brain areas that control pain sensitivity; (2) administration of exogenous cannabinoids to determine
whether endocannabinoid action at appropriate sites would lead to a loss of pain sensitivity; (3) administration of compounds that would affect endocannabinoid action such as antagonists and transport inhibitors to determine whether drug-induced preterbation of cannabinoid action would alter pain sensitivity; (4) studies of genetically altered animals aimed at determining whether pain responses or responses to cannabinergic drugs are altered; and (5) studies that measure the release of endocannabinoids. Converging evidence from each of these research areas indicates that endocannabinoids function to control pain in parallel with endogenous opioids but via different mechanisms.


The hypothalamus plays an important role in the regulation of several visceral processes, including food intake, thermoregulation and control of anterior pituitary secretion. Endogenous cannabinoids and CB(1) cannabinoid receptors have been found in the hypothalamus. In the present review, we would like to clarify the role of the endocannabinoid system in the regulation of the above-mentioned visceral functions. There is historical support for the role of marijuana (i.e. exogenous cannabinoids) in the regulation of appetite. Endocannabinoids also stimulate food intake. Furthermore, the specific CB(1) receptor antagonist SR141716 reduces food intake. Leptin treatment decreases endocannabinoid levels in normal rats and ob/ob mice. These findings provide evidence for the role of the hypothalamic endocannabinoid system in food intake and appetite regulation. Cannabinoids can change body temperature in a dose-dependent manner. High doses cause hypothermia while low doses cause hyperthermia. Cannabinoid administration decreases heat production. It seems that the effects of cannabinoids on thermoregulation is exerted by altering some neurochemical mediator effects at both the presynaptic and postsynaptic level. THC and endocannabinoids have mainly inhibitory effects on the regulation of reproduction. Administration of anandamide (AEA) decreases serum luteinizing hormone (LH) and prolactin (PRL) levels. AEA causes a prolongation of pregnancy in rats and temporarily inhibits the postnatal development of the hypothalamic-pituitary axis in offspring. The action of AEA on the reproductory parameters occurs at both the hypothalamic and pituitary level. CB(1) receptors have also been found in the anterior pituitary. Further, LH levels in CB(1) receptor-inactivated mice were decreased compared with wild-type mice. Taken together, all these observations suggest that the endocannabinoid system is playing an important part in the regulation of the mentioned visceral functions and it provides the bases for further applications of cannabinoid receptor agonists and/or antagonists in visceral diseases regulated by the hypothalamus.


Endogenous cannabinoid systems have been implicated in the physiological regulation of appetite by the ability of cannabinoid receptor agonists to induce hyperphagia. Both the exogenous cannabinoid Delta(9)-THC and the endocannabinoid arachidonoyl ethanolamide (anandamide) stimulate eating in rats. However, there has been no detailed analysis of the adjustments to feeding behaviour underlying this action. We used observational methods to determine the specific components of feeding affected by these compounds. Two groups (n=6) of presatiated, male, Lister hooded rats received either Delta(9)-THC (0, 0.5, 1.0 or 2.0 mg/kg) or anandamide (0, 1.0, 5.0 or 10.0 mg/kg sc), and their behaviour in an open field was recorded for 45 min. Behaviour (eating, drinking, rearing, grooming, sniffing, locomotion, resting/inactivity, sleeping) was continuously monitored to provide data on the latency, temporal distribution, duration and frequency of each category. Under control conditions, a minority of animals ate small quantities of lab chow, with feeding beginning only after a long latency. Both Delta(9)-THC and anandamide selectively stimulated feeding, with a marked reduction in latency. Apart from its rapid onset, cannabinoid-induced eating retained the normal, species-typical sequence, characteristic of untreated, free-feeding rats. Our data suggest that exogenously administered cannabinoids promote eating by increasing the incentive value of food and support a role for endocannabinoids in the regulation of the appetitive aspects of feeding motivation.

Although Delta(9)-tetrahydrocannabinol (THC) produces analgesia, its effects on nociceptive primary afferents are unknown. These neurons participate not only in pain signaling but also in the local response to tissue injury. Here, we show that THC and cannabinol induce a CB(1)/CB(2) cannabinoid receptor-independent release of calcitonin gene-related peptide from capsaicin-sensitive perivascular sensory nerves. Other psychotropic cannabinoids cannot mimic this action. The vanilloid receptor antagonist ruthenium red abolishes the responses to THC and cannabinol. However, the effect of THC on sensory nerves is intact in vanilloid receptor subtype 1 gene knock-out mice. The THC response depends on extracellular calcium but does not involve known voltage-operated calcium channels, glutamate receptors, or protein kinases A and C. These results may indicate the presence of a novel cannabinoid receptor/ion channel in the pain pathway.

CLINICAL SCIENCE


Cannabis, caffeine, and tobacco use are associated with increased mesolimbic dopamine activity. Ascorbic acid (AA) modulates some dopaminergic agent effects, and was recently found to decrease systolic blood pressure (SBP) stress reactivity. To examine how AA SBP stress reactivity protection varies by use of these substances, data from an AA trial (Cetebe, 3000 mg/day for 14 days; N=108) were compared by substance use level regarding SBP reactivity to the anticipation and actual experience phases of a standardized psychological stressor (10 min of public speaking and arithmetic). Self-reported never users of cannabis, persons not currently smoking tobacco, and persons consuming three or more caffeine beverages daily all exhibited AA SBP stress reactivity protection to the actual stressor, but not during the anticipation phase. Conversely, self-reported ever cannabis users, current tobacco smokers, and persons consuming less than three caffeine beverages daily exhibited the AA SBP protection during the anticipation phase, but only the lower caffeine consumption group exhibited AA protection during both phases. Covariates (neuroticism, extraversion, and depression scores, age, sex, body mass index) were all nonsignificant. Results are discussed in terms of dopaminergic effects of these substances, modulation of catecholaminergic and endothelial activity, and AA support of coping styles.


AIMS: Recent epidemiological findings indicate that non-drinkers as well as hazardous/harmful drinkers experience higher levels of distress than moderate drinkers. Little is known about the age at which this develops. This paper examines levels of affect, depression and anxiety over the full range of alcohol consumption in young adults. DESIGN: Cross-sectional findings from the first wave of a prospective, longitudinal study are presented. PARTICIPANTS: The general population sample comprised of 2404 young adults (aged 20-24 years). living in the Canberra region. Measures included: the Goldberg Depression and Anxiety scales, the Positive and Negative Affect Schedule, and the Alcohol Use Disorders Identification Test. FINDINGS: For men, both non/occasional and hazardous/harmful consumption were associated with lower levels of positive affect and higher levels of anxiety and depression. The higher levels of distress evident for male abstainers were related to being less extroverted and less healthy and not to past hazardous/harmful alcohol consumption, current tobacco or marijuana use. For women, only hazardous/harmful drinkers were found to have higher levels of depression and negative affect. Hazardous/harmful consumption was related to using marijuana, tobacco and recent stressful events in both men and women. CONCLUSIONS: Higher levels of distress are already evident in male non-drinkers in early adulthood. The findings counter theories that distress in non-drinkers is due to past hazardous/harmful alcohol consumption, marijuana or tobacco use, or characteristics in common with hazardous/harmful drinkers. Alcohol use disorders and mental health problems
are pertinent issues for young adults. However, more understanding is needed of the experiences of non-drinkers in an alcohol consuming culture.


The effects of cannabis/methaqualone/tobacco smoking on the epithelial cells of the tongue, buccal mucosa and floor of the mouth were examined. Oral mucosal smears for detection of cellular changes were taken from 4 sites in 16 patients. The tongue blade scraping technique was used. The sites sampled included the buccal mucosa (left and right sides), the posterior dorsum of the tongue and the anterior floor of the mouth. Tobacco smoking and non-smoking controls were also examined. The only significant difference between cannabis users and controls was the greater prevalence of bacterial cells in the smears taken from cannabis users. However, there were also greater numbers of degenerate and atypical squamous cells in cannabis smokers than in cigarette-smoking and non-smoking controls. Epithelial cells in smears taken from cannabis users and tobacco-smoking controls also showed koilocytic changes, which were not seen in smears taken from non-smoking controls. Koilocytosis is indicative of human papilloma virus infection, although no apparent lesions were seen in the patients from whom smears had been taken. It would appear that there is a greater tendency towards damaged and immature surface epithelial cells in cannabis smokers.


The "opening" of the post-totalitarian societies of Eastern Europe increased the illegal spread of psychoactive substances (PAS) in the past decade. We studied psychoactive substance acute poisoning (PAS AP) -- types of toxic agents involved, incidence rates, and their changes -- as indirect indicators of the characteristics, magnitude and development of the problem in Bulgaria during the 1990-2000 period of socioeconomic transition and crisis after collapse of communism. The study analyzed retrospectively the caseload of all 571 PAS acute poisonings that occurred in the territory: 417 men (73%) and 154 women (27%); mean age 24.07y (range 10-75). The number of all AP and PAS AP showed a marked increase during the last 3 years of the studied period, especially in 2000. The average PAS AP incidence rate for 1998-2000 (13.50/100,000) compared to the mean value for the preceding period 1990-1997 (5.76/100,000) showed a 2.34 fold increase. Acute alcohol intoxication was 62.7%, of all PAS AP; the opioid 15.2% (heroin 11.0%, other opioids 4.2%); prescribed and over the counter drugs 12.6%; inhalants 1.1%; cannabis 1.1%; and cocaine 0.7%. Amphetamine (or amphetamine-like), hallucinogens and phencyclidine (or phencyclidine-like) AP were not encountered. The average percentage of alcohol AP for 1998-2000 compared to the preceding 1990-1997 dropped from 78.12% to 44.72% (1.75 fold), while that of opioids rose from 6.59% to 26.47% (4.02 fold), and that of the other drugs group from 12.22% to 21.78% (1.78 fold increase). The new non-alcoholic PAS AP (heroin, cocaine, inhalants and cannabis AP, as indirect indicators of narcotic exposure) showed a rapid increase. The data showed they are expanding and catching up with alcohol as a new cause of substance-related problems, thus becoming one of the important health and social problems of post-totalitarian society.


To examine the cannabinoid hypothesis for pathogenesis of schizophrenia, we examined two kinds of polymorphisms of the CNR1 gene, which encodes human CB1 receptor, a subclass of central cannabinoid receptors, in schizophrenics and age-matched controls in the Japanese
population. Allelic and genotypic distributions of polymorphism 1359G/A at codon 453 in the
coding region and AAT triplet repeats in the 3' flanking region in the Japanese population were
quite different from those in Caucasians. Although the polymorphism 1359G/A was not
associated with schizophrenia, the triplet repeat polymorphism of the CNR1 gene was
significantly associated with schizophrenia, especially the hebephrenic subtype (P = 0.0028).
Hebephrenic schizophrenia showed significantly increased rate of the 9 repeat allele (P = 0.032,
OR = 2.30, 95% CI (1.91-2.69)), and decreased rate of the 17 repeat allele (P = 0.011, OR =
0.208, 95% CI (0.098-0.439)). The present findings indicated that certain alleles or genotypes of
the CNR1 gene may confer a susceptibility of schizophrenia, especially of the hebephrenic type.


RATIONALE: There has been controversy about whether the subjective, behavioral or
therapeutic effects of whole plant marijuana differ from the effects of its primary active ingredient,
Delta(9)-tetrahydrocannabinol (THC). However, few studies have directly compared the effects
of marijuana and THC using matched doses administered either by the smoked or the oral
form.OBJECTIVE: Two studies were conducted to compare the subjective effects of pure THC to
whole-plant marijuana containing an equivalent amount of THC in normal healthy volunteers. In
one study the drugs were administered orally and in the other they were administered by
smoking.METHODS: In each study, marijuana users (oral study: n=12, smoking study: n=13)
participated in a double-blind, crossover design with five experimental conditions: a low and a
high dose of THC-only, a low and a high dose of whole-plant marijuana, and placebo. In the oral
study, the drugs were administered in brownies, in the smoking study the drugs were smoked.
Dependent measures included the Addiction Research Center Inventory, the Profile of Mood
States, visual analog items, vital signs, and plasma levels of THC and 11-nor-9-carboxy-
THC.RESULTS: In both studies, the active drug conditions resulted in dose-dependent increases
in plasma THC levels, and the levels of THC were similar in THC-only and marijuana conditions
(except that at the higher oral dose THC-only produced slightly higher levels than marijuana). In
both the oral study and the smoking study, THC-only and whole plant marijuana produced similar
subjective effects, with only minor differences.CONCLUSION: These results support the idea that
the psychoactive effects of marijuana in healthy volunteers are due primarily to THC.

injuries: many are tried, few are helpful." Clin J Pain 18(3): 154-63.

OBJECTIVE: The objective was to investigate, in two community samples of people with
spinal cord injuries, the frequency of use of different pain treatments and the perceived
helpfulness of these treatments. DESIGN AND SETTING: A postal survey was conducted in the
community. PARTICIPANTS: The participants were 471 persons aged 18 years or older who had
spinal cord injuries and pain. There were 2 separate samples (n = 308 and n = 163). OUTCOME
MEASURES: The pain treatments used, the helpfulness of these treatments, and the Chronic
Pain Grade questionnaire answers were assessed. RESULTS: Respondents reported multiple
pain treatments (range of 0-14 and median of 4 in sample 1; range of 0-16 and median of 4 in
sample 2). The most commonly reported treatments were oral medications and physical therapy.
Medication types most commonly reported were nonsteroidal anti-inflammatory drugs (NSAIDs),
acetaminophen, and opioids. The treatments rated as most helpful were opioid medications,
physical therapy, and diazepam therapy, and those rated as least helpful were spinal cord
stimulation, counseling or psychotherapy, administration of acetaminophen, and administration of
amitriptyline. Alternative treatments reported as most helpful were massage therapy and use of
marijuana. Acupuncture was tried by many but was rated as only moderately helpful.
CONCLUSIONS: This survey of two large samples of community-dwelling individuals with spinal
cord injury-related chronic pain indicates that multiple pain treatments are tried but only a few are
rated as more than somewhat helpful. Furthermore, the treatments that are most commonly
reported are not always those that are rated as most helpful. The findings point to a number of
potentially fruitful directions for future research.
BEHAVIOURAL SCIENCE


This article examines the positive rate by drug for all urinalysis specimens tested by the U.S. Army from fiscal year 1991 (FY91) to FY00 and for the Army National Guard (NG) from FY97 to FY00. The average positive rate for the Army from FY91 to FY00 was 0.84%. In FY00, the Army rate reached a 10-year high of 1.04%. From FY97 to FY00, the NG positive rate declined from 3.4% to 2.16% but was significantly ($p < 0.05$) higher than the Army rate during the same period. Marijuana and cocaine are the most abused drugs for both the Army and NG. The positive rate for marijuana in the Army from FY91 to FY00 was 0.51%, and the cocaine rate was 0.19%. The NG marijuana-positive rate from FY97 to FY00 was 1.70%, and the cocaine rate was 0.51%. The positive rate for all other drugs of abuse tested was less than 0.3% for both the Army and NG during the same periods. The overall positive rate for the Army and NG are below those estimated (6.3%) in the civilian population.


There is recent international concern about specific exposures of children and adolescents to toxicants. In general, the situation within the European Union appears as follows. (i) OCCUPATIONAL EXPOSURE: Due to regulatory measures, there are almost no toxicologically significant occupational exposure situations of children to chemical toxicants. This contrasts to the situation in developing countries. There is also strict regulation of occupational exposure of adolescents (aged under 18). In consequence, the number of potentially exposed adolescents has been minimised. (ii) ENVIRONMENTAL EXPOSURE: Specific concern is directed towards exposures of infants, especially to neurotoxic heavy metals and carcinogens, and there is much regional differentiation of environmental exposures. (iii) FOOD: Recent research results are indicative of the general progress made in the field of food safety. (iv) INCIDENTAL ACUTE EXPOSURE: Besides drugs, household chemicals are a source of incidental acute intoxications in children. In Germany, there has been a particular focus on ingestion of lamp petroleum oils since 1989. (v) LIFESTYLE: Paramount problems are associated with increasing consumption of tobacco (mean age of starting smoking in Germany: 13.6 years), alcohol (percentage of addicts at ages 12-24 in Germany 6%) and cannabis among adolescents, calling for new ways of risk communication. In general, it will be necessary to consider children of different ages as separate risk groups.


An enforcement emphasis project, "Operation Truckier Check," was established in order to determine the extent to which commercial tractor-trailer drivers were operating their vehicles while impaired by drugs. A total of 1079 drivers and their vehicles were assessed for driver and equipment violations, and drivers additionally underwent preliminary field sobriety tests conducted by drug recognition expert (DRE) officers. Anonymous urine specimens for drug analysis were requested, and 822 urine specimens were obtained in total. Compliance with the drug-testing portion was voluntary, and there was a 19% refusal rate. Overall, 21% of the urine specimens tested positive for either illicit, prescription, and/or over-the-counter drugs, and 7% tested positive for more than one drug. Excluding caffeine and nicotine, the largest number of positive findings (9.5%) were for CNS stimulants, such as methamphetamine, amphetamine, phentermine, ephedrine/pseudoephedrine, and cocaine. The second most frequently encountered drug class were the cannabinoids, with 4.3% of drivers testing positive for marijuana metabolites. Only 11 drivers (1.3%) were positive for alcohol. Sixteen truck drivers (1.6%) were charged with driving under the influence of drugs after a full DRE evaluation was conducted. The results indicate that in spite of comprehensive drug testing in the trucking industry, some tractor-trailer drivers are
continuing to take illicit and other drugs with the potential of having a negative effect on their driving ability. On the other hand, only a few drivers were, in fact, deemed to be under the influence of drugs at the time of driving when evaluated by DRE officers.


An evaluation of the criminal responsibility of an offender who has consumed cannabis necessitates knowledge of the effect of the product on the offender’s mental state at the time of the alleged offense. However, the effects induced by cannabis are numerous and the forensic psychiatrist should base his diagnosis and his evaluation on facts which are as objective as possible. A selective literature review, using the computerized databases Medline, Psychlit and Embase, has been carried out to aid evaluation from a forensic psychiatry point of view. Biological means of cannabis detection, and the difficulties associated with using them to understand the clinical effect that the product has on any one user, are shown. Eight major categories which can be used in the domain of forensic psychiatry are detailed in this review: Acute usual effects, acute adverse effects, mood disturbance, acute toxic confusion, acute psychotic reaction, chronic paranoid psychosis, amotivational syndrome or other long term effects, and flashbacks. For each of these categories the effects of cannabis intoxication on cognitive and volitional capacities are analyzed, and guidelines for the evaluation of criminal responsibility are proposed.


This study evaluated the substance initiation effects of an intervention combining family and school-based competency-training intervention components. Thirty-six rural schools were randomly assigned to 1 of 3 conditions: (a) the classroom-based Life Skills Training (LST) and the Strengthening Families Program: For Parents and Children 10-14, (b) LST only, or (c) a control condition. Outcomes were examined 1 year after the intervention posttest, using a substance initiation index (SII) measuring lifetime use of alcohol, cigarettes, and marijuana and by rates of each individual substance. Planned intervention-control contrasts showed significant effects for both the combined and LST-only interventions on the SII and on marijuana initiation. Relative reduction rates for alcohol initiation were 30.0% for the combined intervention and 4.1% for LST only.


The September 11, 2001, terrorist attacks were the largest human-made disaster in the United States since the Civil War. Studies after earlier disasters have reported rates of psychological disorders in the acute postdisaster period. However, data on postdisaster increases in substance use are sparse. A random digit dial telephone survey was conducted to estimate the prevalence of increased cigarette smoking, alcohol consumption, and marijuana use among residents of Manhattan, New York City, 5-8 weeks after the attacks. Among 988 persons included, 28.8% reported an increase in use of any of these three substances, 9.7% reported an increase in smoking, 24.6% reported an increase in alcohol consumption, and 3.2% reported an increase in marijuana use. Persons who increased smoking of cigarettes and marijuana were more likely to experience posttraumatic stress disorder than were those who did not (24.2% vs. 5.6% posttraumatic stress disorder for cigarettes; 36.0% vs. 6.6% for marijuana). Depression was more common among those who increased than for those who did not increase cigarette smoking (22.1 vs. 8.2%), alcohol consumption (15.5 vs. 8.3%), and marijuana smoking (22.3 vs. 9.4%). The results of this study suggest a substantial increase in substance use in the acute postdisaster period after the September 11th attacks. Increase in use of different substances may be associated with the presence of different comorbid psychiatric conditions.

Wilson, N., V. Battistich, et al. (2002). "Does elementary school alcohol, tobacco, and marijuana
use increase middle school risk?" *J Adolesc Health* 30(6): 442-7.

**PURPOSE:** To assess whether alcohol, tobacco, and other drug (ATOD) use in elementary school may have serious implications for continued ATOD use in middle school and beyond.

**METHODS:** Longitudinal analyses were conducted on questionnaire data from 331 middle school students who had previously provided ATOD-use data during elementary school. Non-school personnel administered questionnaires in three participating school districts in three different states. The sample of students was ethnically and geographically diverse, including students from a range of low socioeconomic status backgrounds living in rural, urban or inner-city environments.

**RESULTS:** Middle school alcohol use was almost three times as likely to occur if alcohol use had occurred in elementary school (OR = 2.94, p < .001). Elementary school use of tobacco and marijuana also greatly increased the likelihood of middle school use (OR = 5.35, p < .001 and OR = 4.25, p < .05, respectively).

**CONCLUSIONS:** Early use of ATOD is associated with greatly increased odds of later use, which has important implications for the timing of drug prevention programs. Preventive interventions designed for use in pediatric practice settings should commence no later than elementary school, during the middle childhood years.

This newsletter is supported in part by unrestricted educational grants from GW Pharmaceuticals and ICN Pharmaceuticals (Canada).