

**BIOCHEMICAL BASIS FOR USE OF CANNABINOIDS IN VARIOUS CLINICAL CONDITIONS*****Dr. Srinivas R Deshpande MD¹, Dr Mahesh Taru MS², Dr K.I King³, Dr Gayathree L⁴, Dr Somashekhar S C⁵**¹Professor and Head, Department of Biochemistry and Metabolism, Malabar Medical College, Calicut, Kerala, India. Pin 673319²Professor and Head, Department of Anatomy, Malabar Medical College, Calicut, Kerala, India. Pin 673319³Professor and Head, Department of Physiology, Malabar Medical College, Calicut, Kerala, India. Pin 673319⁴Associate Professor, Department of Microbiology, HIMs, Hassan.573201⁵Associate Professor, Department of Pharmacology, Malabar Medical College, Calicut, Kerala, India. Pin 673319**ABSTRACT**

The broad range of potential therapeutic applications of cannabinoids reflects the wide distribution of cannabinoid receptors throughout the body. The possibility of distinct subtypes of cannabinoid receptors and the probable development of new compounds to bind selectively to these receptors, as either agonists or blockers, may well open the door to the selective treatment of a number of disorders. Regulated use of the Cannabinoids can alleviate several disease conditions.

KEY WORDS: Cannabinoids, Δ^9 - tetrahydrocannabinol (Δ^9 -THC), cannabinoid receptors CB1 and CB2, cannabinoid receptor (CB1R) antagonist

INTRODUCTION:

Cannabis sativa contains more than 60 biochemically active compounds; the most psychoactive one being Δ^9 - tetrahydrocannabinol (Δ^9 -THC)(1) Other natural compounds such as Δ^8 - tetrahydrocannabinol (Δ^8 -THC), cannabiol and cannabidiol have also been identified. Cannabiol and cannabidiol, fail to elicit the same psychoactive effects of Δ^9 - THC, but can exhibit anticonvulsant activity and induce hepatic metabolic enzymes (1) Cannabinoids are terpenophenolic drugs that are either derived from cannabis or that induce similar behavioural and physiological effects to cannabis. Broadly they fall into three classes: those that are produced by plants of the Cannabis genus, termed phytocannabinoids (plant cannabinoids); those that are produced within the body, termed endocannabinoids (endogenous cannabinoids); and those that are produced synthetically to mimic the pharmacology of natural cannabinoids (synthetic cannabinoids). Though both opioids and cannabinoids have been used in therapeutics, the cannabinoids may be more efficacious than opioids in the treatment of chronic pain conditions, such as neuropathies, rather than acute pain.

Human endocannabinoid system includes the two endogenous ligands 2-arachidonoylglycerol (2-AG) and *N*-arachidonylethanolamine (anandamide or AEA) and two cannabinoid receptors (CB₁ and CB₂). (2) The effects of cannabinoids have been attributed to the activation of cannabinoid receptors CB1 and CB2 (1, 2). The effects of marijuana (1) in stimulating appetite have justified the use of Δ^9 -THC in cancer cachexia. Dronabinol (Δ^9 -THC in sesame

oil) is an oral form of Δ^9 -THC that is used clinically in the treatment of anorexia and weight loss in HIV infection and in the control of nausea and vomiting associated with cancer chemotherapy (1, 2). Since the onset is gradual and its effects sometimes cause anxiety and dysphoria, there is said to be little risk of abuse. Dronabinol helps in managing the appetite and behavioral problems associated with Alzheimer's disease (3, 4).

The Sanofi-Synthelabo Research Group has presented their results on the effects of SR141716 in obese patients (3, 4). SR141716, now named as rimonabant, is a selective type 1 cannabinoid receptor (CB1R) antagonist which induced a significant decrease of hunger, caloric intake, and weight. Rimonabant has been reported to decrease appetite and body weight, although the former effect seems to be transient and might not explain the sustained body weight loss. Rimonabant treatment showed improvement of obesity and the HDL cholesterol, but had no positive effect on the other cardiovascular risk factors and the quality of life. To date, human studies testing the effect of rimonabant on obesity have demonstrated a significant reduction in waist circumference which serves as a surrogate of visceral adiposity.

ANTI-EMETIC USE:

Cannabinoids have been used in the prevention of nausea and vomiting caused by anticancer drugs. Nabilone and dronabinol have been shown to be as effective as or more effective than phenothiazines, metoclopramide and domperidone for this indication, although they have not

been tested against the 5-HT₃ antagonist ondansetron (1, 3, 4).

IMMUNOMODULATORY EFFECT:

Δ^9 -THC exerts its immunomodulatory effects that alter the normal functions of T and B-lymphocytes, Natural killer T cells, and macrophages in humans and animals. These effects have been observed during both in vivo and in vitro cannabinoid treatment. (7, 8). Actions of Δ^9 -THC on the immune functions may result in decreased host resistance to bacterial and viral infections (4, 5). Studies using human peripheral blood mononuclear cells (PBMCs) from marijuana smokers showed a suppression of lymphocyte proliferation in culture as well as alterations in PBMCs immune cell subsets (4,5). Serum immunoglobulin (Ig) levels were also modulated by marijuana use, with IgG levels decreasing and IgE levels increasing. These functions vary from lymphocyte proliferation and antibody production to cytotoxic activity (5, 6). B-cell proliferation increased in the presence of Δ^9 -THC at nanomolar concentrations and the production of the chemokines and interleukin-8 (IL-8) increased at micromolar concentrations (7, 8). The latter group also observed decreases in the levels of other cytokine after Δ^9 -THC treatment. A correlation between marijuana smoking and herpes-virus infection was observed to increase the risk of mortality in HIV positive marijuana smokers [4,5]. Alveolar macrophages from marijuana smokers were deficient in phagocytosis and bactericidal activity (1,5).

CANNABINOIDS AND EPILEPSY:

Endogenously cannabinoids have been found to be produced under conditions of neuronal excitability and specific intercellular signaling. For example, an epileptic seizure, with its large swings in transmembrane voltage, increases in intracellular calcium, and marked release of neurotransmitters, such as acetylcholine and glutamate that prominently release endocannabinoids. In deep seizures, kainic acid (a glutamate agonist) induced an increase in hippocampal levels of anandamide. This clearly means that seizures-induced release of endocannabinoids, occurs for normal neuro-protection (4). With scanty human data, the role of cannabinoids in epilepsy remains speculative. This also calls for more research involving a greater number of participants. Cannabidiol may have a therapeutic potential, as it does not interact with cannabinoid receptors and has a different profile of anticonvulsant activity in animal models (4,5).

NEURO-IMMUNE CELL COMMUNICATION:

Under inflammatory and pathological conditions, loss of control of the CNS and activation of the immune system result in induction of neuronal damage cascades

that are frequently associated with neurological diseases. On the other hand, processes of neuro-protection and neurorepair after neuronal damage depend on a steady and tightly controlled immune surveillance. Many compounds are reported to protect against uncontrolled immune reactions in different organs such as l-carnitine (4, 6), alpha-lipoic acid and Q10-coenzyme (6-8). Recent studies have revealed that endocannabinoids participate in the brain's negative feedback system. (4, 6) The CNS endocannabinoid system participates crucially in neuronal cell-cell-communication and signal transduction, e.g., by modulating synaptic input and protecting neurons from excitotoxic damage. Also, endocannabinoids show a strong antioxidant action (9). Endocannabinoids play an important role in the communication between immune cells and in the interaction between nerve and immune system during CNS damage. Thus, therapeutic intervention in the CNS endocannabinoid system may help to restore the well-controlled and finely tuned balance of immune reactions in pathological conditions (9). Moreover, Ziring *et al.*, reported that formation of B and T cell subsets requires the cannabinoid receptor CB₂. (4, 10, 13)

SOME MORE POTENTIAL THERAPEUTIC APPLICATIONS:

The broad range of potential therapeutic applications of cannabinoids reflects the wide distribution of cannabinoid receptors throughout the brain and other parts of the body. The possibility of distinct subtypes of cannabinoid receptors and the probable development of new compounds to bind selectively to these receptors, as either agonists or blockers, may well open the door to the selective treatment of a number of disorders. In time, some of these compounds may be targeted specifically to the endogenous cannabinoid system. (4,6-10) Despite the positive appraisal of the therapeutic potential of cannabinoids as an antiemetic and anti-glaucoma agent, they have not been widely used and the clinical research undertaken is limited. Other therapeutic uses for cannabinoids warrant further basic pharmacological and experimental investigation and clinical research into their effectiveness. (10-11)

Dronabinol is currently approved in North America, Netherlands, Israel, Spain, Switzerland for (11)

- (1) Anorexia associated with weight loss in patients with AIDS and
- (2) Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Presently, Dronabinol is considered for five new indications (11): disturbed behaviour in Alzheimer's disease, nausea and vomiting in HIV patients who are receiving combination therapy, spasticity in multiple sclerosis,

intractable pain, and anorexia in cancer and renal disease. In Germany, the substance is used against chronic pain, neurological disorders and appetite loss in cachexia. (11) In Switzerland it is also available for medical purposes after permission of the Ministry of Health. In Italy, a sublingual spray containing dronabinol and cannabidiol in a ratio of 52:48 is approved for the symptomatic relief of neuropathic pains of multiple sclerosis.

BRONCHIAL ASTHMA-BRONCHODILATING EFFECT:

A general study of the effects of marijuana on respiration revealed a bronchodilating action in normal volunteer subjects. Marijuana smoke delivered by smoking cigarettes containing 2.6% THC caused fall of 38% in airway resistance and an increase of 44% in airway conductance, with less change when a 1% THC cigarette was smoked. (4, 6, 10, 11)

GLAUCOMA-LOWERS INTRAOCULAR PRESSURES:

Discovery of the ability of cannabis to lower intraocular pressure (IOP) was more or less fortuitous. Intraocular pressure was measured as part of a multifaceted study of the effects of chronic smoking of large amounts of cannabis. IOP was found to decrease as much as 45% in 9 of 11 subjects, 30 min after smoking. Lowered intraocular pressure lasted 4 to 5 h after smoking a single cigarette. (4, 9, 10, 11)

IN MULTIPLE SCLEROSIS:

In Multiple sclerosis, the ability of neurons to conduct impulses becomes impaired through the loss of myelin, which normally forms the outer covering of many nerve fibers, and through axonal loss. In particular, objective testing has provided evidence that Δ^9 -THC can decrease spasticity, rigidity, and tremor and can improve walking ability, performance in a hand-writing test, and bladder control as well as improving mobility, and quality of sleep; relieves pain; and induces a sense of well-being. In spinal cord injuries, when the effects of Δ^9 -THC and codeine were compared, it was found that oral Δ^9 -THC (5 mg) reduced pain and spasticity, whereas oral codeine (50 mg) had only an analgesic effect (4, 5, 11, 12). In 2005, researchers at Tokyo's National Institute for Neuroscience have concluded that Cannabinoid therapy of Rheumatoid arthritis could provide symptomatic relief of joint pain and swelling as well as suppressing joint destruction and disease progression (18)

MANIPULATING THE ENDOGENOUS CANNABINOID SYSTEM:

Given that the endocannabinoid system represents an important target for addressing symptoms arising from

numerous disease states, the ability to manipulate this system becomes of paramount importance. At present, the only means of activating the endocannabinoid system is with CB1receptor agonists. THC is approved for clinical use in the United States, and nabilone is approved for clinical use in Canada and the United Kingdom. Efforts are under way to develop additional modes of drug delivery. A water-soluble analog of THC that may be useful for intravenous use has been developed [13, 14, 15]. In addition, the inhalational form of THC might prove to be useful by allowing better titration of the dose and greater control over the onset of effects [15, 16, 17]. Efforts are also under way to develop inhibitors of the enzymes that degrade anandamide. Indeed, deletion of this enzyme in mice through genetic engineering resulted in elevated anandamide levels and increased resistance to pain [14-16]. Highly potent inhibitors of this enzyme have been synthesized [15, 16, 17,18]. By elevating anandamide levels, these inhibitors represent an entirely new strategy for activating the endocannabinoid system.

The systematic study of the possible benefits of cannabinoid therapy combined with other drugs may well lead to better methods of clinical use. However, preparations containing THC or other drugs acting on the two known cannabinoid receptors will still suffer from the very broad spectrum of action that gives rise to the unwanted side effects. One possible improvement is to use cannabinoids that do not act on either of the two known cannabinoid receptors and therefore are devoid of the psychoactivity that is usually unwelcomed by patients who have not previously used cannabis for non-medical purposes.(18,19) For example, cannabidiol has the sedative, anticonvulsant, antiinflammatory and neuroprotective effects of THC—but not the psychoactivity—and will probably be explored more fully as a therapeutic agent. However, the fact that natural cannabinoids cannot be patented will deter pharmaceutical companies from investing effort in their therapeutic development unless active semisynthetic modifications of those cannabinoids can be produced. (20,21)

Another way of achieving more selective cannabinoidlike therapeutic action is to produce drugs that either stimulate or inhibit the cell mechanisms for producing and destroying the endocannabinoids, rather than act on the cannabinoid receptors themselves. In the scientific exploration of other neurotransmitters (i.e., the chemical messengers that transmit information between nerve cells), it has been found that the various molecules involved in their actions differ slightly in different tissues. A particular receptor, for example, may be found in the liver in a slightly different form from that of the same receptor in the heart or brain. It seems quite possible that the

constituents of the endocannabinoid systems will also show such variations in different tissues. (18-21) Such variations would make it possible to synthesize cannabinoidlike drugs that specifically target particular tissue to produce a desired therapeutic effect while avoiding the Highly selective cannabinoid derivatives, in forms that can be taken orally or by injection, would permit many more therapeutic uses of this versatile family of drugs.(21) Alternative modes of delivery are being explored to overcome the adverse effects of smoking cannabis. The recently introduced pharmaceutical preparation of cannabinoids is sprayed onto the oral mucosa and absorbed directly from the mouth into the circulation, which has the benefit of avoiding the inhalation of smoke. Clinical studies using delivery systems such as vaporizers that do not involve the combustion of cannabis (and hence do not produce smoke) may be helpful to overcome the health risks associated with smoking cannabis. It seems probable that other developments of this type will be actively pursued.(18-21)

CONCLUSIONS:

Cannabinoids are a group of terpenophenolic compounds present in *Cannabis sativa* L. and are made up of three types, namely natural or herbal cannabinoids, synthetic cannabinoids and endogenous cannabinoids. Currently, there are multiple known endocannabinoid proteins as potential therapeutic targets for developing useful medications in the treatment of a multitude of ailments, such as drug addiction, pain, and motor disorders as well as immuno-suppression in auto-immune disorders and graft rejection. There is also a need for more case-control studies comparing those experiencing cannabis problems, with people who have, and do not have, alcohol and other psychoactive substance use problems. There is a need for controlled studies investigating the relationships between cannabis use, schizophrenia and other health disorders. In particular, there is a need for large scale intervention studies to see whether stopping cannabis use improves their outcomes in treatment.

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