INTRODUCTION

Interested persons are referred to the abstracts of the 2002 International Cannabinoid Research Society meeting held in Monterey, California for a review of current research in this field. The abstracts can be obtained from www.cannabinoidsociety.org.

BASIC SCIENCE


Activation of cannabinoid CB(1) receptors inhibits gastrointestinal motility, propulsion, and transit, whereas selective antagonism of these receptors has the opposite effects, suggesting the presence of endocannabinoid tone. Supporting evidence for presynaptic CB(1) receptors on myenteric neurons has been found in vitro. In this study, selective CB(1) receptor antibodies and neuronal markers were used to identify and characterise myenteric neurons expressing cannabinoid receptors. Whole mounts of rat and guinea pig myenteric preparations were dually labelled with antibodies against the CB(1) receptor and choline acetyltransferase, neurofilament proteins, calbindin, calretinin, synapsin I, microtubule-associated protein-2, calcitonin gene-related peptide, or substance P. The pattern of CB(1) receptor labelling and the neurochemical classification of CB(1) receptor-positive cells were markedly influenced by the species and fixation procedure. Virtually all choline acetyltransferase-immunoreactive myenteric neurons expressed CB(1) receptors in ganglia from both species. Subpopulations of neurons identified with calbindin, calretinin, and microtubule-associated protein-2 did not express CB(1) receptors. A few calcitonin gene-related peptide- and substance P-positive somata coexpressed CB(1) receptor immunoreactivity but showed little colocalisation on individual fibres. There was a close association between CB(1) receptor immunoreactivity and fibres labelled for synaptic protein, suggesting a role in the modulation of transmitter release. Functional responses to cannabinoids in the presence of hexamethonium suggest further that CB(1) receptors occur on excitatory motoneurons. In conclusion, CB(1) receptors are expressed on a variety of cholinergic sensory, interneuronal, and motor neurons in myenteric ganglia. J. Comp. Neurol. 448:410-422, 2002.


Marijuana smoking is recognised to impair human cognition and learning, but the mechanisms by which this occurs are not well characterised. This article focuses exclusively on the hippocampus to review the effects of cannabinoids on hippocampal function and evaluate the evidence that hippocampal cannabinoid receptors play a role in learning and formation of memory. Activation of cannabinoid receptors inhibits release of a variety of neurotransmitters, and modulates a number of intrinsic membrane conductances. Suppression of inhibitory GABAergic synaptic transmission has been repeatedly described, but whether there is also control of excitatory glutamatergic transmission is more controversial. The recognition that the commonly used WIN55,212-2 also acts via non-cannabinoid receptors may help resolve this issue. The involvement of endocannabinoids in depolarisation induced suppression of inhibition (DSI) and the demonstration that activation of metabotropic glutamate receptors can stimulate endocannabinoid release have provided the first insights into the physiological roles of the cannabinoids. Cannabinoids have consistently been reported to inhibit high frequency stimulation...
induced synaptic long-term potentiation but the experimental design of most behavioural experiments have meant it is not possible to categorically demonstrate a role for hippocampal cannabinoid receptors in learning and memory.


Communicated by James L. McGaugh, University of California, Irvine, CA, June 4, 2002 (received for review February 22, 2002) The endogenous cannabinoids (endocannabinoids) are lipid molecules that may mediate retrograde signaling at central synapses and other forms of short-range neuronal communication. The monoglyceride 2-arachidonoylglycerol (2-AG) meets several criteria of an endocannabinoid substance: (i) it activates cannabinoid receptors; (ii) it is produced by neurons in an activity-dependent manner; and (iii) it is rapidly eliminated. 2-AG inactivation is only partially understood, but it may occur by transport into cells and enzymatic hydrolysis. Here we tested the hypothesis that monoglyceride lipase (MGL), a serine hydrolase that converts monoglycerides to fatty acid and glycerol, participates in 2-AG inactivation. We cloned MGL by homology from a rat brain cDNA library. Its cDNA sequence encoded for a 303-aa protein with a calculated molecular weight of 33,367 daltons. Northern blot and in situ hybridization analyses revealed that MGL mRNA is heterogeneously expressed in the rat brain, with highest levels in regions where CB(1) cannabinoid receptors are also present (hippocampus, cortex, anterior thalamus, and cerebellum). Immunohistochemical studies in the hippocampus showed that MGL distribution has striking laminar specificity, suggesting a presynaptic localization of the enzyme. Adenovirus-mediated transfer of MGL cDNA into rat cortical neurons increased MGL expression and attenuated N-methyl-D-aspartate/carbachol-induced 2-AG accumulation in these cells. No such effect was observed on the accumulation of anandamide, another endocannabinoid lipid. The results suggest that hydrolysis by means of MGL is a primary mechanism for 2-AG inactivation in intact neurons.


NF-kappaB is a transcriptional regulator that plays a key role in immunity, inflammation and programmed cell death. We generated a PC12 cell line termed PC12kappaBluc that contains an integrated NF-kappaB-responsive reporter gene to directly measure NF-kappaB activity. The "classical" activators of NF-kappaB, phorbol 12-O-tetradecanoate-13-acetate and tumor necrosis factor alpha, strongly induced NF-kappaB activity in PC12kappaBluc cells. Activation of NF-kappaB could be attenuated by preincubating the cells with the cAMP analogue dbcAMP or via expression of the superrepressor IkappaBalphaS32A/S36A. PC12kappaBluc cells were subjected to several apoptotic paradigms, including treatment with 6-hydroxydopamine, H(2)O(2), K(2)Cr(2)O(7), MnCl(2), C(2)-ceramide or the cannabinoid receptor-1 agonist CP55,940. A simultaneous measurement of the NF-kappaB activity revealed that only administration of 6-hydroxydopamine or CP55,940 increased NF-kappaB activity. Using pharmacological and genetic strategies to attenuate NF-kappaB transcriptional activity, we demonstrate that the elevation of NF-kappaB activity by 6-hydroxydopamine and CP55,940 is not an integral part of the apoptotic signaling cascade in PC12 cells.


Recent reports have demonstrated that Delta(9)-tetrahydrocannabinol (Delta(9)-THC) stimulates locomotor activity at low doses (<2.5 mg/kg), while higher doses (>2.5 mg/kg) produce decreases in spontaneous activity. Using quantitative 2-[(14)C]deoxyglucose (2-DG) autoradiography, we systematically studied the effects of acute Delta(9)-THC on rates of local cerebral glucose utilization. The first series of experiments was designed to determine if Delta(9)-THC-mediated changes in cerebral metabolism followed a clear dose-response relationship. Adult male Sprague-Dawley rats were treated with either vehicle or Delta(9)-THC (0.25-2.5 mg/kg) and the 2-DG procedure was initiated 15 min following exposure. Administration of 2.5
mg/kg Delta(9)-THC produced significant decreases in cerebral metabolism in most brain regions studied. In contrast, administration of 0.25 mg/kg Delta(9)-THC produced no significant alterations in any brain region studied, while 1.0 mg/kg of Delta(9)-THC produced a restricted pattern of metabolic decreases. Significant decreases in metabolism following 1.0 mg/kg were concentrated in structures subserving limbic and sensory functions. In a second series of experiments, the effects of pretreatment with the cannabinoid receptor antagonist SR141716A (1.0 mg/kg) on Delta(9)-THC-induced changes in functional activity were measured. Pretreatment with SR141716A attenuated the majority of functional changes produced by Delta(9)-THC, suggesting that these effects are primarily mediated by central cannabinoid receptors. Moreover, these findings indicate that the effects of Delta(9)-THC on cerebral metabolism are dose-dependent and that there are regional differences in the metabolic response to acute cannabinoid exposure. Synapse 45:134-142, 2002. Copyright 2002 Wiley-Liss, Inc.


Recent studies indicate that sustained opioid administration produces increased expression of spinal dynorphin, which promotes enhanced sensitivity to non-noxious and noxious stimuli. Such increased 'pain' may manifest behaviorally as a decrease in spinal antinociceptive potency. Here, the possibility of similar mechanisms in the antinociception of spinal cannabinoids was explored. Response thresholds to non-noxious mechanical and noxious thermal stimuli were assessed. Antinociception was determined using the 52 degrees C tail-flick test. Mice received repeated WIN 55,212-2, its inactive enantiomer, WIN 55,212-3 or vehicle (i.th., bid, 5 days). WIN 55,212-2, but not WIN 55,212-3 or vehicle, produced a time-related increased sensitivity to non-noxious and noxious stimuli. WIN 55,212-2, but not WIN 55,212-3 or vehicle, elicited a significant increase in lumbar spinal dynorphin content at treatment day 5. Increased sensitivity to mechanical and thermal stimuli produced by WIN 55,212-2 was reversed to baseline levels by i.th. MK-801 or dynorphin antiserum; control serum had no effect. WIN 55,212-2, but not WIN 55,212-3 or vehicle, produced dose-related antinociception and repeated administration resulted in antinociceptive tolerance. While MK-801 and dynorphin antiserum did not alter acute antinociception produced by WIN 55,212-2, these substances significantly blocked antinociceptive tolerance when given immediately prior to WIN 55,212-2 challenge on day 5. Daily MK-801 pretreatments, prior to WIN 55,212-2 injection, also produced a significant block of antinociceptive tolerance. These data suggest that like opioids, repeated spinal administration of a cannabinoid CB1 agonist elicits abnormal pain, which results in increased expression of spinal dynorphin. Manipulations that block cannabinoid-induced pain also block the behavioral manifestation of cannabinoid tolerance.


Cannabinoids, the active components of marijuana and their endogenous counterparts, exert many of their actions on the central nervous system by binding to the CB1 cannabinoid receptor. Different studies have shown that cannabinoids can protect neural cells from different insults. However, those studies have been performed in neurons, while no attention has been focused on glial cells. Here we used the pro-apoptotic lipid ceramide to induce apoptosis in astrocytes and studied the protective effect exerted by cannabinoids. Results show that: (i) cannabinoids rescue primary astrocytes from C2-ceramide-induced apoptosis in a dose- and time-dependent manner; (ii) triggering of this anti-apoptotic signal depends on the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) pathway; (iii) extracellular signal-regulated kinase (ERK) and its downstream target p90 ribosomal S6 kinase (RSK) might be also involved in the protective effect of cannabinoids; and (iv) cannabinoids protect astrocytes from the cytotoxic effects of focal C2-ceramide administration in vivo. In summary, results show that cannabinoids protect astrocytes from ceramide-induced apoptosis via stimulation of the PI3K/PKB pathway. These findings constitute the first evidence for an astroprotective role of cannabinoids.

The cannabinoid CB(1) but not the CB(2) receptor was demonstrated to couple via G(alpha16) to activate phospholipase C after co-expression in COS7 cells. Chimeric CB(1)/CB(2) receptors were used as a model to study receptor-G(alpha16) interaction. Sequences of the second and third intracellular loops and the carboxy-terminus were substituted from the CB(1) into the CB(2) receptor. Only the triple mutant with all three regions replaced activated phospholipase C to a similar extent as the CB(1) receptor, suggesting that all three intracellular regions are required for interacting with G(alpha16). Several sub-domains within the third intracellular loop were identified for receptor-G(alpha16) interaction.


Anandamide (N-arachidonyl ethanolamine), an arachidonic acid derivative, is an endogenous ligand for both the brain-type (CB1-R) and spleen-type (CB2-R) cannabinoid receptors. To investigate the possible effects of anandamide on embryo implantation in the mouse, we used a co-culture system in which mouse embryos are cultured with a monolayer of uterine epithelial cells. Our results indicate that 14 nM anandamide significantly promotes the attachment and outgrowth of the blastocysts on the monolayer of uterine epithelial cells, and those effects could be blocked by CB1-R antagonists SR141716A, but not by SR144528, a CB2-R antagonist. It suggests that the effects of anandamide on embryo attachment and outgrowth are mediated by CB1-R. However, 56 nM anandamide is capable of inhibiting the blastocyst attachment and outgrowth, we, therefore, conclude that anandamide may play an essential role at the outset of implantation.


The pharmacology of G protein-coupled receptors is widely accepted to depend on the G protein subunit to which the agonist-stimulated receptor couples. In order to investigate whether CB(1) agonist-mediated signal transduction via an engineered G(alpha16) system is different than that of the G(i/o) coupling normally preferred by the CB(1) receptor, we transfected the human recombinant CB(1) receptor (hCB(1)) or a fusion protein comprising the hCB(1) receptor and G(alpha 16) (hCB(1)-G(alpha16)) into HEK293 cells. From competition binding studies, the rank order of ligand affinities at the hCB(1)-G(alpha16) fusion protein was found to be similar to that for hCB(1): HU 210 > CP 55,940 >>= SR 141716A > WIN 55212-2 > anandamide > JWH 015. Agonists increased [(35)S]GTPgammaS binding or inhibited forskolin-stimulated cAMP, presumably by coupling to G(i/o), in cells expressing hCB(1) but not hCB(1)-G(alpha16). However, an analogous rank order of potencies was observed for these agonists in their ability to evoke increases in intracellular calcium concentration in cells expressing hCB(1)-G(alpha16) but not hCB(1). These data demonstrate that ligand affinities for the hCB(1) receptor are not affected by fusion to the G(alpha16) subunit. Furthermore, there is essentially no difference in the function of the hCB(1) receptor when coupled to G(i/o) or G (alpha16).


Previous mutation and modeling studies have identified an aromatic cluster in the transmembrane helix (TMH) 3-4-5 region as important for ligand binding at the CB(1) and CB(2) cannabinoid receptors. Through novel mixed mode Monte Carlo/Stochastic Dynamics (MC/SD) calculations, we tested the importance of aromaticity at position 5.39(275) in CB(1). MC/SD calculations were performed on wild-type (WT) CB(1) and two mutants, Y5.39(275)F and Y5.39(275)I. Results indicated that while the CB(1) Y5.39(275)F mutant is very similar to WT, the Y5.39(275)I mutant shows pronounced topology changes in the TMH 3-4-5 region. Site-directed mutagenesis studies of tyrosine 5.39 to phenylalanine (Y-->F) or isoleucine (Y-->I) in both CB(1) and CB(2) were performed to determine the functional role of this amino acid in each receptor subtype. HEK 293 cells transfected with mutant receptor cDNAs were evaluated in radioligand binding and cyclic AMP assays. The CB(1) mutant and WT receptors were also co-expressed.
with G-protein-coupled inwardly rectifying channels (GIRK1 and GIRK4) in Xenopus oocytes to assess functional coupling. The Y-->F mutation resulted in cannabinoid receptors with subtle differences in WT binding and signal transduction. In contrast, the Y-->I mutations produced receptors that could not produce signal transduction or bind to multiple cannabinoid compounds. However, immunofluorescence data indicate that the Y-->I mutation was compartmentalized and expressed at a level similar to that of the WT cannabinoid receptor. These results underscore the importance of aromaticity at position CB(1) 5.39(275) and CB(2) 5.39(191) for ligand recognition in the cannabinoid receptors.


Delta(9)-tetrahydrocannabinol (THC), the main psychoactive component of marijuana has been shown to suppress the immune response. However, the exact mechanism of THC-induced immunosuppression remains unclear. In the current study, we tested the hypothesis that exposure to THC leads to the induction of apoptosis in lymphocyte populations. Splenocytes of C57BL/6 mice cultured in the presence of 10 microM or greater concentrations of THC showed significantly reduced proliferative response to mitogens, including anti-CD3 monoclonal antibodies (mAbs), concanavalin A (Con A), and lipopolysaccharide (LPS) in vitro. Thymocytes and naive and activated splenocytes exposed to 10 microM or 20 microM THC showed significantly increased levels of apoptosis. Treatment with CB2 antagonist inhibited THC-induced apoptosis in thymocytes and activated splenocytes. Administration of 10 mg/kg body weight of THC into C57BL/6 mice led to thymic and splenic atrophy as early as 6 h after treatment. This effect could be partially inhibited by treatment with a caspase inhibitor in vivo. THC exposure led to reductions in the numbers of all subpopulations of splenocytes and thymocytes examined. Functional studies revealed that splenocytes from THC-treated mice had significantly reduced proliferative response to anti-CD3 mAbs, Con A, and LPS in vitro. Finally, thymocytes and splenocytes exposed to THC in vivo exhibited apoptosis upon in vitro culture. Together, these results suggest that in vivo exposure to THC can lead to significant suppression of the immune response by induction of apoptosis.


Background & Aims: Activation of enteric cannabinoid CB(1) receptors inhibits motility in the small intestine; however, it is not known whether endogenous cannabinoids (anandamide and 2-arachidonoylglycerol) play a physiologic role in regulating intestinal motility. In the present study, we investigated the possible involvement of endocannabinoids in regulating intestinal propulsion in the mouse colon in vivo. METHODS: Intestinal motility was studied measuring the expulsion of a glass bead inserted into the distal colon; endocannabinoid levels were measured by isotope-dilution gas chromatography-mass spectrometry; anandamide amidohydrolase activity was measured by specific enzyme assays. CB(1) receptors were localized by immunohistochemistry. RESULTS: Anandamide, WIN 55,212-2, cannabinol (nonselective cannabinoid agonists), and ACEA (a selective CB(1) agonist) inhibited colonic propulsion; this effect was counteracted by SR141716A, a CB(1) receptor antagonist. Administered alone, SR141716A increased motility, whereas the inhibitor of anandamide cellular reuptake, VDM11, decreased motility. High amounts of 2-arachidonoylglycerol and particularly anandamide were found in the colon, together with a high activity of anandamide amidohydrolase. CB(1) receptor immunoreactivity was colocalized to a subpopulation of choline acetyltransferase-immunoreactive neurons and fiber bundles in the myenteric plexus. CONCLUSIONS: We conclude that endocannabinoids acting on myenteric CB(1) receptors tonically inhibit colonic propulsion in mice.


Recent reports have suggested an involvement of the brain cannabinoid system in the morphine-reward pathway. To address this question we evaluated whether CB1 receptor knockout mice would show a conditioned place preference to morphine. CB1 receptor knockout
mice developed a strong place preference to 4 and 8 mg/kg morphine, similar to that in wild-type Swiss-Webster mice. This data thus does not support a contribution of the brain cannabinoid system to morphine reward.


Inhalant abuse remains a significant health problem among the younger segment of society. In fact, the use of inhalants in this population trails only that of nicotine, alcohol, and marijuana. Toluene is a common ingredient in many of the substances sought out for inhalation abuse, apparently for its euphorogenic and hallucinogenic effects. Because drugs of abuse share the common property of altering the activity of mesolimbic dopamine neurons, it is reasonable to suspect that toluene-induced changes in this CNS pathway may underlie its abuse potential. Here we will provide in vivo and in vitro electrophysiological data and behavioral evidence linking toluene exposure in rats to activation of mesolimbic dopamine neurons. Exposure of rats to 11,000 ppm of inhaled toluene produced time-dependent activation of dopamine neurons within the midbrain ventral tegmental area (VTA). In the rat brain slice preparation, perfusion with toluene (23-822 microM) also evoked an increase in activity of both dopamine and nondopamine neurons within the VTA. These excitatory effects could not be found in adjacent non-VTA nuclei, nor were they sensitive to the glutamate antagonists CGS19755 or CNQX. In behavioral studies, systemic administration of toluene produced a dose-dependent locomotor hyperactivity that was attenuated by either pretreatment with the D2 dopamine receptor antagonist remoxipride or by 6-hydroxydopamine lesions of the nucleus accumbens. These findings show that toluene can activate dopamine neurons within the mesolimbic reward pathway, an effect that may underlie the abuse potential of inhaled substances containing toluene.


The peripubertal period appears to be critical in relation to the abuse of cannabinoids and opioids in humans. However there is little information about the acute effects of cannabinoids and their interactions with opioids in young experimental animals. We have studied the effects of the cannabinoid agonist CP 55,940 (0.1, 0.2, 0.4 and 0.6 mg/kg) on the nociceptive responses (tail immersion test) and holeboard activity of 40-day-old rats, and the involvement of the CB(1) receptor (antagonism by SR 141716A, 3 mg/kg). The implication of the opioid system was evaluated using the opioid antagonist naloxone (1 mg/kg) and a combined treatment with subeffective doses of CP 55,940 (0.1 mg/kg) and morphine (1 mg/kg). The effects of CP 55,940 on the serum corticosterone levels (radioimmunoassay) and on the dopamine and DOPAC contents of discrete brain regions (high-performance liquid chromatography) were also assessed. The antinociceptive effect of CP 55,940 was of a similar magnitude at all the doses used. The results show the involvement of the CB(1) receptor. The cannabinoid agonist significantly depressed the holeboard activity in a dose-dependent manner. The results indicate that the CB(1) receptor is involved in the effects on motor activity but not in the effects on the exploratory activity. The behavioural effects of CP 55,940 were modulated by morphine. The cannabinoid agonist (0.6 mg/kg) induced a CB(1)-mediated increase in the serum corticosterone levels, but no effect on the dopaminergic systems of either the striatum or the limbic forebrain was found.


We examined the food additive, butylated hydroxyanisole (BHA), for its capacity to modulate the cytotoxic effects of Delta(9)-tetrahydrocannabinol (THC). THC was not cytotoxic when added to cultures of A549 lung tumor cells at concentrations<5 &mgr;g/ml, but induced cell necrosis at higher levels with an LC(50)=16-18 &mgr;g/ml. BHA alone, at concentrations of 10-200 &mgr;M, produced limited cell toxicity but significantly enhanced the necrotic death resulting from concurrent exposure to THC. In the presence of BHA at 200 &mgr;M, the LC(50) for THC
decreased to 10-12 &mgr;g/ml. Similar results were obtained with smoke extracts prepared from marijuana cigarettes, but not with extracts from tobacco or placebo marijuana cigarettes (containing no THC). Two different mechanisms for this synergistic cytotoxicity were investigated. Experiments were repeated in the presence of either diphenyleneiodonium or dicumarol as inhibitors of the redox cycling pathway. Neither of these compounds protected cells from the effects of combined THC and BHA, but rather enhanced necrotic cell death. Measurements of cellular ATP revealed that both THC and BHA reduced ATP levels in A549 cells, consistent with toxic effects on mitochondrial electron transport. The combination was synergistic in this respect, reducing ATP levels to <15% of control. Exposure to marijuana smoke in conjunction with BHA, a common food additive, may promote deleterious health effects in the lung.


Cannabinoids produce antinociception via specific cannabinoid receptor activation, but there are also non-receptor mediated effects like for example the activation of the arachidonic acid cascade. Here we investigate the influence of cannabinoids (CB) on sleep duration after isoflurane anesthesia. We found that the CB receptor agonists R(-)-7-hydroxy-delta-6-tetrahydrocannabinol-dimethylheptyl (HU-210) (0.1 mg/kg), 2-O-arachidonoylglycerylether (30 mg/kg) and arachidonyl-2-chloroethylamide (3 mg/kg) significantly prolong the duration of isoflurane induced sleep in mice (P<0.05). This effect was absent when co-injecting the selective CB(1) antagonist N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (1 mg/kg). Furthermore, HU-210 was ineffective in CB(1) receptor knockout mice (CB(1)-/-). Our behavioral tests (tail flick, rotarod) indicate that the sleep latency can be prolonged even at low drug dosages which do not influence thermal nociception. In the chosen dosages thimerosal (20 mg/kg), 2-AG (10 mg/kg), R(1)-methanandamide (R(1)-MAEA) (10 mg/kg) and flurbiprofen (27 mg/kg) were ineffective to increase sleep duration.


Delta9-Tetrahydrocannabinol, a major psychoactive component of marijuana, has been shown to interact with specific cannabinoid receptors, thereby eliciting a variety of pharmacological responses in experimental animals and human. In 1990, the gene encoding a cannabinoid receptor (CB1) was cloned. This prompted the search for endogenous ligands. In 1992, N-arachidonoylethanolamine (anandamide) was isolated from pig brain as the endogenous ligand, and in 1995, 2-arachidonoylglycerol was isolated from rat brain and canine gut as another endogenous ligand. Both anandamide and 2-arachidonoylglycerol exhibit various cannabimimetic activities. The results of structure-activity relationship experiments, however, revealed that 2-arachidonoylglycerol, but not anandamide, is the intrinsic natural ligand for the cannabinoid receptor. 2-Arachidonoylglycerol is a degradation product of inositol phospholipids that links the function of cannabinoid receptors with the enhanced inositol phospholipid turnover in stimulated tissues and cells. The possible physiological roles of cannabinoid receptors and 2-arachidonoylglycerol in various mammalian tissues such as those of the nervous system are discussed.


It was shown recently that Delta9-tetrahydrocannabinol, like several other drugs eliciting euphoria, stimulates dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens. The aim of the present work was to clarify the mechanism of this stimulatory effect. Our hypothesis was that cannabinoids depress the GABAergic inhibition of dopaminergic neurons in the VTA. Electrophysiological properties of VTA neurons in rat coronal midbrain slices were studied with the patch-clamp technique. GABAA receptor-mediated inhibitory postsynaptic currents (IPSCs) were evoked by electrical stimulation in the vicinity of the
recorded neurons. The amplitude of IPSCs was depressed by the synthetic mixed CB1/CB2 cannabinoid receptor agonist WIN55212-2 (10-6 and 10-5 m). The CB1 cannabinoid receptor antagonist SR141716A (10-6 m) prevented the inhibition produced by WIN55212-2 (10-5 m). Two observations showed that IPSCs were depressed with a presynaptic mechanism. WIN55212-2 (10-5 m) did not change the amplitude of miniature IPSCs recorded in the presence of tetrodotoxin. Currents evoked by pressure ejection of muscimol from a pipette were also not changed by WIN55212-2 (10-5 m). The results indicate that activation of CB1 cannabinoid receptors inhibits GABAergic neurotransmission in the VTA with a presynaptic mechanism. Depression of the GABAergic inhibitory input of dopaminergic neurons would increase their firing rate in vivo. Accordingly, dopamine release in the projection region of VTA neurons, the nucleus accumbens, would also increase.


Cannabinoids are drugs that are frequently abused not only alone, but also in combination with other drugs. The present study investigated possible functional interactions between the psychostimulant methamphetamine and the cannabinoid receptor agonists anandamide, or R-(+)-methanandamide and cannabinoid antagonist AM 251 in the rat model of i.v. drug self-administration. In rats trained to self-administer methamphetamine, the intake was significantly decreased by the cannabinoid antagonist and tended to be dose-dependently increased by pre-treatment with cannabinoid receptor agonists. Possible mechanisms for these drug interactions are discussed and the use of the cannabinoid antagonist for the treatment of drug abuse is considered.


The goal of the present study was to formulate a Delta(9)-tetrahydrocannabinol (Delta(9)-THC) metered-dose inhaler (MDI) that can be used to provide a systemic dose of Delta(9)-THC via inhalation. Following physiochemical characterization and accelerated stability testing of the aerosol, mice were exposed to the aerosol and evaluated for pharmacological effects indicative of cannabinoid activity, including hypomotility, antinociception, catalepsy, and hypothermia. The fine particle dose of Delta(9)-THC was 0.22+/-.03 mg (mean+/-S.D.) or 25% of the emitted dose and was not affected by accelerated stability testing. A 10-min exposure to aerosolized Delta(9)-THC elicited hypomotility, antinociception, catalepsy, and hypothermia. Additionally, Delta(9)-THC concentrations in blood and brain at the antinociceptive ED(50) dose were similar for both inhalation and intravenous routes of administration. Finally, pretreatment with the CB(1) receptor antagonist SR 141716A (10 mg/kg, i.p.) significantly antagonized all of the Delta(9)-THC-induced effects. These results indicate that an MDI is a viable method to deliver a systemic dose of Delta(9)-THC that elicits a full spectrum of cannabinoid pharmacological effects in mice that is mediated via a CB(1) receptor mechanism of action. Further development of a Delta(9)-THC MDI could provide an appropriate delivery device for the therapeutic use of cannabinoids, thereby reducing the need for medicinal marijuana.


The zebrafish retina is rapidly becoming a major preparation for the study of molecular genetic mechanisms underlying neural development and visual behavior. Studies utilizing retinal mutants would benefit by the availability of a data base on the distribution of neurotransmitter systems in the wild-type fish. To this end, the neurochemical anatomy of the zebrafish retina was surveyed by light microscopic immunocytochemistry. An extensive series of 60 separate antibodies were used to describe the distribution of major transmitter systems and a variety of neuron-associated membrane channels and proteins. These include markers (i.e., antibodies against enzymes, receptors, transporters) for transmitters: GABA, glycine, glutamate, biogenic amines, acetylcholine, cannabinoids and neuropeptides; as well as a sample of voltage-gated channels and synapse associated membrane proteins. Discussion of the comparative localization of these antibodies is restricted to other teleost fishes, particularly goldfish. Overall, there was
great similarity in the distribution of the various markers, as might be expected. However, there were some notable differences, including several antibodies that did not label zebrafish at all, even though goldfish retinas that were processed in parallel, labeled beautifully. This survey is extensive, but not exhaustive, and hopefully will serve as a valuable resource for future studies of the zebrafish retina.

CLINICAL SCIENCE

OBJECTIVE: To present the cannabinoid system together with recent findings on the pharmacology of these compounds in the treatment of pain. DATA SOURCES: Search through Medline database of articles published in French and English since 1966. Also use of other publications such as books on cannabis. STUDY SELECTION: All the relevant documents within the theme of this review were used. DATA EXTRACTION: All the data linked to the present topic were searched. DATA SYNTHESIS: Recent advances have dramatically increased our understanding of cannabinoid pharmacology. The psychoactive constituents of Cannabis sativa have been isolated, synthetic cannabinoids described and an endocannabinoid system identified, together with its component receptors and ligands. Strong laboratory evidence now underwrites anecdotal claims of cannabinoid analgesia in inflammatory and neuropathic pain. Sites of analgesic action have been identified in brain, spinal cord and the periphery, with the latter two presenting attractive targets for divorcing the analgesic and psychotrophic effects of cannabinoids. Clinical trials are now required, but are hindered by a paucity of cannabinoids of suitable bioavailability and therapeutic ratio. CONCLUSION: The cannabinoid system is a major target in the treatment of pain and its therapeutic potential should be assessed in the near future by the performance of new clinical trials.


Cannabis consuming schizophrenic patients are younger at onset, are likely to have started abuse before onset of schizophrenia and show more prominent positive symptoms than nonabusers. It has been suggested that cannabis is a risk-factor for schizophrenia. Our aim was to assess prevalence and pattern of cannabis use in 125 chronic male schizophrenic subjects and its impact on socioepidemiological and clinical variables as well as which disorder precedes the other in onset. Assessment of consumption was made with a semi-structured clinical interview. Clinical status was assessed by means of the SANS, SAPS, PANSS and BPRS scales. Cannabis consumption was found in 54 subjects (43 %), 66.7 % of whom started it at least three years before onset of schizophrenia. Consumers were younger and with lower negative symptoms, specially abusers and polysubstance abusers. Family history positive for psychosis was more frequent in consumers, especially when consumption started before onset of schizophrenia. Subjects whose onset of schizophrenia preceded the beginning of cannabis abuse had more positive symptoms than those who started abuse before the onset of schizophrenia. On these grounds, our sample could be subdivided into two main groups, one that uses substances to counter distressing symptoms of schizophrenia and another in which cannabis might be one of the factors predisposing to the disease; the former had less negative symptoms than nonabusers. Our data support both heterogeneity of schizophrenia and genetic susceptibility to environmental agents.


The aim of this study was to assess the presence of alcohol, illicit drugs and medicinal drugs among Spanish drivers involved in fatal road accidents between 1991 and 2000. Samples were obtained for 5745 drivers killed in road accidents from January 1991 to December 2000. Of the samples, 91.7% represented males and 8.3% females; 40.7% were under 30 years of age, 31.9% were under 31-50 years of age, 19.5% were over 51 years of age, and for 7.9% the age was unknown. Between 1991 and 2000, some type of psychoactive substance was detected
among 50.1% of those drivers killed in road accidents, this being mainly alcohol (43.8%) and, less frequently, illicit drugs (8.8%) and medicinal drugs (4.7%). In all the cases, in which alcohol was detected, combined use with other substances accounted for only 12.5%, whilst in the case of illicit and medicinal drugs, figures representing combined use with other substances were 75.6% for the former and 65.8% for the latter. For one in every three cases (32.0%), a blood alcohol level over 0.8g/l was recorded; cocaine (5.2%), opiates (3.2%) and cannabis (2.2%) were the three illicit drugs most frequently detected. Among medicinal drugs, were benzodiazepines (3.4%), anti-depressant drugs (0.6%) and analgesics (0.4%). The results show the frequent presence of psychoactive substances, particularly alcohol, among Spanish motor vehicle users involved in fatal road accidents. It should be pointed out that illicit and medicinal drugs in combination with other substances were a common feature.


Background: This is an epidemiological study of a possible causal role of marijuana use in the development of Major Depressive Episode (MDE). Male-female differences in the suspected causal association have also been studied. Method: Data are from 6,792 National Comorbidity Survey participants aged 15-45 years, assessed via the University of Michigan modified version of the Composite International Diagnostic Interview (UM-CIDI). Survival analysis methods were used to estimate cumulative risk of MDE by levels of marijuana use and to estimate suspected causal associations after adjustment for other influences. Results: The risk of first MDE was moderately associated with the number of occasions of marijuana use and with more advanced stages of marijuana use. Relative to never users, non-dependent marijuana users had 1.6 times greater risk of MDE (95% Confidence Interval: 1.1, 2.2), even with statistical adjustment for sex, birth cohorts, alcohol dependence, and history of daily tobacco smoking. Conclusions: There was male-female variation in the degree of association between stage of marijuana involvement and MDE, but the strength of the association is modest at best.


OBJECTIVE: To examine the characteristics of 'diagnostic orphans' among cannabis users-those who report one or two symptoms of DSM-IV dependence but do not meet diagnostic criteria for DSM-IV abuse or dependence. METHOD: Data were collected from a representative population cohort of 1601 young adults aged 20-21 years. Those who reported that they had used cannabis at least weekly at some point within the past year were assessed for symptoms of DSM-IV cannabis abuse and dependence using the Composite International Diagnostic Interview. RESULTS: Approximately 2.8% of the cohort could be classified as diagnostic orphans, with another 3.0 and 7.5% meeting criteria for abuse and dependence, respectively. Diagnostic orphans were: similar to those who met criteria for cannabis abuse or dependence in terms of demographic characteristics; similar to those who met criteria for cannabis abuse in terms of cannabis use patterns; and similar to those who met criteria for abuse and dependence in their rates of heavy alcohol use and DSM-IV alcohol dependence. However, they did not appear to have elevated rates of illicit drug use or mental health problems compared to non users. CONCLUSIONS: Diagnostic orphans reported using cannabis in a manner similar to persons meeting criteria for cannabis abuse, and had similar rates of alcohol dependence and other illicit drug use. Strict adherence to DSM-IV diagnoses of abuse and dependence may overlook a substantial proportion of young persons who experience cannabis-related problems. There is a need to consider (a) subthreshold levels of cannabis-related problems among those seeking treatment for other problems; and (b) interventions for this group to prevent escalation of such problems.


Studies have shown that the Delta(9)-tetrahydrocannabinol (Delta(9)-THC) concentration in marijuana cigarettes is an important factor for the maintenance of marijuana self-administration. Yet, the impact of oral Delta(9)-THC treatment on marijuana self-administration is unknown. Because other agonist therapies have been demonstrated to be effective for the treatment of substance use disorders, the objective of this study was to evaluate the influence of oral Delta(9)-THC maintenance on choice to self-administer smoked marijuana. During this 18-day residential study, 12 healthy research volunteers received one of three doses of oral Delta(9)-THC capsules (0, 10, 20 mg QID) for 3 consecutive days, followed by 3 consecutive days of matching placebo. The order of active Delta(9)-THC administration was counterbalanced. Each morning, except on days 6, 12, and 18, participants smoked the 'sample' marijuana cigarette (1.6% Delta(9)-THC w/w) and received a $2 voucher (redeemable for cash at study's end). Following the sample, volunteers participated in a four-trial choice procedure during which they had the opportunity to self-administer either the dose of marijuana they sampled that morning or to receive the $2 voucher. Relative to placebo Delta(9)-THC maintenance, participants' choice to self-administer marijuana was not significantly altered by either of the two active Delta(9)-THC maintenance conditions. Some 'positive' subjective drug-effect ratings following the sample marijuana cigarette were reduced: by day 3 of active oral Delta(9)-THC maintenance, participants' rating of 'Good Drug Effect' and 'High' were significantly decreased. Smoked marijuana-related total daily caloric intake was not significantly altered under any maintenance conditions. Finally, the effects of smoked marijuana on psychomotor task performance were only minimally affected by oral Delta(9)-THC maintenance. These data indicate that participants' choice to self-administer marijuana was unaltered by the oral Delta(9)-THC dosing regimen used in the present investigation.


OBJECTIVE: Although several treatments for adolescent substance abuse have been identified as promising by reviewers and federal agencies, treatment effects extending beyond 12 months have not been demonstrated in randomized clinical trials. The primary purpose of this report was to examine the 4-year outcomes of an evidence-based treatment of substance-abusing juvenile offenders. METHOD: Eighty of 118 substance-abusing juvenile offenders participated in a follow-up 4 years after taking part in a randomized clinical trial comparing multisystemic therapy (MST) with usual community services. A multimethod (self-report, biological, and archival measures) assessment battery was used to measure the criminal behavior, illicit drug use, and psychiatric symptoms of the participating young adults. RESULTS: Analyses demonstrated significant long-term treatment effects for aggressive criminal activity (0.15 versus 0.57 convictions per year) but not for property crimes. Findings for illicit drug use were mixed, with biological measures indicating significantly higher rates of marijuana abstinence for MST participants (55% versus 28% of young adults). Long-term treatment effects were not observed for psychiatric symptoms. CONCLUSIONS: Findings provide some support for the long-term effectiveness of an evidenced-based family-oriented treatment of substance-abusing juvenile offenders. The clinical, research, and policy implications of these findings are noted.


The aim of the present paper is to present information about a kif preparation smoked by the Moroccan population. Results are considered as an advance of our actual investigations
undertaken in the Rif zone to observe an improvement in night vision after smoking kif [International Cannabinoid Research Society (ICRS) meeting, in preparation].


Abstinence prior to entering treatment is common among individuals seeking substance abuse treatment. The current study examined the relationship between abstinence at a pretreatment intake assessment and treatment response during outpatient treatment for marijuana dependence. At the intake assessment, 142 marijuana-dependent individuals completed past 30 day calendars of daily drug use. Forty-four (31%) participants were pretreatment abstainers, as defined by reports of one or more consecutive days of marijuana abstinence prior to the day of the intake assessment. Non-abstainers (69%) reported marijuana use the day prior or the day of the assessment. Pretreatment abstainers were more likely to enter treatment (P<0.05) and showed better treatment response than non-abstainers. Abstainers provided 50% more marijuana-negative urine screens during treatment (P<0.05), and more than three times as many abstainers reported no marijuana use (P<0.01). The groups did not differ on treatment completion. Marijuana abstinence at the time of initial clinic contact appears to be a strong predictor of success during treatment. Pretreatment abstinence may prove useful as a pretreatment matching strategy that could improve outcomes and cost-effectiveness. Clinical trials might consider including pretreatment abstinence status as a stratification variable during participant assignment or as a covariate in outcome analyses.


There is a large amount of evidence to support the view that the psychoactive ingredient in cannabis, delta9-tetrahydrocannabinol (delta9-THC), and cannabinoids in general, can reduce muscle spasticity and pain under some circumstances. Cannabinoid (CB1) receptors in the CNS appear to mediate both of these effects and endogenous cannabinoids may fulfil these functions to some extent under normal circumstances. However, in the context of multiple sclerosis (MS), it is still questionable whether cannabinoids are superior to existing, conventional medications for the treatment of spasticity and pain. In the case of spasticity, there are too few controlled clinical trials to draw any reliable conclusion at this stage. In the case of pain, most of the available trials suggest that cannabinoids are not superior to existing treatments; however, few trials have examined chronic pain syndromes that are relevant to MS. Whether or not cannabinoids do have therapeutic potential in the treatment of MS, a further issue will be whether synthetic cannabinoids should be used in preference to cannabis itself. Smoking cannabis is associated with significant risks of lung cancer and other respiratory dysfunction. Furthermore, delta9-THC, as a broad-spectrum cannabinoid receptor agonist, will activate both CB1 and CB2 receptors. Synthetic cannabinoids, which target specific cannabinoid receptor subtypes in specific parts of the CNS, are likely to be of more therapeutic use than delta9-THC itself. If rapid absorption is necessary, such synthetic drugs could be delivered via aerosol formulations.


AIM: To assess the possible effects of tobacco and cannabis smoking on lung function in young adults between the ages of 18 and 26. SETTING AND PARTICIPANTS: A group of over 900 young adults derived from a birth cohort of 1037 subjects born in Dunedin, New Zealand in 1972/73 were studied at age 18, 21 and 26 years. MEASUREMENTS: Cannabis and tobacco smoking were documented at each age using a standardized interview. Lung function, as measured by the forced expiratory volume in one second/vital capacity (FEV1/VC) ratio, was
obtained by simple spirometry. A fixed effects regression model was used to analyse the data to take account of confounding factors. FINDINGS: When the sample was stratified for cumulative use, there was evidence of a linear relationship between cannabis use and FEV1/VC (P < 0.05). In the absence of adjusting for other variables, increasing cannabis use over time was associated with a decline in FEV1/VC with time; the mean FEV1/VC among subjects using cannabis on 900 or more occasions was 7.2%, 2.6% and 5.0% less than non-users at ages 18, 21 and 26, respectively. After controlling for potential confounding factors (age, tobacco smoking and weight) the negative effect of cumulative cannabis use on mean FEV1/VC was only marginally significant (P < 0.09). Age (P < 0.001), cigarette smoking (P < 0.05) and weight (P < 0.001) were all significant predictors of FEV1/VC. Cannabis use and daily cigarette smoking acted additively to influence FEV1/VC. CONCLUSIONS: Longitudinal observations over 8 years in young adults revealed a dose-dependent relationship between cumulative cannabis consumption and decline in FEV1/VC. However, when confounders were accounted for the effect was reduced and was only marginally significant, but given the limited time frame over which observations were made, the trend suggests that continued cannabis smoking has the potential to result in clinically important impairment of lung function.


Accumulating evidence suggests that treatment-seeking substance abusers have high rates of gambling problems. However, relatively little is known about the relation between gambling problems and specific psychoactive substances apart from alcohol and methadone-treated opiate addicts. In this study of 580 individuals admitted to a residential addictions program, 10.5% were found to score in the pathological gambling range on the South Oaks Gambling Screen (SOGS) within the past year. The rate of pathological gambling was much higher for cannabis abusers (24%) than for alcohol (4%), cocaine (11.5%), and opiate abusers (4.8%). Men also reported higher rates of pathological gambling (11.9%) than women (7.5%). Individuals with a pathological gambling problem tended to report family histories of gambling problems as well.


BEHAVIOURAL SCIENCE


OBJECTIVES: This study examined whether adolescents’ recall of antidrug advertising is associated with a decreased probability of using illicit drugs and, given drug use, a reduced volume of use. METHODS: A behavioral economic model of influences on drug consumption was developed with survey data from a nationally representative sample of adolescents to determine the incremental impact of antidrug advertising. RESULTS: The findings provided evidence that recall of antidrug advertising was associated with a lower probability of marijuana and cocaine/crack use. Recall of such advertising was not associated with the decision of how much marijuana or cocaine/crack to use. Results suggest that individuals predisposed to try marijuana are also predisposed to try cocaine/crack. CONCLUSIONS: The present results provide support for the effectiveness of antidrug advertising programs.

It is known that many male juvenile delinquents commit violent crimes while intoxicated with flunitrazepam (FZ), often in combination with alcohol or other drugs. We have also noted the combined abuse of FZ with, for example, alcohol in male forensic psychiatric patients. Our objective was to study violent behavior, impulsive decision-making, and amnesia in male forensic psychiatric patients who were intoxicated predominantly with FZ, to increase knowledge of the abuse of FZ in vulnerable subjects. We studied five forensic psychiatric patients, all of whom were assessed in 1998. All of the subjects reported earlier reactions to FZ, including hostility and anterograde amnesia. At the time of their crimes they were all intoxicated with FZ, often in combination with alcohol or other drugs, such as amphetamine or cannabis. In contrast to their behavior based on their ordinary psychological characteristics, their crimes were extremely violent, and the subjects lacked both the ability to think clearly and to have empathy with their victims. Our observations support the view that FZ abuse can lead to serious violent behavior in subjects characterized by vulnerable personality traits, and that this effect is confounded by the concurrent use of alcohol or other drugs. It is evident that FZ causes anterograde amnesia. Previous research and the results presented herein allow us to draw the following conclusion: on the basis of the neuropsychopharmacologic properties of FZ, legal decisions, such as declaring FZ an illegal drug, are needed in countries where it is now legal.


AIMS: To examine childhood antecedents of marijuana and cocaine use in adulthood. DESIGN: Epidemiological, longitudinal cohort study of African American first graders (age 6) followed to age 32. PARTICIPANTS: Children (N=1242) and families in the 57 first grade classrooms from Woodlawn, an inner-city community in Chicago. First grade teachers, mothers and children provided assessments over the life course. During adulthood, 952 participants were re-interviewed. MEASUREMENTS: First grade teacher behavior ratings, readiness for school tests, self-reports of adolescent drug use, social bonds and adult self-reports of drug use were the primary variables. FINDINGS: Males who were both shy and aggressive in first grade were more likely to be adult drug users compared to those who were neither. Shy females in first grade were less likely to be adult marijuana users than non-shy females. Adolescent social bonds did not moderate the relationships of earlier childhood behavior to adult drug use. Males who had a 'high/superior' readiness to learn scores in first grade were less likely to be cocaine users as adults, even though in earlier work we showed that they were more likely to initiate adolescent drug use. Females scoring as poor performers in first grade were less likely to ever use cocaine compared to females with higher scores. CONCLUSIONS: The combination of shy and aggressive behavior is an important antecedent for later male drug use and may help distinguish those who will be persistent users in adulthood from those who experiment in adolescence.


The present study was designed to assess the influence of deviant peer affiliations on crime and substance use in adolescence/young adulthood. Data were used from a 21-year longitudinal study of health, development, and adjustment of a birth cohort of 1,265 New Zealand children. Annual assessments of deviant peer affiliations were obtained for the period from age 14-21 years, together with measures of psychosocial outcomes including, violent crime, property crime, alcohol abuse, cannabis abuse, and nicotine dependence. Affiliating with deviant peers was found to be significantly associated with each of these outcomes (p < .0001). Statistical control for confounding by both fixed and time dynamic factors reduced the strength of association between deviant peer affiliations and outcome measures. Nevertheless, deviant peer affiliations remained significantly associated (p < .0001) with all outcomes. For violent/property crime, cannabis and alcohol abuse there was significant evidence of age-related variation in the strength of association with deviant peer affiliations, with deviant peer affiliations having greater influence on younger participants (14-15 years) than older participants (20-21 years). These
results suggest that deviant peer affiliations are associated with increased rates of a range of adjustment problems in adolescence/young adulthood with deviant peer affiliations being most influential at younger ages.


Tobacco smokers are more likely to use marijuana than those who do not smoke tobacco. Little is known about how marijuana use affects the probability of tobacco smoking cessation. This analysis was based on 431 adults less than 45 years of age who reported recent tobacco smoking in the 1981 baseline interview in the household-based Baltimore Epidemiologic Catchment Area study and were re-interviewed 13 years later. At baseline, 41% of the tobacco smokers reported ever use of marijuana, 27% reported use of marijuana in the previous 30 days, and 9% reported daily use of marijuana for 2 weeks or more in the last 30 days. Marijuana users in the past 30 days at baseline were more likely than nonusers to still be using tobacco at follow-up after adjusting for race, educational level and marital status (OR=1.94, 95% CI=1.03, 3.63). Daily use of marijuana at baseline was even more strongly related to continued tobacco smoking 13 years later. Difficulty in tobacco cessation might be considered one of the most important adverse effects of marijuana use. Clinicians working with patients who are trying to stop tobacco smoking may be aided by routinely assessing marijuana use history, particularly with the recent increase in co-smoking of marijuana and tobacco.


PROBLEM/CONDITION: Priority health-risk behaviors, which contribute to the leading causes of mortality and morbidity among youth and adults, often are established during youth, extend into adulthood, are interrelated, and are preventable. REPORTING PERIOD COVERED: This report covers data during February-December 2001. DESCRIPTION OF SYSTEM: The Youth Risk Behavior Surveillance System (YRBSS) monitors six categories of priority health-risk behaviors among youth and young adults; these behaviors contribute to unintentional injuries and violence; tobacco use; alcohol and other drug use; sexual behaviors that contribute to unintended pregnancy and sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) infection; unhealthy dietary behaviors; and physical inactivity. The YRBSS includes a national school-based survey conducted by CDC as well as state, territorial, and local school-based surveys conducted by education and health agencies. This report summarizes results from the national survey, 34 state surveys, and 18 local surveys conducted among students in grades 9-12 during February-December 2001. RESULTS: In the United States, approximately three fourths of all deaths among persons aged 10-24 years result from only four causes: motor-vehicle crashes, other unintentional injuries, homicide, and suicide. Results from the 2001 national Youth Risk Behavior Survey demonstrated that numerous high school students engage in behaviors that increase their likelihood of death from these four causes: 14.1% had rarely or never worn a seat belt during the 30 days preceding the survey; 30.7% had ridden with a driver who had been drinking alcohol; 17.4% had carried a weapon during the 30 days preceding the survey; 47.1% had drunk alcohol during the 30 days preceding the survey; 23.9% had used marijuana during the 30 days preceding the survey; and 8.8% had attempted suicide during the 12 months preceding the survey. Substantial morbidity and social problems among young persons also result from unintended pregnancies and STDs, including HIV infection. In 2001, 45.6% of high school students had ever had sexual intercourse; 42.1% of sexually active students had not used a condom at last sexual intercourse; and 2.3% had ever injected an illegal drug. Two thirds of all deaths among persons aged > or = 25 years result from only two causes: cardiovascular disease and cancer. The majority of risk behaviors associated with these two causes of death are initiated during adolescence. In 2001, 28.5% of high school students had smoked cigarettes during the 30 days preceding the survey; 78.6% had not eaten > or = 5 servings per day of fruits and vegetables during the 7 days preceding the survey; 10.5% were overweight; and 67.8% did not attend physical education class daily. PUBLIC HEALTH ACTIONS: Health and education officials at national, state, and local levels are using these YRBSS data to analyze and improve policies and programs to reduce priority health-risk behaviors among youth. The YRBSS data also are
being used to measure progress toward achieving 16 national health objectives for 2010 and 3 of the 10 leading health indicators.


The study sought to examine, for South African adolescents: 1) the reliability of sub-scales of the Communities that Care Youth Survey (CTC Youth Survey) of risk and protective factors for drug use and anti-social behavior; and 2) the extent to which tobacco, alcohol and marijuana use can be predicted from community, family, school, and peer-individual factors based on sub-scales of the CTC Youth Survey. On two occasions, 92 male and 31 female, Grade 8 and 11 students completed measures concerning: 1) their past month tobacco, alcohol and marijuana use; and 2) various community, family, school, and peer-individual factors. Cronbach alpha coefficients of sub-scales of the questionnaire ranged between .60 and .94. Kappa values were at least moderate (above .40) on 19 sub-scales, and on the remaining sub-scales observed agreement levels ranged between .49 and .94. Each domain predicted tobacco, alcohol, and marijuana use. Multiple logistic regression analyses revealed that alcohol use was most strongly accounted for by the peer domain, tobacco use by the school domain, and marijuana use by the peer and community domains. The findings support use of the CTC Youth Survey, with slight revisions, among South African high school students.


OBJECTIVES: To compare personal and situational influences on incidents involving drink driving with those involving sober driving. METHODS: Information on a range of road safety practices was sought in face to face interviews conducted with 969 members of the Dunedin Multidisciplinary Health and Development Study cohort at age 26 years. A total of 750 study members reported an incident that involved the opportunity to consume alcohol and also travel by motor vehicle. Of these, 87 were classified as "drink drive incidents" and 663 as "sober drive incidents". RESULTS: Study members who were male, of lower socioeconomic status, had no school qualifications, or were dependent on alcohol or marijuana at age 21 were significantly more likely to report a drink drive incident at age 26. Compared with the sober drive incidents, the drink drive incidents were more commonly associated with driving alone, drinking at bars, and no advanced planning. For drink drive incidents the amount of alcohol consumed was influenced by the conviviality of the occasion, whereas for sober drive incidents it was the need to drive. One quarter of those reporting drink drive incidents stated they had used marijuana and/or LSD at the event at which they drank. CONCLUSIONS: Drink drive and sober drive incidents differed, particularly with regard to decisions made before the event. Prevention efforts could usefully be targeted toward these decisions.


AIMS: To (1) describe the South African Community Epidemiology Network on Drug Use (SACENDU), (2) describe trends and associated consequences of alcohol and other drug (AOD) use in South Africa for January 1997 to December 1999 and (3) outline selected policy implications identified by SACENDU participants. METHODS: A descriptive epidemiological study of AOD indicators based on data gathered from multiple sources, including specialist treatment centres, trauma units and quantitative studies of target groups such as school students and arrestees. Networks were established in five sentinel sites to facilitate the collection, interpretation and dissemination of data. RESULTS: Over time alcohol has been the most frequently reported primary substance of abuse across sites. Trauma and psychiatric data highlight the burden associated with alcohol abuse. Cannabis and Mandrax (methaqualone), alone or in combination, are the most frequently reported illicit drugs of abuse, generally comprising the largest proportions of drug-related arrests, drug-related psychiatric diagnoses and drug-positive trauma patients. From 1997 to 1999, a significant increase in indicators for cocaine/crack and heroin
occurred in two sites. Ecstasy (MDMA) use, alone or in combination with other substances, is reported among young people. CONCLUSIONS: A broad range of globally abused substances is present in South Africa and the use and burden of illicit substances appears to be increasing. This points to the importance of ongoing monitoring of AOD trends. Through regular, systematic data collection the SACENDU project has made available more evidence-based information to direct AOD abuse policy and practice and has had an impact on research agendas.


The objectives of this study, carried out in 1995, were to assess both licit and illicit substance use among rural male and female Costa Rican adolescents, and associated health, psychological, and psychosocial problems. A sample of 304 students from rural schools was randomly selected. The mean age for females was 14.7 years (S.D. = 1.71), and for males was 14.4 years (S.D. = 1.62). The data were collected using the Latin-American version of Drug Use Screening Inventory (DUSI). Results showed a high prevalence of past-year alcohol use for both males and females (56.6% and 47.4%, respectively), and a lower prevalence of past-year tobacco use (44.0% and 7.7%). There results also showed a low level of use of solvent inhalants and benzodiazepines. In terms of illicit drugs, males preferred cocaine and marijuana, while females only reported amphetamine use. An analysis of adolescent functioning showed differences among alcohol users and nonusers in behavior patterns and peer relationships. However, no significant differences were found regarding rebellion, depression, and social isolation. The implications of these results are discussed, along with the importance of enhancing prevention, as well as early detection and intervention.