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ESSENTIALS OF THE ENDOGENOUS CANNABINOID SYSTEM AND CANNABIS: POTENTIAL MEDICAL BENEFITS

Introduction

Review of the legislation concerning possession, sale, transport and cultivation of marijuana (cannabis) and its use for both medical and recreational purposes has become a topic of considerable debate in South Africa. At the time of writing, cannabis remains illegal in this country. Nevertheless, there is increasing support for decriminalising and legalising possession of the plant for personal use. Furthermore, a number of studies indicate that there may also be potential benefits of cannabinoids for a variety of medical conditions, based on the activity of components of the cannabis plant and synthetic cannabinoids at endogenous cannabinoid receptors.

The following is a brief review of the function of the endogenous cannabinoid system and the potential medical uses of cannabinoids.

KEY MESSAGES

- The endogenous cannabinoids (endocannabinoids) are small lipids that regulate various aspects of brain function and behaviour, including learning, memory, reward, emotion, sensory function and pain, sleep, feeding, motor function, and neurogenesis, neuroplasticity and protection against acute excitotoxicity
- Tetrahydrocannabinol (THC) is responsible for the psychoactive properties associated with recreational use of products derived from the *Cannabis sativa* plant
- Potential medical uses of THC include effects on chronic pain, chemotherapy-induced nausea and vomiting, muscle spasticity in multiple sclerosis and glaucoma
- A second phytocannabinoid, cannabidiol (CBD), is non-psychoactive and has attracted much interest in its therapeutic potential, including for neurological disorders such as epilepsy and seizures, psychosis, anxiety, movement disorders (e.g. Huntington's disease and amyotrophic lateral sclerosis) and multiple sclerosis
- There is currently insufficient evidence to recommend the use of cannabinoids for medical purposes over and above currently available treatments
- Cannabis use is currently illegal in South Africa, but changes in legislation are anticipated that will at least decriminalise possession and use
- Approximately 9% of those who experiment with cannabis will become addicted, but the risk of addiction and other adverse outcomes, including altered brain development, is increased when drug use begins in or before adolescence.

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The endogenous cannabinoid system: the endocannabinoids

The endogenous cannabinoids (endocannabinoids) are small lipids that regulate various aspects of brain function and behaviour, including learning, memory, reward, emotion, sensory function and pain, sleep, feeding, motor function, and neurogenesis, neuroplasticity and protection against acute excitotoxicity. They are also active in peripheral tissues, where they are essential for maintenance of normal function of the gut, liver, immune system, muscles and skin and in regulation of pregnancy.[1,2]

The two most studied endocannabinoids are anandamide and 2-arachidonoylglycerol (2-AG). In the central nervous system, they differ from traditional neurotransmitters in that they are not stored in vesicles, but are rapidly and separately synthesised in an activity-dependent manner (on demand) from phospholipid precursors in the postsynaptic membranes of neurones and from glial cells. Both have multiple biosynthetic pathways.[3,4]

Unlike most neurotransmitters, the primary site of action of the endocannabinoids is not postsynaptic. After release from the postsynaptic membrane, they act as fast retrograde synaptic messengers, binding to and activating receptors on the presynaptic membrane, by which means they modulate the release (frequently causing inhibition) of presynaptic neurotransmitters, including the primary excitatory and inhibitory neurotransmitters glutamate and gamma-amino butyric acid. Endocannabinoid-induced inhibition of the release of these two neurotransmitters leads to the phenomena of depolarisation-induced suppression of excitation or inhibition, respectively. In addition, the endocannabinoids may also modulate the activity of other slower-acting transmitters/modulators, including opioids, acetylcholine, dopamine, noradrenaline and cholecystokinin.[5,6]

Two endogenous cannabinoid G-protein-coupled receptors (GCPRs) have been identified. The predominant presynaptic endocannabinoid receptor is the CB1 receptor. It is located in areas of the peripheral and central nervous systems related to pain control, including the distal ends of primary afferent neurons, the dorsal horn of the spinal cord, the periaqueductal grey matter, the ventroposterolateral thalamus, and cortical regions associated with central pain processing, including the anterior cingulate cortex and prefrontal cortex. There are also high concentrations of CB1 receptors in other areas of the brain that regulate appetite, memory, fear extinction, motor responses and posture (Table 1). CB1 receptors are also found in nonneural tissues, including in the gastrointestinal tract, adipocytes, liver and skeletal muscle. A second GCPR, the CB2 receptor, is expressed to a limited extent in the brain, but occurs mainly in macrophages and macrophage-derived cells, such as microglia, osteoclasts and osteoblasts. Activation of CB2 receptors reduces the release of proinflammatory mediators, with immunomodulatory and neuroinflammatory properties that may also be important in modulation of pain and inflammation.[6-8]

The endocannabinoids differ in their activity at the CB1 and CB2 receptors. Anandamide has a high affinity for the CB1 receptor, where it acts as a selective partial agonist. It has little or no affinity for the CB2 receptor. In contrast, 2-AG is a full agonist at both CB1 and CB2, but has only low-to-moderate affinity for these receptors.[9]

Among others, neurotransmitters that directly cause endocannabinoid release include glutamate and acetylcholine. Binding of these neurotransmitters to postsynaptic receptors depolarises the membrane, activating calcium channels and mobilising intracellular calcium, which is necessary for endocannabinoid production. In this way, endocannabinoid-mediated retrograde signalling acts as a negative-feedback mechanism through which excessive neurotransmitter release may be regulated via CB1 receptors on the presynaptic membrane.[10]

However, CB1 and other endocannabinoid receptors (e.g. TRPV1) have been shown to exist not only on presynaptic membranes, but also on the postsynaptic neurone. Furthermore, the endocannabinoids are considered to be 'promiscuous' in that, unlike most neurotransmitters, neuropeptides, hormones and cytokines, they interact not only with cannabinoid receptors, but also activate or inhibit several other molecular targets, including ion channels, nuclear receptors and

other GCPRs. The balance of activity between anandamide, 2-AG and other endocannabinoids (e.g. N-arachidonoyl-dopamine [NADA], noladin ether and virodhamine) combined with cross-talk between these receptors acts to regulate levels of endocannabinoid production and to either enhance or counteract their activity, allowing for a very high degree of differential flexibility of their actions.[9] Regulation and production of endocannabinoids can have a profound effect on long-term excitation and inhibition of synaptic function, leading to changes in synaptic communication and modulation of synaptic plasticity.[10]

Table 1. Distribution of CB1 receptors in the brain[6-8,10]

Location	Function
Cerebellum	Cognition, coordination
Hippocampus	Learning, memory
Cortex	Cognitive function, executive function and control, integration of sensory input (taste, touch, smell, hearing, sight)
Basal ganglia	Motor control, planning
Ventral striatum (including nucleus accumbens)	Prediction, feeling of reward
Dorsal striatum	Movement, executive function, learning
Amygdala	Anxiety, emotion, fear
Hypothalamus	Appetite, hormone levels, sexual behaviour
Brain stem and spinal cord	Vomiting, pain

Phytocannabinoids

The cannabis plant, *Cannabis sativa*, has been used throughout history for both medical and recreational purposes. Descriptions of its use for various medical ailments date back to around 2350 BC, in ancient Egypt.[10]

Although more than 100 phytocannabinoids have been identified in the cannabis plant, two have received the most attention in terms of medical relevance. Tetrahydrocannabinol (THC) is responsible for the psychoactive properties associated with recreational cannabis use, and which arise as a consequence of its ability to act as a partial CB1 receptor agonist.[8-10] Other CB1-related effects, at least some of which may be of medical interest, include relaxation, analgesia, appetite stimulation, anti-emesis, decreased muscle spasticity and a reduction in intraocular

Table 2. Physiological properties of phytocannabinoids[10,11]

THC	CBD
• Impaired psychomotor coordination and sedation	• Anxiolytic
• Sense of euphoria and relaxation	• Antidepressant
• Perceptual distortion, time distortion, intensification of sensory experiences	• Antipsychotic
• Impairment of attention, concentration, short-term memory, information processing and reaction time	• Anticonvulsant
• Intensification of emotional and physical sensitivity	• Anti-nausea
• Anxiety, panic, paranoia	• Antioxidant
• Sedation	• Anti-inflammatory
• Analgesia	• Anti-arthritic
• Catalepsy	• Antineoplastic
• Hypothermia	
• Increased appetite	
• Increased heart rate, decreased blood pressure	
• Conjunctival injection	
• Dry mouth	

pressure (Table 2). Potential medical uses include effects on chronic pain, chemotherapy-induced nausea and vomiting, muscle spasticity in multiple sclerosis, and glaucoma.

A second phytocannabinoid of interest, cannabidiol (CBD), has very low affinity for both CB1 and CB2 receptors. CBD is the most abundant cannabinoid in hemp. It has various physiological effects, including analgesic and anti-inflammatory properties, but is non-psychoactive. Consequently it has attracted much interest in relation to therapeutic potential. It exerts analgesic actions by binding to multiple other receptors and proteins related to pain, and inhibits the degradation of endogenous anandamide, which may be important to its analgesic activity and may also reduce pain by limiting inflammation at the site of injury. CBD antagonises several of the adverse effects associated with THC, including sedation, tachycardia, anxiety and the psychoactive effects. Potential medical uses include symptom relief in neurological disorders such as epilepsy and seizures, psychosis, anxiety, movement disorders (e.g. Huntington's disease and amyotrophic lateral sclerosis) and multiple sclerosis.[8,9]

Recreational use of phytocannabinoids and potential harms

Cannabis-derived products may be consumed in a variety of ways, including smoking or inhaling (e.g. cigarettes, pipes, vaping), eating or drinking, vapourising, and sublingual and topical application. The amounts and ratios of the different cannabinoids may vary considerably depending on the source plant and the part of the plant that is used to derive the product for consumption (e.g. flower, leaf, resin, oil), whether the product has been purified, and in synthetic cannabinoid products.

According to the United Nations, approximately 4% of the global population uses cannabis, equating to around 183 million people.[12] In South Africa, surveys of local schools indicate that among adolescents there is a high rate of experimentation with drugs, including cannabis. Estimates of regular cannabis use range from 2% to 9% among adolescents and are around 2% in adults.[13,14] In South African drug rehabilitation facilities, behind alcohol, cannabis is the second most frequent substance of choice (51% and 21%, respectively).[15]

Potential health risks associated with recreational cannabis use are listed in Table 3.

In line with current estimates of the prevalence of addiction to other substances, approximately 9% of those who experiment with cannabis will become addicted. Drug use beginning at an earlier age and frequent use increases the risk of addiction, such that approximately one in six who start using cannabis in adolescence and up to 50% of those who use it daily will become addicted. Because the brain and the endocannabinoid system continue to undergo development throughout early adulthood, adolescents who regularly use cannabis are also most at risk of altered brain development, with potential adverse effects on learning, memory, and cognitive and executive function. Especially among people with a genetic vulnerability, heavier cannabis use and exposure at an earlier age increase the risk of cannabis-associated psychotic episodes, including the development of schizophrenia. However, because of the bidirectional relationship between substance use and mental illness, causality is difficult to prove.[16]

Table 3. Potential health risks associated with recreational cannabis use[16]

• Risk of addiction
• Altered brain development
• Poor educational outcome, dropping out of school
• Cognitive impairment
• Diminished life satisfaction and achievement
• Unemployment
• Symptoms of chronic bronchitis
• Increased risk of psychotic disorders and schizophrenia
• Psychosocial harm, violence and accidents

Medical treatment with cannabinoids

There are currently three cannabinoid-based drugs licensed for use in the USA. None are registered in South Africa and cannabis use remains illegal in this country. As with other unregistered medicines, in terms of the Medicines and Related Substances Act, if there are exceptional circumstances, medical practitioners can apply to the Medicines Control Council for permission to access and prescribe medicinal cannabis for a particular patient. However, both the recreational use and medical use of cannabis are currently under discussion and review, with a number of interested parties making submissions. The Medical Research Council is involved in these deliberations.

A large number of studies have investigated the clinical utility of cannabinoids. Results are variable and difficult to interpret because of the variable quality of study design and lack of standardisation, both in routes of administration and types and concentrations of cannabinoids administered. In terms of studies using plant extracts, it is important to recognise that different strains of the cannabis plant contain different proportions of THC and CBD as well as other plant components that will not be present in purified THC or CBD products. Hemp oil contains whole-plant extracts and is not illegal in South Africa. Results from studies using plant extracts from a particular cannabis strain will not be applicable to other strains of the plant. Importantly, in the South African context, results from studies using cannabis products obtained from Australia and the Netherlands will not be applicable to cannabis products sourced in South Africa; studies will have to be repeated with South African strains.

Evidence for medicinal cannabinoids

Most studies of cannabinoids for pain have used synthetic mono-element products. Results will not be applicable to patients using natural whole-plant extracts.

A comprehensive review of published studies of cannabinoids for medical purposes was published in 2015.[17] In 79 studies, including 6462 subjects, cannabinoids were shown to be associated with a significant complete response to nausea and vomiting, reduction in pain, and average reduction in Ashworth spasticity scale. The review concluded that there is moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain (including neuropathic and cancer pain) and spasticity due to multiple sclerosis. Low-quality evidence suggests they may be associated with improvement in chemotherapy-associated nausea and vomiting (vs comparator drugs and placebo), weight gain in HIV infection, sleep disorders and Tourette's syndrome. Common adverse events included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance and hallucination. There was no clear evidence of a difference in either beneficial or harmful effects based on the type of medicinal cannabinoid or mode of administration. There was low- or very low-quality evidence for no effect on psychosis and depression.

Should cannabis be legalised?

Since cannabis use is common and has potential medical benefits, and considering that the vast majority of occasional recreational users have low potential for cannabis-associated harm, cannabis use has been legalised in a number of countries around the world. The best data for outcomes of cannabis legalisation in the USA come from Colorado and Washington, where cannabis has been legal for some time.[12] Legalisation of cannabis has been associated with increased prevalence of cannabis use, which is mainly driven by increased use among young adults aged 18-25 years. It is unknown whether trends in cannabis use will change over time as the demand curve evolves in response to changes in price, availability and social norms. Innovation in commercial markets has led to increased availability of a wide range of cannabis products, with varying (and often increasing) potency. The difficulty in regulating these products has raised concerns about potential adverse health effects. Increasing reports of accidental ingestion or over-intoxication,

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especially among children and inexperienced users, and of accidents or injuries associated with cannabis use are also of concern. In 2014, within one year of legalisation of cannabis in Colorado, there was a 29% and 38% increase in the number of cannabis-related emergency room visits and hospitalisations, respectively. In contrast, social benefits of cannabis legalisation include increased tax revenues and reductions in the number of arrests and court cases associated with cannabis-related offences.

In a South African position statement on cannabis published in the *South African Medical Journal* in 2016, the Executive Committee of the Central Drug Authority made the following recommendations:[14]

- There is a necessity for supply reduction, demand reduction and harm reduction strategies for combating alcohol and substance use and abuse in South Africa;
- Harm reduction strategies should pay particular attention to school children and adolescents;
- There is little evidence that supply reduction via criminalisation is effective in reducing cannabis abuse, but conversely there is insufficient evidence that legalising cannabis will not be harmful;
- Products related to the medical use of cannabis should undergo standard evaluation by the Medicines Control Council for benefits and risks;
- More research and resources are required in relation to mental and neurological effects of substance use and substance use disorder;
- Focus should shift to decriminalisation rather than to legalisation of cannabis.

Conclusions

Relaxation of restrictions on use of cannabinoids for medical purposes is likely to become a reality in South Africa. However, the appropriate indications and identification of which patients are likely to benefit from these substances still remain to be confirmed. South African studies are ongoing in this regard.

Considering the ease with which cannabis plant products can be obtained, and especially if legislation on personal use of the plant is changed, it is likely that patients may be motivated to self-medicate. In order to guide patients and the general public, health professionals in South Africa need to be well informed about the risks and benefits associated with various cannabis products and to be aware of the changes in legislation and regulations that are currently under discussion.

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