



Clinical Pharmacology and Use of Cannabis

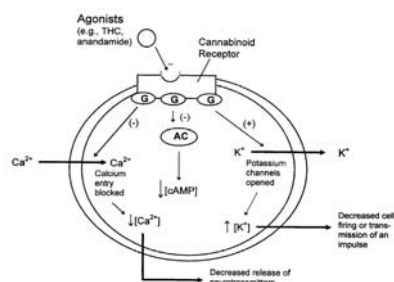
MediCann Physician Seminar

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Cannabis Characteristics: Cannabis is the material derived from the herbaceous plant *Cannabis sativa*. A sticky resin which covers the flowering tops and upper leaves is secreted most abundantly by the female plant and this resin contains the active agents of the plant. Cannabis contains more than 400 chemicals. Among these are more than 60 cannabinoid compounds (C₂₁ terpenes and their derivatives), such as cannabidiol (CBD) and cannabinol (CBN), the primary psychoactive constituent is delta-9-tetrahydrocannabinol or THC, the concentration of which determines the potency of the cannabis preparation. Cannabidiol CBD – is not psychoactive, but is anticonvulsant, sedative and has other actions. The cannabinoids represent a unique pharmacological class of compounds. They have not been found in any other plant.

Science of Cannabinoids: In 1986, it was shown that cannabinoids inhibit the enzyme that synthesizes cyclic AMP in cultured nerve cells. The characterization of a specific cannabinoid receptor in brain followed soon after, in 1988. The gene for the cannabinoid receptor in rat brain was cloned in 1990. The diverse pharmacological action of the various cannabinoids implies the existence of receptor subtypes - CB1 and CB2. The localization of cannabinoid receptors in the brain in greatest abundance were found in the rat cortex, cerebellum, hippocampus and striatum, with smaller but significant binding in the hypothalamus, brainstem and spinal cord. The lower brainstem area has few cannabinoid receptors. *This may explain why high doses of THC are not lethal.*



Cannabinoid Receptor

The CB receptors are G-protein coupled receptors. They modulate the chemical reactions inside cells through cAMP. Activity at the receptors can decrease Ca influx, increase K conductance. Also affected are inhibitory and excitatory signals at GABA and glutamatergic systems. Cannabinoids can be neuroprotective – inhibit the release of excitatory glutamate and reactive oxygen species, thereby exhibiting anti-oxidant properties. CB1- distributed in human brain tissue, where it is thought to be the most plentiful G-protein-coupled receptor. It is found peripherally in lower concentrations and inhibits cAMP production. It is also found on enteric nerves, which mediate GI effects. CB1 also mediates vagal complex of brainstem – vomiting. CB2 is found in immune tissues and cells. It may be involved in anti-nociceptive, and anti-inflammatory activity. (Cannabinoids have immunosuppressive effects on macrophages, T-lymphocytes and NK cells.) Possibly CB3 is yet to be found in human brain.

Definition: Cannabinoid Agonists - Compounds that bind to cannabinoid receptors

Plant-derived cannabinoid compounds

⁹-THC - Main psychoactive cannabinoid in the marijuana plant; largely responsible for psychological and physiological effects.

⁸-THC - Slightly less potent than ⁹-THC and much less abundant in the marijuana plant, but otherwise similar.

11-OH-⁹-THC - Bioactive compound formed when the body breaks down ⁹-THC. Presumed to be responsible for some of the effects of marijuana.

Cannabinoid agonists found in animals

Anandamide - (arachidonyl-ethanolamide) Appears to be primary endogenous cannabinoid agonist in mammals. Chemical structure very different from plant cannabinoids, and related to prostaglandins. (Named "anandamide" from a Sanskrit word meaning bliss).

2-AG - (arachidonyl glycerol) Endogenous agonist. Structurally similar to anandamide. More abundant but less potent than anandamide.

Synthetic Agonists

THC : GW2000-02 – THC marketed in Great Britain.

Sativex – THC and Cannabidiol marketed in Great Britain.

THC analogues : Dronabinol - Synthetic THC. Marketed in the US under the name Marinol®. Approved as an appetite stimulant by the FDA.

Nabilone - THC analogue. Marketed in the UK under the name Cesamet®.

CP 55,940 - THC analogue.

Levonantradol - THC analogue.

Dexanabinol – HU-211 – THC analogue.

HU-210 - THC analogue, 100-800 fold greater potency than THC.

Chemical structure unlike THC or anandamide

WIN-55,212 - Chemical structure different from known cannabinoids, but binds to both cannabinoid receptors. Chemically related to cyclo-oxygenase inhibitors, which include anti-inflammatory drugs.

Antagonists (Receptor Blockers)

Rimonabant - SR 141716A - Synthetic CB₁ antagonist, developed in 1994. Now being tested for treatment of obesity and hyperlipidemia.

SR 144528 - Synthetic CB₂ antagonist; developed in 1997.

AM 1241 - CB₂ antagonist- analgesic effects in neuropathic pain.

Forms and Potency of Cannabis: Marijuana is prepared from the dried flowering tops and leaves of the harvested plant. The flowering tops and bracts (known as "heads") are highest in THC concentration. Some varieties of the cannabis plant contain little or no THC, such as the hemp varieties. The concentration of THC in marijuana may range from 0.5 - 20 percent. Hashish consists of dried cannabis resin and compressed flowers. The concentration of THC ranges from 2 - 20 percent. Oils prepared from marijuana or hash using an organic solvent to extract THC produces concentrations between 15 - 70 percent. Increasing levels of THC in cannabis and more potent strains have merged in recent years.

Metabolism of Cannabinoids: Blood plasma levels of THC depend on the potency and method of delivery. When cannabis is smoked, peak concentrations are attained in 3-10 minutes, effects peak at 30-60 minutes, and last for several hours. Bioavailability of THC is 1 to 24 percent. Ingestion of cannabis is more erratic, with peak concentrations and effects available for 1 to 6 hours. Bioavailability is 5 to 20 percent. The plasma half-life can vary ranging from several hours to several weeks. THC is lipophilic and stored in fatty tissue with subsequent slow release into the bloodstream. Tolerance rapidly develops with regular use of cannabis.

Dosage: A typical joint contains between 0.5g and 1.0g of cannabis, which varies in THC content between 5mg and 150mg, typically between 1 percent and 15 percent THC. Not all of the available THC is ingested; the actual amount of THC delivered in the smoke has been estimated at 20 to 70 percent, with the rest being lost through combustion or escaping in side stream smoke. The bioavailability of THC from marijuana cigarettes (the fraction of THC in the cigarette which reaches the bloodstream) has been reported to range between 5 percent to 24 percent. For all these reasons, the actual dose of THC that is absorbed when cannabis is smoked is not easily estimated. In general, only a small amount of smoked cannabis (e.g. 2mg to 3mg of available THC) is required to produce an effect. Heavy users in Jamaica, for example, may consume up to 420mg THC per day.

In human experimental research, THC doses of 10mg, 20mg and 25mg have been administered as low, medium and high doses.

Long Term Effects: Long term use can cause mood disturbances in otherwise healthy individuals, including depression, apathy, or social isolation. There is a documented withdrawal syndrome after the cessation of marijuana use after 48 hours, which peaks within 2-6 days, and remits after 1-2 weeks. The symptoms are irritability, insomnia, mood swings, and mild depression. Studies have shown that rCBF changes revert after 2 weeks of abstinence. A drug holiday of 1 to 3 weeks every 3 - 4 months is recommended to mitigate the long term effects and to reduce tolerance.

Neurological Effects: Cannabinoids increase regional cerebral blood flow to frontal, limbic, and cerebellar areas of the brain. It is unknown what results from the increased regional blood flow. EEG changes show an increase in alpha wave activity consistent with relaxation and drowsiness. There is a reduction in REM sleep with increase in total sleep time. There are also sensory alterations, psychomotor slowing and decreased physical coordination. Cannabis produces an Impairment of recent memory, but shows no sign of long term memory impairment. Cannabis is neuroprotective, after head trauma, where anandamide (endocannabinoid) levels in rats are elevated.

Pain: THC has an antinociceptive (analgesic) effect. Cannabinoids produce analgesia by modulating neuronal activity in the medulla similar to but distinct from opiates. Neuropathic pain is especially affected. Cannabinoids have a synergistic effect with opiates and other drugs. Migraine headaches are especially responsive to cannabis.

Pulmonary Effects: Smoking releases tars, carbon monoxide, acids, aldehydes, pyrobenzenes, and particulate irritants. Heavy smoking for 6-8 weeks appears to cause mild mid airway or bronchial irritation. Cannabinoids have anti-phlegmatic and expectorant effects as well as a bronchodilator effects that help asthma.

Cardiovascular Effects: Cannabinoids produce tachycardia proportional to the dose, increasing the work of the heart, with a decrease in orthostatic blood pressure. Chronic long term use can result in a mild lowering of blood pressure. Cannabis is vasodilatory. Cannabinoids may be cardioprotective – reduce infarct size.

Immune System Effects: Cannabinoids have immune suppressant properties, producing impaired cell-mediated and humoral system responses. Cannabinoids decrease host resistance to infection from bacterial and viral infection in animals. Cannabinoids suppress the production and action of Tumor Necrosis Factor and other cytokines (anti-inflammatory) – this is a possible benefit in autoimmune disease (i.e. rheumatoid arthritis).

Muscular Effects: Cannabis reduces muscle spasm as well as spasticity, tics and tremors. Cannabis is also anti-ataxic. Cannabis may have anti-convulsant effects, having had documented use for seizure disorders since the 1800. Cannabis may also be neuroprotective as well as relieving the spasticity in MS.

Gastrointestinal Effects: Cannabinoids decrease muscle spasms of the GI tract. There is a slowed gastric emptying time effect and patients exhibit stimulated appetite and an increase in adipose (fat) tissue. Cannabis decreases nausea and vomiting, which is very helpful in chemotherapy. In experimental studies with rimonabant (CB1 receptor antagonist) showed a 27% increase in HDL, an 11% drop in triglycerides, and a 27% drop in CRP. Cannabinoids may be an anti-inflammatory solution for ulcerative colitis.

Ophthalmic: Cannabis lowers intraocular eye pressure in normal patients and those with glaucoma. Duration has been measured at 3-4 hours. Side effects may include dry eye, and conjunctival hyperemia (dilated blood vessels). It is thought that cannabis produces these effects by a mechanism other than that used by standard glaucoma agents implying an additive effect. Cannabis may be neuroprotective for retinal degeneration.

Psychological: Subjective and behavioral effects vary widely, and are influenced by set (a person's expectations and psychic state) and setting. Effects are dependent on use, chronicity, tolerance and personality. There seems to be an increase in right brain activities. Positive effects - euphoria, relaxation, enhanced sensitivity, intensified sensation. Negative effects – panic, anhedonia, dysphoric mood changes, poor judgment, difficulty concentrating.

Effects on Cancer: Cannabinoids show anti-proliferative properties slowing the rate of cancer cell growth in rat models. THC inhibits lung-adenocarcinoma cell growth and slows the growth of tumor xenografts – gliomas, thyroid epitheliomas, skin carcinomas and lymphomas. Cannabis reduces the nausea of chemotherapy.