INTRODUCTION

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BASIC SCIENCE


The aim of this study was to investigate whether prenatal exposure to the cannabinoid CB1 receptor agonist WIN 55,212-2 (WIN) at a daily dose devoid of overt signs of toxicity and/or gross malformations (0.5 mg/kg, gestation days 5-20), influences cortical glutamatergic neurotransmission, learning and emotional reactivity in rat offspring. Basal and K(+)–evoked extracellular glutamate levels were significantly lower in cortical cell cultures obtained from pups exposed to WIN during gestation with respect to those measured in cultures obtained from neonates born from vehicle-treated dams. The addition of NMDA to cortical cell cultures from neonates born from vehicle-treated dams concentration-dependently increased glutamate levels, and this was absent in cell cultures obtained from WIN-exposed pups. WIN-exposed rats also revealed a poorer performance in homing (10-12 days of age) and active avoidance tests (80 days of age) as well as a decrease in the rate of separation-induced ultrasonic emission (10 days of age). Finally, prenatal exposure to WIN induced a reduction in the number of cortical neuronal population. These findings (i) provide evidence for a deficit in cortical glutamatergic neurotransmission and behaviour in the rat neonate following prenatal exposure to WIN; and (ii) suggest that the reduction in cortical glutamatergic neurotransmission, NMDA receptor activity and alterations in neuronal development might underlie, at least in part, the learning deficit and decreased emotional reactivity observed in the offspring.


We have investigated the effect of 2-arachidonylethanolamide (Noladin) on food consumption, weight, activity, and cognitive function in mice during diet restriction for 17 days and subsequent ad libitum feeding for 32 days. Female Sabra mice were given food for 2.5h/day (equal to 60% diet restriction), received Noladin (0.001, 0.01, 0.1mg/(kg day) intraperitoneally (i.p.)) with or without the CB1 antagonist SR141716A (1mg/kg i.p.) during days 3-17. Noladin (0.001mg/kg) significantly increased food consumption without a change in body weight, probably due to increased activity and there was no change in cognitive function. A higher dose (0.1mg/kg) did not affect food consumption, but increased activity and slightly decreased weight 32 days after termination of Noladin administration; however, cognitive deterioration was observed. At all doses tested, Noladin did not affect weight during the diet-restriction period, whereas the CB1 antagonist (with or without Noladin) caused a very significant decline in weight in this phase. Weight catch-up was observed 1 month after administration of Noladin was discontinued. Weight at day 32 after the termination of Noladin (0.1mg/(kg day)) treatment was 5% less than control. Female C57BL/6 mice (same protocol, with 0.001mg/(kg day) Noladin) gave similar results to 0.1mg/kg in Sabra mice as regards weight. CB1 antagonist treatment caused very significant
decline in both weight and food consumption; cognition and activity were unchanged. These results indicate that Noladin has a significant dose-dependent effect on food consumption, cognition and weight maintenance after weight loss. Low doses of Noladin may possibly allow an increase in food intake without a gain in weight after dieting. Thus, Noladin could be of potential clinical benefit in treating disorders of body weight. Noladin seems to signal food consumption and weight through CB1 receptors based on effects observed with the CB1 antagonist, while the cognition and activity are probably mediated by non-cannabinoid receptors.


Recent evidence supports the notion that the endocannabinoid system may play a crucial role in neuroinflammation. We explored the changes that some elements of this system exhibit in a macaque model of encephalitis induced by simian immunodeficiency virus. Our results show that profound alterations in the distribution of specific components of the endocannabinoid system occur as a consequence of the viral infection of the brain. Specifically, expression of cannabinoid receptors of the CB2 subtype was induced in the brains of infected animals, mainly in perivascular macrophages, microglial nodules, and T-lymphocytes, most likely of the CD8 subtype. In addition, the endogenous cannabinoid-degrading enzyme fatty acid amide hydrolase was overexpressed in perivascular astrocytes as well as in astrocytic processes reaching cellular infiltrates. Finally, the pattern of CB1 receptor expression was not modified in the brains of infected animals compared with that in control animals. These results resemble previous data obtained in Alzheimer's disease human tissue samples and suggest that the endocannabinoid system may participate in the development of human immunodeficiency virus-induced encephalitis, because activation of CB2 receptors expressed by immune cells is likely to reduce their antiviral response and thus could favor the CNS entry of infected monocytes.


While cannabinoid receptors activate multiple signaling pathways in the brain, it remains unclear what influence the inhibition of adenylylcyclase has on the inhibition of glutamate release. In cerebrocortical nerve terminals, the cannabinoid receptor agonist WIN55,212-2 reduced KCl-evoked glutamate release through a mechanism that restricted the rise of cytoplasmic free Ca(2+), but not the changes in plasma membrane depolarization. These effects were consistent with the inhibition of Ca(2+) channels. Furthermore, WIN55,212-2 reduced 4-aminopyridine (4AP) evoked glutamate release to a larger extent by modulating the behavior of both Ca(2+) and K(+)channels. The inhibition of 4AP-evoked release was associated with a decrease in cytoplasmic free Ca(2+) and in plasma membrane depolarization that was reverted by the potassium channel blocker, tetraethylammonium. Interestingly, the reduction of KCl- and 4AP-evoked release by WIN55,212-2 was independent of adenylylcyclase activity and did not affect cAMP. Forskolin and the beta-adrenergic receptor increase intrasynaptosomal cAMP and promote a PKA-dependent tetrodotoxin (TTX)-sensitive increase in the spontaneous release of glutamate. These two responses were reduced by WIN55,212-2. However, the glutamate release induced by Sp-8-Br-cAMPS, which directly activated PKA without affecting cAMP, was also similarly reduced by WIN55,212-2. Hence, we conclude that the inhibition of glutamate release by WIN55,212-2 is unrelated to changes in cAMP and that the inhibition of release that a decrease in cAMP might produce is occluded by the activation of additional pathways such as the inhibition of Ca(2+) channels and/or the activation of K(+)channels that strongly depress glutamate release.


BACKGROUND AND AIMS: Anandamide is an endocannabinoid that evokes hypotension by interaction with peripheral cannabinoid CB1 receptors and with the perivascular transient receptor potential vanilloid type 1 protein (TRPV1). As anandamide has been implicated in the vasodilated state in advanced cirrhosis, the study investigated whether the mesenteric bed...
from cirrhotic rats has an altered and selective vasodilator response to anandamide. METHODS: We assessed vascular sensitivity to anandamide, mRNA and protein expression of cannabinoid CB1 receptor and TRPV1 receptor, and the topographical distribution of cannabinoid CB1 receptors in resistance mesenteric arteries of cirrhotic and control rats. RESULTS: Mesenteric vessels of cirrhotic animals displayed greater sensitivity to anandamide than control vessels. This vasodilator response was reverted by CB1 or TRPV1 receptor blockade, but not after endothelium denudation or nitric oxide inhibition. Anandamide had no effect on distal femoral arteries. CB1 and TRPV1 receptor protein was higher in cirrhotic than in control vessels. Neither CB1 mRNA nor protein was detected in femoral arteries. Immunohistochemistry showed that CB1 receptors were mainly in the adventitia and in the endothelial monolayer, with higher expression observed in vessels of cirrhotic rats than in controls. CONCLUSIONS: These results indicate that anandamide is a selective splanchnic vasodilator in cirrhosis which predominantly acts via interaction with two different types of receptors, CB1 and TRPV1 receptors, which are mainly located in perivascular sensory nerve terminals of the mesenteric resistance arteries of these animals.


A simple procedure based on a common silica gel column chromatography for the isolation of Delta(9)-tetrahydrocannabinolic acid A (Delta(9)-THCA-A) from hemp in a milligram scale is presented. Further, the decarboxylation reaction of Delta(9)-THCA-A to the toxicologically active Delta(9)-tetrahydrocannabinol (Delta(9)-THC) at different analytical and under-smoking conditions is investigated. Maximal conversion in an optimised analytical equipment yields about 70% Delta(9)-THC. In the simulation of the smoking process, only about 30% of the spiked substance could be recovered as Delta(9)-THC.


We have observed that systemic administration of cannabinoid CB(1) antagonists exerts antiparkinsonian effects in rats with very severe nigral lesion (>95% cell loss), but not in rats with a less severe lesion (85-95% cell loss). Local injections into denervated striatum and corresponding globus pallidus reduced parkinsonian asymmetry. Infusions into lesioned substantia nigra enhanced motor asymmetries, but this effect was absent after very severe striatum lesion. At the striatal level, CB(1) antagonists act enhancing dopamine D(1) receptor function and reducing D(2) receptor function. Striatal dopaminergic denervation did not affect cannabinoid CB(1) receptor coupling to G proteins. These results suggest that (i) systemic administration of CB(1) antagonists in rats with severe nigral degeneration is ineffective because striatopallidal-mediated motor effects are antagonized by nigra-mediated activity, and (ii) CB(1) antagonists exert antiparkinsonian effects after very severe nigral degeneration because nigra-mediated inhibition disappears. CB(1) receptor antagonists that lack psychoactive effects might be of therapeutic value in the control of very advanced stage of Parkinson's disease in humans.


The appetite-stimulating effects of the cannabis plant (Cannabis sativa) have been known since ancient times, and appear to be effected through the incentive and rewarding properties of foods. Investigations into the biological basis of the multiple effects of cannabis have yielded important breakthroughs in recent years: the discovery of two cannabinoid receptors in brain and peripheral organ systems, and endogenous ligands (endocannabinoids) for these receptors. These advances have greatly increased our understanding of how appetite is regulated through these endocannabinoid receptor systems. The presence of endocannabinoids in the developing brain and in maternal milk have led to evidence for a critical role for CB(1) receptors in oral motor control of suckling during neonatal development. The endocannabinoids appear to regulate energy balance and food intake at four functional levels within the brain and periphery: (i) limbic...
system (for hedonic evaluation of foods), (ii) hypothalamus and hindbrain (integrative functions), (iii) intestinal system, and (iv) adipose tissue. At each of these levels, the endocannabinoid system interacts with a number of better known molecules involved in appetite and weight regulation, including leptin, ghrelin, and the melanocortins. Therapeutically, appetite stimulation by cannabinoids has been studied for several decades, particularly in relation to cachexia and malnutrition associated with cancer, acquired immunodeficiency syndrome, or anorexia nervosa. The recent advances in cannabinoid pharmacology may lead to improved treatments for these conditions or, conversely, for combating excessive appetite and body weight, such as CB(1) receptor antagonists as antiobesity medications. In conclusion, the exciting progress in the understanding of how the endocannabinoid CB receptor systems influence appetite and body weight is stimulating the development of therapeutic orexigenic and anorectic agents. Furthermore, the role of cannabinoid CB(1) receptor activation for milk sucking in newborns may open new doors toward understanding nonorganic failure-to-thrive in infants, who display growth failure without known organic cause.


(-)-Cannabidiol (CBD) is a major, non-psychotropic constituent of cannabis. It has been shown to cause numerous physiological effects of therapeutic importance. We have reported that CBD derivatives in both enantiomeric series are of pharmaceutical interest. Here we describe the syntheses of the major CBD metabolites, (-)-7-hydroxy-CBD and (-)-CBD-7-oic acid and their dimethylheptyl (DMH) homologs, as well as of the corresponding compounds in the enantiomeric (+)-CBD series. The starting materials were the respective CBD enantiomers and their DMH homologs. The binding of these compounds to the CB(1) and CB(2) cannabinoid receptors are compared. Surprisingly, contrary to the compounds in the (-) series, which do not bind to the receptors, most of the derivatives in the (+) series bind to the CB(1) receptor in the low nanomole range. Some of these compounds also bind weakly to the CB(2) receptor.


The interaction of the cannabinoid CB(1) receptor with its endogenous ligands plays an essential role in extinction of aversive memories (Marsicano, G., Wotjak, C.T., Azad, S.C., Bisogno, T., Rammes, G., Cascio, M.G., Hermann, H., Tang, J., Hofmann, C., Zieglgansberger, W., Di, M., V, Lutz, B., 2002. The endogenous cannabinoid system controls extinction of aversive memories. Nature 418, 530-534). The present study tested the generality of this observation in respect to positively-reinforced memories. To this end, male cannabinoid CB(1) receptor deficient mice (CB(1)R(−/−)) and their wild-type littermate controls (CB(1)R(+/+)) were trained in an appetitively-motivated operant conditioning task, in which food-deprived animals received a food reward on nose-poking into an illuminated hole. During training, CB(1)R(−/−) turned out to be less motivated to participate in the task. After further restriction of daily food consumption, however, CB(1)R(−/−) reached the same level of performance as CB(1)R(+/+) as far as number of correct responses and errors of omission are concerned. The accuracy of performance served as a measure for the memory of the light-reward association and was stable at similarly high levels over a retention period of 9 days without additional training (97.6+-0.5% vs. 97.0+-0.9% correct responses). During subsequent extinction training, the positive reinforcement was omitted. As a consequence, both CB(1)R(−/−) and CB(1)R(+/+) showed a similar decline in accuracy of performance and total number of correct responses, accompanied by an increase in errors of omission. These data demonstrate that the cannabinoid CB(1) receptor is not essential for extinction of the stimulus-response association in an appetitively-motivated learning task.


BACKGROUND & AIMS: Hepatic myofibroblasts are central for the development of liver fibrosis associated with chronic liver diseases, and blocking their accumulation may prevent fibrogenesis. Cannabinoids are the active components of marijuana and act via 2 G-protein-coupled receptors, CB1 and CB2. Here, we investigated whether liver fibrogenic cells are a target
of cannabinoids. METHODS: CB2 receptors were characterized in biopsy specimens of normal human liver and active cirrhosis by immunohistochemistry, and in cultures of hepatic stellate cells and hepatic myofibroblasts by reverse-transcription polymerase chain reaction (RT-PCR), immunocytochemistry, and GTPgammaS assays. Functional studies were performed in cultured hepatic myofibroblasts and activated hepatic stellate cells. Carbon tetrachloride-induced liver fibrosis was studied in mice invalidated for CB2 receptors. RESULTS: In liver biopsy specimens from patients with active cirrhosis of various etiologies, CB2 receptors were expressed in nonparenchymal cells located within and at the edge of fibrous septa in smooth muscle alpha-actin-positive cells. In contrast, CB2 receptors were not detected in normal human liver. CB2 receptors were also detected in cultured hepatic myofibroblasts and in activated hepatic stellate cells. Their activation triggered potent antifibrogenic effects, namely, growth inhibition and apoptosis. Growth inhibition involved cyclooxygenase-2, and apoptosis resulted from oxidative stress. Finally, mice invalidated for CB2 receptors developed enhanced liver fibrosis following chronic carbon tetrachloride treatment as compared with wild-type mice. CONCLUSIONS: These data constitute the first demonstration that CB2 receptors are highly up-regulated in the cirrhotic liver, predominantly in hepatic fibrogenic cells. Moreover, this study also highlights the antifibrogenic role of CB2 receptors during chronic liver injury.


Introduction. The purpose of this study was to examine the effects of AM281, a cannabinoid receptor antagonist, on systemic haemodynamics, internal carotid artery blood flow and mortality during septic shock in rats. METHODS: The study included three sets of experiments: measurements of changes in systemic haemodynamics and left internal carotid artery flow (30 animals divided into three groups of 10); measurements of biochemical variables (n=30); assessment of mortality (n=30). Male Wistar rats (7 weeks old) were randomly divided into three groups: group 1, control; group 2, lipopolysaccharide (LPS) i.v., Escherichia coli endotoxin 10.0 mg kg(-1) i.v., bolus; group 3, LPS 10.0 mg kg(-1) i.v.+AM281 1 mg kg(-1) i.v. Systemic haemodynamics, carotid artery flow changes and biochemical variables were assessed at pretreatment and 1, 2 and 3 h after the treatment was performed. RESULTS: Administration of AM281 could prevent the haemodynamic changes induced by sepsis. Tumour necrosis factor-alpha and interleukin 1-beta increased in the LPS i.v. and LPS i.v.+AM281 groups at 1, 2 and 3 h after treatment; significant differences were observed in these levels in the two groups at these times. Internal carotid artery blood flow remained fairly constant in the control and LPS i.v.+AM281 groups compared with baseline values. In the LPS i.v. group, it decreased at 2 and 3 h after the treatment compared with baseline values [at 2 h: control 12.7 (SD 0.9) ml min(-1), LPS i.v. 8.7 (1.4) ml min(-1) (P<0.05), LPS i.v.+AM281 11.5 (0.9) ml min(-1); at 3 h: control 12.7 (0.4) ml min(-1), LPS i.v. 7.7 (1.3) ml min(-1) (P<0.05), LPS i.v.+AM281 11.6 (1.0) ml min(-1)]. Significant differences in mortality within 6 and 12 h were found between the LPS i.v. and LPS i.v.+AM281 groups [6 h mortality: LPS i.v. 5/10 (50%), LPS i.v.+AM281 2/10 (20%), P<0.05; 12 h mortality: LPS i.v. group 10/10 (100%), LPS i.v.+AM281 5/10 (50%), P<0.05]. CONCLUSIONS: Administration of AM281 prevented changes in systemic haemodynamic and internal carotid artery blood flow and could improve mortality in experimentally induced septic shock in rats. These findings may have significant therapeutic implications in the treatment of septic shock.


2-Arachidonoylglycerol is an endogenous ligand for the cannabinoid receptors (CB1 and CB2). Evidence is gradually accumulating which shows that 2-arachidonoylglycerol plays important physiological roles in several mammalian tissues and cells, yet the details remain ambiguous. In this study, we first examined the effects of 2-arachidonoylglycerol on the motility of human natural killer cells. We found that 2-arachidonoylglycerol induces the migration of KHYG-1 cells (a natural killer leukemia cell line) and human peripheral blood natural killer cells. The migration of natural killer cells induced by 2-arachidonoylglycerol was abolished by treating the cells with SR144528, a CB2 receptor antagonist, suggesting that the CB2 receptor is involved in
the 2-arachidonoylglycerol-induced migration. In contrast to 2-arachidonoylglycerol, anandamide, another endogenous cannabinoid receptor ligand, did not induce the migration. Delta(9)-Tetrahydrocannabinol, a major psychoactive constituent of marijuana, also failed to induce the migration; instead, the addition of Delta(9)-tetrahydrocannabinol together with 2-arachidonoylglycerol abolished the migration induced by 2-arachidonoylglycerol. It is conceivable that the endogenous ligand for the cannabinoid receptor, that is, 2-arachidonoylglycerol, affects natural killer cell functions such as migration, thereby contributing to the host-defense mechanism against infectious viruses and tumor cells.


In the current study, we tested the central hypothesis that exposure to Delta-9-tetrahydrocannabinol (Delta(9)-THC), the major psychoactive component in marijuana, can lead to enhanced growth of tumors that express low to undetectable levels of cannabinoid receptors by specifically suppressing the antitumor immune response. We demonstrated that the human breast cancer cell lines MCF-7 and MDA-MB-231 and the mouse mammary carcinoma 4T1 express low to undetectable levels of cannabinoid receptors, CB1 and CB2, and that these cells are resistant to Delta(9)-THC-induced cytotoxicity. Furthermore, exposure of mice to Delta(9)-THC led to significantly elevated 4T1 tumor growth and metastasis due to inhibition of the specific antitumor immune response in vivo. The suppression of the antitumor immune response was mediated primarily through CB2 as opposed to CB1. Furthermore, exposure to Delta(9)-THC led to increased production of IL-4 and IL-10, suggesting that Delta(9)-THC exposure may specifically suppress the cell-mediated Th1 response by enhancing Th2-associated cytokines. This possibility was further supported by microarray data demonstrating the up-regulation of a number of Th2-related genes and the down-regulation of a number of Th1-related genes following exposure to Delta(9)-THC. Finally, injection of anti-IL-4 and anti-IL-10 mAbs led to a partial reversal of the Delta(9)-THC-induced suppression of the immune response to 4T1. Such findings suggest that marijuana exposure either recreationally or medicinally may increase the susceptibility to and/or incidence of breast cancer as well as other cancers that do not express cannabinoid receptors and are resistant to Delta(9)-THC-induced apoptosis.


Fatty acid amide hydrolase (FAAH) is a mammalian integral membrane enzyme that degrades the fatty acid amide family of endogenous signaling lipids, which includes the endogenous cannabinoid anandamide and the sleep-inducing substance oleamide. FAAH belongs to a large and diverse class of enzymes referred to as the amidase signature (AS) family. Investigations into the structure and function of FAAH, in combination with complementary studies of other AS enzymes, have engendered provocative molecular models to explain how this enzyme integrates into cell membranes and terminates fatty acid amide signaling in vivo. These studies, as well as their biological and therapeutic implications, are the subject of this review. Expected online publication date for the Annual Review of Biochemistry Volume 74 is June 2, 2005. Please see http://www.annualreviews.org/catalog/pub_dates.asp for revised estimates.


RATIONALE: A growing body of evidence suggests that cannabinoid CB1 receptor antagonists have potential therapeutic utility as appetite suppressants. However, the specific mechanisms underlying the reduction in food intake produced by these drugs are not well understood. OBJECTIVE: Considering the known antiemetic and motor-suppressive effects of CB1 agonists, the present studies were conducted to determine if the reductions in food intake induced by the CB1 antagonist AM 251 could result from nausea or impairments in intake-related motor control, rather than solely from appetite suppression. METHODS: Three experiments were conducted to examine the effects of AM 251 (2.0, 4.0, or 8.0 mg/kg or vehicle) on detailed
parameters of food intake, on the development of conditioned taste avoidance, and on taste reactivity. RESULTS: In the first experiment, acute administration of AM 251 dose-dependently decreased food intake; nevertheless, feeding rate (grams consumed per time spent eating) and food handling were unaffected, which suggests that food intake was not reduced because of severe motor impairments. In the second experiment, AM 251 dose-dependently reduced intake of a flavor with which it had previously been associated, indicating that conditioned taste avoidance had developed. Lastly, AM 251 was found to induce conditioned rejection reactions in a dose-dependent manner. CONCLUSIONS: The CB1 antagonist AM 251 may reduce food intake in part by inducing nausea or malaise, but not because of incoordination or motor slowing related to feeding.


In order to understand how structurally distinct ligands regulate CB1 receptor interactions with Gi1, Gi2 and Gi3, we quantitated the Galphai and betagamma proteins that communoprecipitate with the CB1 receptor from a detergent extract of N18TG2 membranes in the presence of ligands. An equilibrium between A, R, GGDP and ARGGDP complexes was supported by aminoalkylindole WIN55212-2 for all three RGalphai complexes, cannabinoid desacetylleovantradol for Galphai1 and Galphai2, and eicosanoid (R)-methanandamide for Galphai3. Desacetylleovantradol maintained RGalphai3 complexes and (R)-methanandamide maintained RGalphai1 and RGalphai2 complexes even in the presence of a non-hydrolyzable GTP analog. The biaryl pyrazole SR141716 maintained all three RGalphai complexes, but supported some equilibrium mixtures in the presence of the GTP analog. Gbeta proteins, and to a certain extent Ggamma2, exhibited the same association/dissociation pattern as the Galphai proteins. A GDP analog had no influence on any of these equilibrium reactions, and failed to promote non-stoichiometric sequestration of G proteins. These results can be explained by invoking the existence of an inverse agonist-supported inactive state in the ternary complex equilibrium model. WIN55212-2 is an agonist at all three Gi subtypes, SR141716 is an inverse agonist at all three Gi subtypes, desacetylleovantradol is an agonist at Gi1 and Gi2, and an inverse agonist at Gi3, and (R)-methanandamide is an inverse agonist at Gi1 and Gi2, and an agonist at Gi3. These ligand-selective G protein responses imply that multiple conformations of the receptor could be evoked by ligands in order to regulate individual G proteins.


The presence of halogens within the classical cannabinoid structure leads to large variations in the compounds' potencies and affinities for the CB1 receptors. To explore the structure activity relationships within this class of analogs we have used a series of halogen-substituted (-)-Delta8-tetrahydrocannabinol analogs and compared their affinities for the CB1 cannabinoid receptor. Our results indicate that halogen substitution at the end-carbon of the side chain leads to an enhancement in affinity with the bulkier halogens (Br, I) producing the largest effects. Conversely, 2-iodo substitution on the phenolic ring leads to a 2-fold reduction in affinity while iodo-substitution in the C1'-position of the side chain lowers the compound's affinity for CB1 by more than 8-fold. The pharmacophoric requirements resulting from halogen-substitution are explored using computer modeling methods.


2-Arachidonoylglycerol is an endogenous ligand for the cannabinoid receptors. Two types of cannabinoid receptors have been identified to date. The CB1 receptor is abundantly expressed in the brain, and assumed to be involved in the attenuation of neurotransmission. On the other hand, the physiological roles of the CB2 receptor, mainly expressed in several types of inflammatory cells and immunocompetent cells, have not yet been fully elucidated. In this study, we investigated possible pathophysiological roles of the CB2 receptor and 2-arachidonoylglycerol in acute inflammation in mouse ear induced by the topical application of 12-O-
We found that the amount of 2-arachidonoylglycerol was markedly augmented in inflamed mouse ear. In contrast, the amount of anandamide, another endogenous cannabinoid receptor ligand, did not change markedly. Importantly, 12-O-tetradecanoylphorbol-13-acetate-induced ear swelling was blocked by treatment with SR144528, a CB2 receptor antagonist, suggesting that the CB2 receptor is involved in the swelling. On the other hand, the application of AM251, a CB1 receptor antagonist, exerted only a weak suppressive effect. The application of SR144528 also reduced the 12-O-tetradecanoylphorbol-13-acetate-induced production of leukotriene B4 and the infiltration of neutrophils in the mouse ear. Interestingly, the application of 2-arachidonoylglycerol to the mouse ear evoked swelling, which was abolished by treatment with SR144528. Nitric oxide was suggested to be involved in the ear swelling induced by 2-arachidonoylglycerol. These results suggest that the CB2 receptor and 2-arachidonoylglycerol play crucial stimulative roles during the course of inflammatory reactions.


Cannabinoids have been reported to have analgesic properties in animals of acute nociception or of inflammatory and neuropathic pain models, but the mechanisms by which they exert such alleviative effects are not yet fully understood. We investigated whether the CB(1)-cannabinoid-receptor agonist HU210 modulates the capsaicin-induced (45)Ca(2+) influx and substance P-like immunoreactivity (SPLI) release in cultured rat dorsal root ganglion (DRG) cells. HU210 attenuated the capsaicin-induced (45)Ca(2+) influx and this effect was reversed by the CB(1) antagonist AM251. Treatment of DRG cells with 100 nM bradykinin for 3 h potentiated capsaicin-induced SPLI release accompanied with the induction of cyclooxygenase-2 mRNA expression. The potentiation of SPLI release by bradykinin was reversed by HU210 or the protein kinase A (PKA) inhibitor H-89. HU210 also reduced forskolin-induced cyclic AMP production and forskolin-induced potentiation of SPLI release. These results suggest that CB(1) could inhibit either the capsaicin-induced Ca(2+) influx or the potentiation of capsaicin-induced SPLI release by a long-term treatment with bradykinin through involvement of a cyclic-AMP-dependent PKA pathway. In conclusion, CB(1)-receptor stimulation modulates the activities of transient receptor potential vanilloid receptor 1 in cultured rat DRG cells.


We reported earlier that closed head injury (CHI) in mice causes a sharp elevation of brain 2-arachidonoylglycerol (2-AG) levels, and that exogenous 2-AG reduces brain edema, infarct volume and hippocampal death and improved clinical recovery after CHI. The beneficial effect of 2-AG was attenuated by SR141716A, a CB(1) cannabinoid receptor antagonist, albeit at relatively high doses. In the present study, we further explored the role of CB(1) receptors in mediating 2-AG neuroprotection. CB(1) receptor knockout mice (CB(1)(−/−)) showed minor spontaneous recovery at 24 h after CHI, in contrast to the significant improvement in neurobehavioral function seen in wild-type (WT) mice. Moreover, administration of 2-AG did not improve neurological performance and edema formation in the CB(1)(−/−) mice. In addition, 2-AG abolished the three- to four-fold increase of nuclear factor kappab (NF-kappab) transactivation, at 24 h after CHI in the WT mice, while it had no effect on NF-kappab in the CB(1)(−/−) mice, which was as high as in the WT vehicle-treated mice. We thus propose that 2-AG exerts its neuroprotection after CHI, at least in part, via CB(1) receptor-mediated mechanisms that involve inhibition of intracellular inflammatory signaling pathways. Journal of Cerebral Blood Flow & Metabolism advance online publication, 23 February 2005; doi:10.1038/sj.jcbfm.9600047.


Abstract The role of endocannabinoid (eCB) signalling in restraint stress-induced neuronal activation was studied. Male mice exposed to 30 min of restraint exhibit increased Fos protein within prefrontal cortex (PFC), lateral septum (LS), nucleus accumbens (Acb) and medial amygdala. SR141716 (2 mg/kg) itself had no effect on Fos but pretreatment with SR141716...
significantly potentiated restraint-induced Fos expression in cingulate, LS and Acb. SR141716 also significantly increased the time spent in active escape behaviours during the restraint. In restraint-habituated mice (mice exposed to four previous restraint episodes), the fifth restraint exposure resulted in decreased expression of active escape behaviours compared to the first exposure and only induced Fos protein in the central and medial amygdala. Administration of SR141716 prior to the fifth restraint episode resulted in greater potentiation of restraint-induced Fos induction than the first; significant increases occurred within all regions of PFC examined, LS and Acb. Brain regional eCB content was measured immediately after restraint. N-arachidonylethanolamine content within the amygdala was significantly decreased after both restraint episodes. 2-Arachidonylglycerol content was significantly increased in both the limbic forebrain and amygdala after the fifth restraint but not the first. Restraint had no effect on cerebellar eCB content. These data suggest that eCB activation of CB(1) receptors opposes the behavioural and neuronal responses to aversive stimuli. Because repeated homotypic stress increased both limbic 2-AG and resulted in a greater effect of SR141716 on limbic Fos expression, we hypothesize that increased CB(1) receptor activity contributes to the expression of habituation to homotypic stress.


Alzheimer's disease (AD) is characterized by enhanced beta-amyloid peptide (betaA) deposition along with glial activation in senile plaques, selective neuronal loss, and cognitive deficits. Cannabinoids are neuroprotective agents against excitotoxicity in vitro and acute brain damage in vivo. This background prompted us to study the localization, expression, and function of cannabinoid receptors in AD and the possible protective role of cannabinoids after betaA treatment, both in vivo and in vitro. Here, we show that senile plaques in AD patients express cannabinoid receptors CB1 and CB2, together with markers of microglial activation, and that CB1-positive neurons, present in high numbers in control cases, are greatly reduced in areas of microglial activation. In pharmacological experiments, we found that G-protein coupling and CB1 receptor protein expression are markedly decreased in AD brains. Additionally, in AD brains, protein nitration is increased, and, more specifically, CB1 and CB2 proteins show enhanced nitration. Intracerebroventricular administration of the synthetic cannabinoid WIN55,212-2 to rats prevent betaA-induced microglial activation, cognitive impairment, and loss of neuronal markers. Cannabinoids (HU-210, WIN55,212-2, and JWH-133) block betaA-induced activation of cultured microglial cells, as judged by mitochondrial activity, cell morphology, and tumor necrosis factor-alpha release; these effects are independent of the antioxidant action of cannabinoid compounds and are also exerted by a CB2-selective agonist. Moreover, cannabinoids abrogate microglia-mediated neurotoxicity after betaA addition to rat cortical cocultures. Our results indicate that cannabinoid receptors are important in the pathology of AD and that cannabinoids succeed in preventing the neurodegenerative process occurring in the disease.


The anorectic effect of AM 251 (N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide), a CB1 receptor antagonist, was studied in rats. AM 251 (0.5-2.0 mg/kg i.p.) significantly and dose-dependently reduced food intake in both free-feeding and food-deprived rats. The obtained results support the anorectic activity of CB1 receptors antagonists.


Cannabinoids, the active components of Cannabis sativa Linnaeus (marijuana) and their derivatives have received renewed interest in recent years due to their diverse pharmacologic activities such as cell growth inhibition, anti-inflammatory effects and tumor regression. Here we show that expression levels of both cannabinoid receptors, CB1 and CB2, are significantly higher in CA-human papillomavirus-10 (virally transformed cells derived from adenocarcinoma of human
prostate tissue), and other human prostate cells LNCaP, DU145, PC3, and CWR22Rnu1 than in human prostate epithelial and PZ-HPV-7 (virally transformed cells derived from normal human prostate tissue) cells. WIN-55,212-2 (mixed CB1/CB2 agonist) treatment with androgen-responsive LNCaP cells resulted in a dose- (1-10 micromol/L) and time-dependent (24-48 hours) inhibition of cell growth, blocking of CB1 and CB2 receptors by their antagonists SR141716 (CB1) and SR144528 (CB2) significantly prevented this effect. Extending this observation, we found that WIN-55,212-2 treatment with LNCaP resulted in a dose- (1-10 micromol/L) and time-dependent (24-72 hours) induction of apoptosis (a), decrease in protein and mRNA expression of androgen receptor (b), decrease in intracellular protein and mRNA expression of prostate-specific antigen (c), decrease in secreted prostate-specific antigen levels (d), and decrease in protein expression of proliferation cell nuclear antigen and vascular endothelial growth factor (e). Our results suggest that WIN-55,212-2 or other non-habit-forming cannabinoid receptor agonists could be developed as novel therapeutic agents for the treatment of prostate cancer.


Acute rewarding properties are essential for the establishment of cocaine addiction, and multiple neurochemical processes participate in this complex behavior. In the present study, we used the self-administration paradigm to evaluate the role of CB1 cannabinoid receptors in several aspects of cocaine reward, including acquisition, maintenance, and motivation to seek the drug. For this purpose, both CB1 receptor knockout mice and wild-type littermates were trained to intravenously self-administer cocaine under different schedules. Several cocaine training doses (0.32, 1, and 3.2 mg/kg/infusion) were used in the acquisition studies. Only 25% of CB1 knockout mice vs 75% of their wild-type littermates acquired a reliable operant responding to self-administer the most effective dose of cocaine (1 mg/kg/infusion), and the number of sessions required to attain this behavior was increased in knockout mice. Animals reaching the acquisition criteria were evaluated for the motivational strength of cocaine as a reinforcer under a progressive ratio schedule. The maximal effort to obtain a cocaine infusion was significantly reduced after the genetic ablation of CB1 receptors. A similar result was obtained after the pharmacological blockade of CB1 receptors with SR141716A in wild-type mice. Moreover, the cocaine dose-response curve was flatted in the knockout group, suggesting that the differences observed between genotypes were related to changes in the reinforcing efficacy of the training dose of cocaine. Self-administration for water and food was not altered in CB1 knockout mice in any of the reinforcement schedules used, which emphasizes the selective impairment of drug reinforcement in these knockout mice. Finally, cocaine effects on mesolimbic dopaminergic transmission were evaluated by in vivo microdialysis in these mice. Acute cocaine administration induced a similar enhancement in the extracellular levels of dopamine in the nucleus accumbens of both CB1 knockout and wild-type mice. This work clearly demonstrates that CB1 receptors play an important role in the consolidation of cocaine reinforcement, although are not required for its acute effects on mesolimbic dopaminergic transmission.

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Relatively few studies have compared the effects of tetrahydrocannabinols and anandamide-like cannabinoids following repeated dosing. Whereas pronounced tolerance develops to many of the in vivo pharmacological effects of Delta(9)-tetrahydrocannabinol with repeated dosing, tolerance to anandamide-induced effects is typically less noted. In the present study, we examined cross-tolerance between Delta(9)-tetrahydrocannabinol and anandamide-like compounds (anandamide, 2-methylanandamide, and O-1812) in a tetrad of in vivo tests sensitive to cannabinoid action, including spontaneous activity, tail flick, rectal temperature, and a ring immobility test of catalepsy. Six intraperitoneal injections of Delta(9)-tetrahydrocannabinol 10 mg/kg over a period of 4 days resulted in the development of pronounced tolerance to all of its in vivo effects. In contrast, task specificity was observed in cross-tolerance to anandamide and its analogs: antinociception (all three compounds), suppression of spontaneous activity (2-
methylanandamide and O-1812), catalepsy (O-1812), and hypothermia (none of the compounds). Furthermore, when it occurred, the magnitude of cross-tolerance was notably smaller. These results suggest that anandamide-like cannabinoids may have a unique pharmacology that only partially overlaps with that of Delta(9)-tetrahydrocannabinol and other traditional cannabinoids. Although the basis for this unique pharmacology has not as yet been determined, it is possible that regional specificity of cannabinoid CB(1) receptor downregulation and endocannabinoid release induced by repeated dosing with Delta(9)-tetrahydrocannabinol may play a role.

**CLINICAL SCIENCE**


**OBJECTIVE:** To review the pharmacology, pharmacokinetics, clinical efficacy, and safety of rimonabant, a new selective cannabinoid receptor antagonist. **DATA SOURCES:** Primary literature and review articles were obtained via a MEDLINE search (1966-November 2004) using the key terms obesity, smoking cessation, cannabinoid, rimonabant, SR 141716, and SR 141716a. Additional studies and abstracts were identified from the bibliographies of reviewed literature. **STUDY SELECTION AND DATA EXTRACTION:** Studies and review articles related to rimonabant and the endocannabinoid system were reviewed. Data pertinent to this article were included. **DATA SYNTHESIS:** Rimonabant is a selective cannabinoid receptor antagonist. Recent data have demonstrated beneficial effects of rimonabant in obesity, smoking cessation, and metabolic syndrome. Animal studies using rimonabant have shown a positive role for reducing hunger, caloric intake, and body weight and in increasing satiety. In humans, rimonabant appears to be effective for treatment of obesity and smoking cessation. Ongoing studies will examine the effect of rimonabant on obesity, metabolic syndrome, smoking cessation, and alcohol abuse. To date, the incidence of adverse effects with rimonabant has been slightly greater than placebo, with the most common being nausea. **CONCLUSIONS:** Rimonabant appears to be a promising drug in an entirely new class called selective cannabinoid CB1 receptor antagonists. The drug may be approved for treatment of obesity and smoking cessation in 2005. Additional studies are ongoing that may provide information on other clinical uses for this medication.


**QUESTION:** One of my breastfeeding patients is using marijuana to combat chronic pain. Is it safe for her to breastfeed? **ANSWER:** Lactating mothers should refrain from consuming cannabinoids. Advising mothers to discontinue breastfeeding if they cannot stop using cannabinoids must incorporate the known risks of formula feeding. Cannabinoid exposure through milk has not been shown to increase neonatal risk, but there are no appropriate studies of this. In every case, nursing babies should be closely monitored.


**ABSTRACT** Aim: To examine possible causal linkages between cannabis use and psychosis using data gathered over the course of a 25-year longitudinal study. Design A 25-year longitudinal study of the health, development and adjustment of a birth cohort of 1265 New Zealand children (635 males, 630 females). Setting: The Christchurch Health and Development Study, a general community sample. Participants A total of 1055 participants from the Christchurch Health and Development Study (CHDS) cohort for whom data on cannabis use and psychotic symptoms were available on at least one occasion from 18, 21 and 25 years. Measurements As part of this study, data were gathered on frequency of cannabis use and psychotic symptoms at ages 18, 21 and 25 years. Findings: Regression models adjusting for
observed and non-observed confounding suggested that daily users of cannabis had rates of psychotic symptoms that were between 1.6 and 1.8 times higher (P < 0.001) than non-users of cannabis. Structural equation modelling suggested that these associations reflected the effects of cannabis use on symptom levels rather than the effects of symptom levels on cannabis use. Conclusions: The results of the present study add to a growing body of evidence suggesting that regular cannabis use may increase risks of psychosis. The present study suggests that: (a) the association between cannabis use and psychotic symptoms is unlikely to be due to confounding factors; and (b) the direction of causality is from cannabis use to psychotic symptoms.


In determining the effects of regular marijuana use on neurocognition, abilities within specific relevant cognitive domains prior to regular drug use have not been available. The present study examined effects of current and past regular use of marijuana in subjects for whom pre-drug performance had been ascertained in a prospective, longitudinal fashion. A total of 113 young adults, assessed since infancy, were evaluated using neurocognitive tests for which commensurate measures were obtained prior to the initiation of marijuana smoking. Marijuana users, determined by urinalysis and self-report, were categorized as light (<5 joints per week) and heavy (>5 joints per week) current users and former users, the latter having used the drug regularly in the past (>1 joint per week) but not for at least 3 months. A third of the subjects were using marijuana on a regular basis at the time of assessment with half being heavy users. Among former, regular users, approximately half had been smoking 5 or more joints per week. Overall IQ, memory, processing speed, vocabulary, attention, and abstract reasoning were assessed. After accounting for potentially confounding factors and pre-drug performance in the appropriate cognitive domain, current regular heavy users did significantly worse than non-users in overall IQ, processing speed, immediate, and delayed memory. In contrast, the former marijuana smokers did not show any cognitive impairments. It was concluded that residual marijuana effects are evident beyond the acute intoxication period in current heavy users after taking into account pre-drug performance but similar deficits are no longer apparent 3 months after cessation of regular use, even among former heavy using young adults.


Three young people developed psychosis during/ after cannabis intake. The 17-year-old male after only a few marijuana cigarettes, the 22-year-old patient after two years of addiction developed schizoid psychosis; the 20-year-old patient after six years of cannabis addiction had schizoaffective psychosis. The first two patients become symptom-free on the antipsychotics and during the drug-free period. The third patient, who had cannabis during the psychotic symptoms, still has the schizoid psychosis. CONCLUSIONS: The connection between cannabis and psychosis is clear in our three patients. Marihuana is working on the dopamin system and may cause schizoid psychosis, sometimes permanent psychosis. Cannabis, this light drug might not a "safe" agent.


The authors investigated the indications for cannabis prescription in the Netherlands and assessed its efficacy and side effects. A majority (64.1%) of patients reported a good or excellent effect on their symptoms. Of these patients, approximately 44% used cannabis for >/=5 months. Indications were neurologic disorders, pain, musculoskeletal disorders, and cancer anorexia/cachexia. Inhaled cannabis was perceived as more effective than oral administration. Reported side effects were generally mild.


Psychoses are relatively low prevalence disorders that have a disproportionately negative impact on individuals and society. Cannabis use is one factor that can exacerbate the negative...
consequences associated with psychotic disorders. Relatively few studies have examined the effects or reasons for using cannabis self-reported by individuals with psychosis. The present study is the first known to compare directly such factors in individuals with and without psychosis, within a single study. At baseline and follow-up participants with psychosis most commonly reported using cannabis for positive mood alteration (36% and 42%), coping with negative affect (27% and 29%) and for social activity reasons (38% and 29%). The control group most commonly reported using cannabis for relaxation (34% and 43%) and social activity reasons (49% and 51%). Participants with psychosis were less likely to report relaxation as the most important effect after use (27%) or expect it at follow-up (49%) compared to the control group (53% and 70%). In both groups, addiction and positive affect enhancement were the composite variable scores correlated most consistently with concurrent amount and frequency of use.


Neuropsychological investigations of substance abusers have reported impairments on tasks mediated by the frontal executive system, including functions associated with behavioral inhibition and decision making. The higher order or executive components which are involved in decision making include selective attention and short term storage of information, inhibition of response to irrelevant information, initiation of response to relevant information, self-monitoring of performance, and changing internal and external contingencies in order to "stay the course" towards the ultimate goal. Given the hypothesized role of frontal systems in decision making and the previous evidence that executive dysfunctions and structural brain changes exist in subjects who use illicit drugs, we applied fMRI and diffusion tensor imaging (DTI) techniques in a pilot investigation of heavy cannabis smokers and matched control subjects while performing a modification of the classic Stroop task. Marijuana smokers demonstrated significantly lower anterior cingulate activity in focal areas of the anterior cingulate cortex and higher midcingulate activity relative to controls, although both groups were able to perform the task within normal limits. Normal controls also demonstrated increased activity within the right dorsolateral prefrontal cortex (DLPFC) during the interference condition, while marijuana smokers demonstrated a more diffuse, bilateral pattern of DLPFC activation. Similarly, although both groups performed the task well, marijuana smokers made more errors of commission than controls during the interference condition, which were associated with different brain regions than control subjects. These findings suggest that marijuana smokers exhibit different patterns of BOLD response and error response during the Stroop interference condition compared to normal controls despite similar task performance. Furthermore, DTI measures in frontal regions, which include the genu and splenium of the corpus callosum and bilateral anterior cingulate white matter regions, showed no between group differences in fractional anisotropy (FA), a measure of directional coherence within white matter fiber tracts, but a notable increase in trace, a measure of overall isotropic diffusivity in marijuana smokers compared to controls. Overall, results from the present study indicate significant differences in the magnitude and pattern of signal intensity change within the anterior cingulate and the DLPFC during the Stroop interference subtest in chronic marijuana smokers compared to normal controls. Furthermore, although chronic marijuana smokers were able to perform the task reasonably well, the functional activation findings suggest they utilize different cortical processes from the control subjects in order to do so. Findings from this study are consistent with the notion that substance abusers demonstrate evidence of altered frontal neural function during the performance of tasks that involve inhibition and performance monitoring, which may affect the ability to make decisions.


This paper evaluates three hypotheses about the relationship between cannabis use and psychosis in the light of recent evidence from prospective epidemiological studies. These are that: (1) cannabis use causes a psychotic disorder that would not have occurred in the absence of cannabis use; (2) that cannabis use may precipitate schizophrenia or exacerbate its symptoms; and (3) that cannabis use may exacerbate the symptoms of psychosis. There is limited support for the first hypothesis. As a consequence of recent prospective studies, there is now stronger
support for the second hypothesis. Four recent prospective studies in three countries have found relationships between the frequency with which cannabis had been used and the risk of receiving a diagnosis of schizophrenia or of reporting psychotic symptoms. These relationships are stronger in people with a history of psychotic symptoms and they have persisted after adjustment for potentially confounding variables. The absence of any change in the incidence of schizophrenia during the three decades in which cannabis use in Australia has increased makes it unlikely that cannabis use can produce psychoses that would not have occurred in its absence. It seems more likely that cannabis use can precipitate schizophrenia in vulnerable individuals. There is also reasonable evidence for the third hypothesis that cannabis use exacerbates psychosis.


Smoking is one of the few risk factors that have been identified for functional ovarian cysts, and results of one epidemiologic study suggest that body mass index (BMI; weight (kg)/height (m)(2)) may modify the effect of this exposure. The current study assessed the association of cigarette smoking and marijuana use with functional ovarian cyst risk by using data from a population-based 1990-1995 case-control study of 586 incident functional ovarian cyst cases and 757 age-matched controls in a large health maintenance organization in Washington State. In multivariate analyses controlling for age, education, and reference year, the authors found an increase in risk associated with current cigarette smoking among women whose BMI was <20 (odds ratio (OR) = 2.48, 95% confidence interval (CI): 1.32, 4.64) or 20-25 (OR = 1.60, 95% CI: 1.04, 2.45) but not >25 (OR = 0.85, 95% CI: 0.53, 1.37). Corresponding risks associated with current marijuana use were BMI <20, OR = 2.05 (95% CI: 0.89, 4.75); BMI 20-25, OR = 1.78 (95% CI: 1.00, 3.17); and BMI >25, OR = 0.72 (95% CI: 0.36, 1.42). Study results indicate that increased BMI may attenuate the adverse effect of smoking on the risk of functional ovarian cyst.


Marijuana (Cannabis sativa) is the most commonly used illicit drug by pregnant women, but information is limited about the effects of prenatal cannabis exposure on fetal development. The present study evaluated the influence of early maternal marijuana use on fetal growth. Women electing voluntary saline-induced abortions were recruited at a mid-gestational stage of pregnancy (weeks 17-22), and detailed drug use and medical histories were obtained. Toxicological assays (maternal urine and fetal meconium) were used in conjunction with the maternal report to assign groups. Subjects with documented cocaine and opiate use were excluded. Main developmental outcome variables were fetal weight, foot length, body length, and head circumference; ponderal index was also examined. Analyses were adjusted for maternal alcohol and cigarette use. Marijuana (n=44)- and non-marijuana (n=95)-exposed fetuses had similar rates of growth with increased age. However, there was a 0.08-cm (95% CI -0.15 to -0.01) and 14.53-g (95% CI -28.21 to 0.86) significant reduction of foot length and body weight, respectively, for marijuana-exposed fetuses. Moreover, fetal foot length development was negatively correlated with the amount and frequency of marijuana use reported by the mothers. These findings provide evidence of a negative impact of prenatal marijuana exposure on the mid-gestational fetal growth even when adjusting for maternal use of other substances well known to impair fetal development.


It has long been known that acute marijuana administration impairs working memory (e.g., the discrimination of stimuli separated by a delay). The determination of which of the individual components of memory are altered by marijuana is an unresolved problem. Previous human studies did not use test protocols that allowed for the determination of delay-independent
(initial discrimination) from delay-dependent (forgetting or retrieval) components of memory. Using methods developed in the experimental analysis of behavior and signal detection theory, we tested the acute effects of smoked marijuana on forgetting functions in 5 humans. Immediately after smoking placebo, a low dose, or a high dose of marijuana (varying in delta9-THC content), subjects completed delayed match-to-sample testing that included a range of retention intervals within each test session (0.5, 4, 12, and 24 s). Performances (discriminability) at each dose were plotted as forgetting functions, as described and developed by White and colleagues (White, 1985; White & Ruske, 2002). For all 5 subjects, both delta9-THC doses impaired delay-dependent discrimination but not delay-independent discrimination. The outcome is consistent with current nonhuman studies examining the role of the cannabinoid system on delayed matching procedures, and the data help illuminate one behavioral mechanism through which marijuana alters memory performance.


The present study investigated whether maternal cigarette smoking and marijuana use during pregnancy were associated with an increased risk of initiation and daily/regular use of such substances among one hundred fifty-two 16- to 21-year-old adolescent offspring. The participants were from a low risk, predominately middle-class sample participating in an ongoing, longitudinal study. Findings indicated that offspring whose mothers reported smoking cigarettes during their pregnancy were more than twice as likely to have initiated cigarette smoking during adolescence than offspring of mothers who reported no smoking while pregnant. Offspring of mothers who reported using marijuana during pregnancy were at increased risk for both subsequent initiation of cigarette smoking (OR=2.58) and marijuana use (OR=2.76), as well as daily cigarette smoking (OR=2.36), as compared to offspring of whose mothers did not report using marijuana while pregnant. There was also evidence indicating that dose-response relationships existed between prenatal exposure to marijuana and offspring's use of cigarettes and marijuana. These associations were found to be more pronounced for males than females, and remained after consideration of potential confounds. Such results suggest that maternal cigarette smoking and marijuana use during pregnancy are risk factors for later smoking and marijuana use among adolescent offspring, and add to the weight of evidence that can be used in support of programs aimed at drug use prevention and cessation among women during pregnancy.


During the last few years, the debate over the use of marijuana for medical purposes has moved from the legislative arena into the public forum. Thirty six states and the District of Columbia have had statutes that address the medical utility of marijuana within the past 26 years. However, several of those states have either repealed the laws or allowed them to sunset. Since 1996, 11 states have enacted laws that allow individuals to use marijuana with a doctor's consent.


The third in a series reviewing the HIV/AIDS antiretroviral drugs, this report summarizes the interactions between antiretrovirals and common drugs of abuse. In an overview format for primary care physicians and psychiatrists, the metabolism and drug interactions in the context of antiretroviral therapy are presented for the following drugs of abuse: alcohol, benzodiazepines,
cocaine, GHB (liquid X), ketamine (special K), LSD (acid), MDMA (Ecstasy), opiates, PCP (angel dust), and THC (marijuana).


BEHAVIOURAL SCIENCE


Objectives: The study presents data about age of onset of alcohol, cigarette and cannabis use and investigates the association between age of onset and later drug use patterns. Methods: Using a sample from a cross-sectional multi-site study, personal interviews were conducted with 3,503 individuals aged 12-49 years. Last-month prevalence, age of onset and associations with subsequent use patterns were investigated. Results: Having started with cannabis before the age of 16 years was associated with an odds ratio of 1.6 for heavy cannabis use. For males, the odds ratio of heavy cannabis use was 1.7, when cannabis was already initiated by the age of 16. Heavy use of ecstasy, amphetamines, hallucinogens and cocaine is associated with use of cigarettes before 13 (OR = 1.9). For males, the odds ratio was 2.2 and for women 1.9. Conclusions: Early use of alcohol, according to this data, does not seem to be related to subsequent heavy drug use. Early onset cannabis users show increasing probabilities of heavy use patterns. Preventive intervention programs have to start earlier than school-based programs normally do and specific developmental pathways need to be addressed. Copyright (c) 2005 S. Karger AG, Basel.


A recent rise in cannabis use in Indigenous communities in northern Australia may have compounded existing patterns of other substance use. This paper describes these patterns in Arnhem Land in the "Top End" of the Northern Territory (NT). Economic impacts of the cannabis trade are also described. In a descriptive cross-sectional study, random samples included 336 people (169 males, 167 females) aged 13 - 36 years. Consensus classification of lifetime and current use of cannabis, alcohol, tobacco, kava, inhalants (petrol) and other drugs was derived based on health workers' proxy assessments. A sample (n = 180, aged 13 - 36) was recruited opportunistically for interview. Lifetime cannabis users among those interviewed (n = 131, 81 males, 50 females) described their current cannabis use, usual quantities purchased and consumed, frequency and duration of cannabis use and other substance use. In the random samples, 69% (63 - 75%) of males and 26% (20 - 31%) of females were lifetime cannabis users (OR = 7.4, 4.5 - 12.1, p < 0.001). The proportion of males currently using cannabis was 67% (60 - 73%) while the proportion of females currently using cannabis was 22% (16 - 27%) (OR = 7.9, 4.8 - 13.1, p < 0.001). Current cannabis users were more likely than non-users to be also using alcohol (OR = 10.4, 4.7 - 23.3, p < 0.001), tobacco (OR = 19.0, 7.9 - 45.8, p < 0.001) and to have sniffed petrol (OR = 9.1, 4.6 - 18.0, p < 0.001) but were less likely to be using kava (OR = 0.4, 0.2 - 0.9, p < 0.001). Among those interviewed, higher tobacco consumption in current users and greater alcohol use in lifetime users was associated with increased cannabis use. Action is required to reduce cannabis use, especially in combination with other substances.


ABSTRACT Aims To assess whether cannabis use, recently taken up by many indigenous Australians in remote communities, has reinforced tobacco use. Design Cross-sectional study. Setting Three eastern Arnhem Land communities (Northern Territory, NT); total population = 3384, in 2001. Participants From 1247 people aged 17-36 years, 190 (120 males, 70 females) were opportunistically recruited. Measurements Self-reported life-time and current
tobacco, cannabis and other substance use were confirmed by local health workers and using clinic records. Participants reported level of substance use, frequency and duration (years used). Associations with tobacco use were calculated (odds ratios: OR) using logistic regression with age, sex, alcohol use and a history of petrol sniffing as confounders. Findings In univariate analyses current tobacco users were more likely than non-users to be using cannabis (OR = 3.1, 1.5-6.2, P = 0.002) and this association remained in multivariate analyses (OR = 3.0, 1.4-6.8, P = 0.006). Tobacco use was associated with the number of years of cannabis use (P = 0.035). The likelihood that tobacco users were also cannabis users increased as quantity of cannabis used increased (P = 0.008). Current tobacco use was no more likely in those who initiated cannabis from 1998 onwards than in those who initiated cannabis before 1998 (OR = 1.1, 0.4-3.2, P = 0.881). One-third of life-time users of both tobacco and cannabis initiated their use at or near the same time, and very few of these (12%) had discontinued either cannabis or tobacco. Conclusions Cannabis appears to have influenced the continued use of tobacco in these populations with possible additional burdens for cardiovascular and respiratory diseases and challenges for interventions.


Because alcohol or other drug use following adolescent substance abuse treatment is common, understanding mediators of posttreatment outcome could help improve treatment interventions. The authors conducted path analyses based on data from 552 adolescents (aged 12-18; 82% male) with cannabis abuse or dependence who participated in outpatient treatment. The analysis used the Family Conflict and Cohesion subscales, from the Family Environment Scale, and several scales and indices from the Global Appraisal of Individual Needs. Family conflict, family cohesion, and social support indirectly predicted substance use and substance-related problems as mediated by recovery environment and social risk. This model replicated across 4 follow-up waves (3, 6, 9, and 12 months postintake). These results support the idea of targeting environmental factors during continuing care as a way to improve treatment outcomes for adolescents with cannabis disorders.


Several studies have showed that driving under the influence of alcohol and/or certain illicit or medicinal drugs increases the risk of a (severe) crash. Data with respect to the question whether this also leads to a more severe accident are sparse. This study examines the relationship between the use of alcohol, illicit drugs and/or medicinal drugs and the severity of an accident within a group of drivers that were involved in a crash in The Netherlands. Blood samples of 993 drivers, collected in the period from October 1998 through September 1999, were linked to accident characteristics as available from the National Transport Research Centre. The outcome measure was the severity of the accident. An accident was considered severe when the accident had resulted in hospital admission or death. All the blood samples obtained after the accident were screened for the presence of alcohol, illicit drugs (opiates, amphetamines and amphetamine-like substances, cocaine and metabolites, methadone, cannabinoids) and medicinal drugs (benzodiazepines, barbiturates and tricyclic antidepressants). The strength of the associations between exposure to the different classes of alcohol/drugs/medicines and the severity of the accident was evaluated using logistic regression analysis and were expressed as odds ratios (OR), adjusted for age, gender, time of the day, day of the week and urban area. The most frequently detected drugs were cannabinoids, benzodiazepines and cocaine. Our results showed no clear association between the use of alcohol, illicit drug and/or medicinal drug use and the severity of the accident. Given the process of obtaining blood samples from drivers involved in accidents and the retrospective nature of the study, we cannot rule out the occurrence of selection bias. Therefore, our findings need further confirmation.

BACKGROUND: Marijuana use during adolescence has various adverse psychological and health outcomes. It is poorly understood whether the same risk factors influence different stages in the development of marijuana involvement. OBJECTIVE: To establish which risk factors best explain different stages of marijuana involvement. DESIGN: Data were collected at 2 points using computer-assisted personal interview (wave 1 and wave 2 were separated by 1 year). Twenty-one well-established risk factors of adolescent substance use/abuse were used to predict 5 stages of marijuana involvement: (1) initiation of experimental use, (2) initiation of regular use, (3) progression to regular use, (4) failure to discontinue experimental use, and (5) failure to discontinue regular use. Data were analyzed using logistic regression analysis. PARTICIPANTS: Middle school and high school students (N = 13,718, aged 11-21 years) participating in the National Longitudinal Study of Adolescent Health (Add Health). RESULTS: Three risk factors (own and peer involvement with substances, delinquency, and school problems) were the strongest predictors of all stages. Their combined presence greatly increased risk of initiation of experimental (odds ratio, 20) and regular (odds ratio, 87) marijuana use over the next year. Personality, family, religious, and pastime factors exerted stage-specific, sex-specific, and age-specific influences. CONCLUSIONS: Assessment of substance, school, and delinquency factors is important in identifying individuals at high risk for continued involvement with marijuana. Prevention and/or intervention efforts should focus on these areas of risk.


BACKGROUND: We examined the association between the use of inhalants, marijuana, and other drugs and recent DSM-IV substance use disorders among adolescents aged 12-17 years. METHODS: Data were drawn from 2000 to 2001 National Household Surveys on Drug Abuse. Adolescents aged 12-17 years who reported having ever used an illicit drug in their lifetime were categorized into four mutually exclusive groups: inhalant users (16%), marijuana users (53%), inhalant and marijuana users (16%), and other drug users (15%). Logistic regression models were used to estimate associations with recent substance use diagnoses among lifetime adolescent drug users (N=10,180). RESULTS: We found that 31% of lifetime drug users reported having never used marijuana. One half of these atypical drug users were predominantly nonmedical users of pain relievers. Adolescents who used inhalants or other drugs but not marijuana were least likely to report multidrug use. Adolescents who reported using both inhalants and marijuana were most likely to use three or more classes of drugs (73%) and to receive a diagnosis of past year alcohol (35%) and drug (39%) abuse or dependence. CONCLUSIONS: Our study findings suggest that among lifetime adolescent drug users, those who use both inhalants and marijuana are at very high risk for alcohol and drug use disorders.