MÆDICA - a Journal of Clinical Medicine

STATE-OF-THE-ART

About the endocannabinoids – *Short outline*

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ABSTRACT

Objectives: *The vital roles of neuroendocrine systems – such as the sympathetic and the renin-angiotensin-aldosterone systems; parasympathetic nervous system and the endothelin have become increasingly evident. Nonetheless, the endocannabinoid system (ECS) has been added to the list. The ECS consists of endogenous ligands and their receptors that act both peripherally and centrally to regulate body weight, particularly central or visceral obesity, and diverse metabolic processes. Therefore, ECS plays a decisive role in the level of cardiometabolic risk, especially in regard to the clustering of cardiovascular risk factors now grouped together as the cardiometabolic syndrome. Furthermore, an increasing amount of data highlights the role of the ECS in the stress response (by influencing the hypothalamic-pituitary-adrenal axis) and in the control of reproduction (by modifying gonadotropin release, fertility, and sexual behaviour). Cannabinoid receptors, endocannabinoids, and the machinery for their synthesis and degradation represent the elements of novel endogenous signalling system, so-called endocannabinoid system, which is involved in a plethora of physiological functions. One important physiological role of endocannabinoids seems to be neuroprotection. Looking back, what is interesting about endocannabinoids as an anticonvulsant is, that we have not seen yet any indication of an excitatory effect on central nervous system, perhaps being unique as an anticonvulsant.*

Key words: endocannabinoids, cardiometabolic risk factors, rimonabant, obesity, CB1 receptor, anandamide, progenitor cell proliferation

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I. BACKGROUND

The cannabis, marihuana or hemp plant is one of the oldest psychoactive plants cultivated in China by 4000 B.C. and in Turkistan by 3000 B.C. (1). The cannabis plant contains a family of chemically related 21 carbon alkaloids, which are termed "cannabinoids". The main pharmacoactive constituents are Δ9-tetrahydocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN). Marijuana is also a common term applied to the leaves, stems, and tops of the plant *Cannabis sativa,* which contains cannabinoids, the most active of which is Δ9-tetrahydrocannabinol (THC). Looking back, the first evidence of the use of cannabis was found in China, where archeological and historical findings indicate the agriculture of plant for fibers since 4,000 B.C. (2). It is well known its broadly (see Table 1) uses as medicine in China, the Middle East, India, Southeast Asia, South Africa, and South America, and mainly for malaria, rheumatic pains, constipation, and childbirth, including as surgical analgesic in association with alcohol (1).

- China: rheumatic pain, intestinal constipation, disorders of the female reproductive system, malaria, and others (3); the combination with wine used during surgical interventions (2);
- India: mostly as a part of old religious appointments; analgesic in toothache, neuralgia, and headache; anticonvulsant for epilepsy, tetanus, and rabies; hypnotic and tranquilizer for hysteria, anxiety, and mania; anesthetic or anti-inflammatory for rheumatism and other inflammatory diseases; antibiotic for topical use on skin infections, erysipelas, or tuberculosis; antiparasite; antispasmodic for colic or diarrhea; as digestive, or appetite stimulant; diuretic; antitussive; and expectorant for bronchitis or asthma (3);
- Africa: for malaria, dysentery, asthma, malaria, anthrax and other forms of fever; for snakebite or any blood poisoning; for childbirth (3);
- Nepal: kitchen oil (3);
- Tibet: used to facilitate meditation (3);
- Persia: biphasic effect with clear difference between its initial euphoric and its late dysphoria effects (3,4);
- Arabia: for diuresis, digestion, anti-flatulent, increased attention, and to relieve ears' pain (5), epilepsy (6);
- Western medicine: for rheumatism, convulsions, and mainly for muscular contractions from tetanus and rabies (4);
- USA: the first clinical conference about cannabis (1860) chaired by the Ohio State Medical Society (7);
- 1895: isolation of cannabinol;
- 1934: isolation of cannabidiol;
- 1964: isolation of D9-tetrahydrocannabinol (C21H30O2);
- Since 1985: restricted medical use in USA of synthetic THC (dronabinol);
- 1988: CB1 receptor is discovered;
- 1992: discover of anandamide;
- 1993: CB2 receptor is discovered.

TABLE 1. Shortly outlook starting with old recommendations for cannabinoids in different areas of the world history

Consequently, it should be stressed the efforts of Galen and other physicians from the older times to underline the largely applications of cannabis. Despite of everything, cannabis was studied and used as medicine by O'Shaughnessy WB, a young Irish professor from the Medical College of Calcutta from India. Later, marijuana was listed in the United States Pharmacopoeia from 1850 until 1942, and was prescribed for numerous disorders including labour pains, nausea, and rheumatism. Unfortunately, the political antimarijuana attitude of the United States and the consequent prohibition on the 1930s did not help to encourage scientific studies on cannabinoids during this period of time (1).

Increased understanding of the endogenous cannabinoid (endocannabinoid) system through last years led to a marked expansion in the medicinal indications for cannabinoid drugs (8). Among many attempts of worldwide researchers, it is important to remind the hard work of Raphael Mechoulam who identified Ä9-tetrahydrocannabinol (Δ9-THC), anandamide and 2-arachydonyl glycerol, and reported the endocannabinoid transmitters' role in the cardiovascular system (1); the role of Roger Pertwee, who was working on discovering CB1 and CB2 receptors and the related antagonists (1); or the role of Matsuda and Munro on synthetic cannabinoids and the cloning process of endocannabinoid receptors (1).

Interesting, our modern society use at least three well-known definitions for cannabis (9): 1) a "broad" definition (applied mainly by France, Greece and Sweden), according to which cannabis is any plant of *Cannabis sativa* L.; 2) an "international" definition derived from the United Nations Conventions, as "the flowering tops of the female plant of *Cannabis sativa L.*"; and 3) a "European" definition, which permits the industrial utilisation of hemp, including *Cannabis sativa,* if its THC content is less than 0.2 %. ❑

II. A BRIEFLY SKETCH OF ENDOCANNABINOID SYSTEM

As we mentioned above, cannabinoids are typically known as the active ingredients acquired from the marijuana plant named

"Cannabis sativa" (10). There are three classes of cannabinoids: 1) endogenous to animals (endocannabinoids): anandamide (N-arachydonyl-ethanolamine, AEA), 2-arachidonylglycerol (2-AG), nolandin ether; O-arachidonoylethanolamine (virodhamine), N arachidonoyl dopamine (NADA), N-palmitoylethanolamide (PEA) and N-arachydonyl-L-serine (11); 2) endogenous to cannabis plants (or exogenous cannabinoids): The exogenous cannabinoids are represented by the cannabinoids identified as (-) 3, 4-Trans-delta-l-tetrahydrocannabinol (delta-1-THC, delta-9-THC, Δ-9-THC or THC); cannabidiol (CBD); cannabinol; etc (12); and 3) synthetic cannabinoids: WIN55212,2; HU210; CPP55940; nabilone; etc.

From a practical viewpoint, the elements of the endocannabinoid system consist of 1) the cannabinoid receptors (named cannabinoid receptor type 1 or CB1 receptor or "brain/central type" and cannabinoid receptor type 2 or CB2 receptor); 2) the endogenous lipid ligands (endocannabinoids), and 3) the structures implied in their biosynthesis and metabolism (1).

Endocannabinoids are endogenous lipid messengers which attach to the cannabinoid (CB) receptors. Specifically, the two most common investigated endocannabinoids are the anandamide (AEA) and the 2-arachidonoylglycerol (2-AG) which is synthesized "on demand" by the cell membrane in a tissue specific manner, having prompt agonistic effects on the cannabinoid receptors via autocrine or paracrine mediated pathways (13, 14). These endocannabinoids are released from a postsynaptic cell on demand in response to increase of intracellular calcium (Ca2+) (15). triggered by either depolarization or activation of metabotrophic glutamate receptors (16-18), and finally acting on the presynaptic terminals as a "retrograde messengers". The releasing mechanism is through an unknown mechanism (19). Therefore, endocannabinoids include many different types which are synthesized on demand, are not stored in vesicles; are not released from presynaptic terminals; and are not specific. Some negative effects of cannabis/cannabinoids include the triggering of underlying psychotic illness, mild sensory distortions; altered motor coordination; impaired cognition; diminished short-term memory; altered perception of time; mild hallucinations; acute depressive reactions; acute panic reactions; mild paranoia; deteriorated mental coordination; and appetite stimulant. Given the omnipresent distribution and highly concentrated levels of the CB1 (cannabinoid 1) receptors in the nervous system, endogenous cannabinoids are considered a major class of neuromodulators (20).

Overall, the endocannabinoid signalling is a multi-step process which includes:

1. Neurotransmitter released from vesicles within the presynaptic neuron activates the postsynaptic neuron;
2. Activation of the postsynaptic neuron leads to the biosynthesis and nonvesicular release of an endocannabinoid, likely via a calcium mediated process (18, 21);
3. The endogenous CB1 ligand diffuses back to and binds to the presynaptic CB1 receptor (18);
4. The CB1 receptor activates a G protein which can lead to a number of presynaptic downstream events (e.g., effects on ion currents) that result in the inhibition of neurotransmitter release (19, 22),
5. Exogenous cannabinoids avoid this multistep process by directly activating on CB1 receptors and stimulating the endogenous cannabinoid system (23), mimicking or improving its natural functions.

Dopaminergic inputs from the central nervous system modulate the activity of these cannabinoids pathways, triggering an excitatory effect on the direct both way and an inhibitory effect on the indirect pathway (24). The **direct pathway** is largely used by exogenous cannabinoids and makes possible the initiation of motor processes by striatal neurons which largely express D1 dopamine receptors and project to the globus pallidus (internal segments)/substanta nigra pars reticulata. These striatal neurons produce a phasic inhibition of the globus pallidus (internal segments)/substanta nigra pars reticulata, leading to activation of the thalamus and brainstem motor areas. The **indirect pathway** implicates striatal neurons with D2 receptors and project to the external globus pallidus. Since the external globus pallidus tonically inhibits the subthalamic nucleus, activation of the indirect pathway disinhibits the subthalamic nucleus secondary with increasing subthalamic nucleus activity with the boost in

inhibitory output from the globus pallidus (internal segments)/substanta nigra, and inhibition of motor programs.

So that, the best well-known two cannabinoid receptor isoforms are cannabinoid receptor type 1 (CB1) with 470 amino acids in length, and cannabinoid receptor type 2 (CB2) with 360 amino acids in length, both being members of the seven transmembrane G protein coupled receptors (25). Both receptors are members of the 7-transmembrane class A, GPCR receptor superfamily. In this regard, both cannabinoid receptors have been cloned. CB1 was cloned in 1990 and is a G-protein coupled, with various effects including inhibition of adenylate cyclase, modulation of voltage-dependent calcium, and potassium channels. The most known CB1 antagonist is SR141716A (or Remonibant). However, both CB1 and CB2 receptors are coupled to Gi/o proteins, and their activation triggers complex transduction cascades. These include inhibition of adenylate cyclase, inhibition of Ca2+ channels, activation of potassium (K+) channels, activation of mitogen activated protein kinase and phosphatidylinositol-3 kinase pathways, and regulation of calcineurin and other phosphatases. In addition, anandamide may act via several non-G proteins coupled mechanisms, including direct activation of the vainilloid receptor 1 (VR1) receptors (16, 26). It should be stressed that the CB1 is negatively coupled to adenylate cyclase through Gi/o proteins; but CB2 receptors are negatively coupled on adenylate cyclase but not on the calcium channels. As mentioned earlier, the CB1 receptor, encoded by the CNR1 gene, is mostly expressed in the central nervous system, but also in several peripheral organs including liver, muscle, and adipose tissue, whereas the CB2 receptor is restricted primarily in the immune and hematopoietic systems (16). In conclusion, the CB1 receptors from central nervous system are measurable (1) predominantly in the olfactory bulb, cortical regions (neocortex, pyriform cortex, hippocampus, and amygdale), and several parts of basal ganglia, thalamic and hypothalamic nuclei, cerebellar cortex, and brainstem nuclei. Inside the limbic forebrain CB1 receptors are found particularly in the hypothalamus and in the anterior cingulated cortex. In the adult central nervous system, presynaptic Gi/o protein–coupled CB1 receptors may be the sites of action of marijuana and of the endocannabinoids (anandamide and 2-arachidonoylglycerol) (19). Activation of presynaptic CB1 receptors results in inhibition of release of glutamate, g-aminobutyric acid (GABA), and other neurotransmitters (18). Most important, the endocannabinoid system from the hypothalamus and nucleus accumbens is involved in the regulation of food intake, particularly for tasty food (27). In conclusion, CB1 receptors are also expressed in the peripheral tissue as thyroid gland, adrenal gland, vascular endothelium, adipocytes, the gastrointestinal tract, and the reproductive organs (28). From a practical perspective, emerging evidence showed that during brain development, CB1 receptors are the first expressed in early neural progenitors (29), with receptor levels increasing throughout neuronal specification and synaptogenesis (30).

By contrast, **CB2 receptors** are expressed predominantly in cells of the immune system including the spleen, tonsils, monocytes, and B and T cells. However, they may also be located at low rank in neurons of the central nervous system (31, 32). Basically, CB_2 receptors are expressed in cerebral microglial cells under inflammatory conditions, and recent studies using human neutrophils indicate that the CB_2 receptor may suppress neutrophils migration during inflammation. It is also worth discussing that in pathological pain conditions, CB2 messenger RNA (mRNA) is also detected in the lumbar dorsal horn concurrently with the appearance of activated microglial process. Further testing revealed that the partial absence of the cannabinoid receptors from brainstream nucle, may explain the low toxicity of cannabinoids when given in overdose (33). However, CB2 receptors may also exert functions in non-immune cells such as keratinocytes. An increasing number of reports and pharmacological evidence suggest that endocannabinoids might also exert their biological effects through non-CB1/ CB2 receptors (34-36). Although not proven conclusively, currently functional evidence for novel CB receptors suggest that the novel cannabinoid receptor has mixed vanilloid / cannabinoid pharmacology expressed in hippocampus; it is less potent than CB1 receptor and is activated by WIN55212, 2, but may be blocked by a vanilloid antagonist (37).

The **pharmacokinetics of synthetic cannabinoids** (THC) varies depending on the route

of administration. The bioavailability is 20–60%, and much smaller amounts of the metabolite, 11-hydroxy-THC, are produced with smoking than oral use. Oral cannabis has 6–20% bioavailability, and it is subject to a very high first-pass effect. In addition, a large volume of distribution (~10L) has been noted (38). Inhalation of marijuana results in maximal plasma concentrations within minutes. Psychotropic effects start within seconds, reach a peak after 15 to 30 minutes, and taper off over 2 to 3 hours. With oral ingestion, onset of effects have a delay of 30 to 90 minutes, peak in 2 to 3 hours, and may last 4 to 12 hours depending on dose (38). Heart rate increases by 20% to 50% within minutes of inhalation and may remain elevated for 3 hours. **Overdosing** may precipitate anxiety or panic feelings as well as further increase of heart rate. Naive consumers are most predisposed to panic sensations that could discourage further use. Sudden respiratory arrest with marijuana use alone in humans is not reported, probably because of an absence of CB-1 receptors in the brainstem. THC effects include euphoria and relaxation, perceptual alterations, time distortion, and intensification of sensory experiences such as eating, watching video, or listening to music (39). Cannabinoid withdrawal syndrome is defined based on the Budney criterias (40): over =4 symptoms (anger or aggression, decreased appetite or weight loss, irritability, nervousness or anxiety, restlessness, sleep difficulties or strange dreams, chills, depression, stomach pain, shakiness, sweating) **plus** "evidence that these symptoms produced clinically significant distress or dysfunction". ❑

III. THE PERSPECTIVES OF CANNABINOIDS IN CURRENTLY MEDICINE: WHERE WE STAND?

The endocannabinoid system has been implicated in a large variety of functions, including regulation of appetite and energy metabolism, pain and inflammation, neuro protection, and modulation of basal ganglia circuits (16). As already noted, the complexity of endocannabinoid system, particularly the various enzymes and receptors that control endocannabinoid biosynthesis, degradation and signal transduction could be practically drug targets for obesity, cancer, pain, inflammation, and psychiatric disorders (41-43). Not surprisingly, 2% of Canadian population use cannabis for medical purposes (44). Nonetheless, the endocannabinoid system has raised great interest as a potential pharmacologic target from management of disorders as obesity, pain, nausea, and neurologic conditions such as multiple sclerosis and movement disorders.

In this regard, the currently published literature recommend the endocabinnoids for the severe nausea and vomiting of cancer chemotherapy, glaucoma, epilepsy, multiple sclerosis, the spasm and pain of paraplegia and quadriplegia, AIDS, chronic pain, migraine, rheumatic diseases (osteoarthritis and ankylosing spondylitis), premenstrual syndrome, hyperemesis gravidarum or labor pains; ulcerative colitis; Cohn's disease; phantom limb pain; and depression. ❑

Pain and other clinical manifestations suppression from different disorders

Central cannabinoid receptors are localized in neuroanatomical regions involved in the process of transmission and modulation of pain signals, such as the periaqueductal gray, the rostral ventromedial medulla, and the dorsal horn of the spinal cord (1,11). Endocannabinoids may also downregulate pain perception through CB1 receptors in the rostral ventromedial medulla, through the same circuits involved in morphine-mediated pain suppression. Analgesic sites of action have been identified in brain areas, in the spinal cord, and in the periphery (45). Therefore, emerging evidence from animal studies and clinical observations indicate that cannabinoids have some analgesic properties (46-48). Another study showed that fifty patients on smoked cannabis reduced daily pain by 34%, and greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group. The first cannabis cigarette reduced chronic pain by a median of 72% vs. 15% with placebo (49). There is now clear evidence that endogenous opioid and endocannabinoid systems cooperate to produce analgesia (for doses see Table 2). More interesting, the association of inactive doses of cannabinoids to low doses of opioid agonists appears to potentate opioid antinociception. In keeping with this, animal studies have strongly suggested that a combination of a CB1 antagonist with an opioid may allow use of opioids for pain control without the occurrence

of addiction (50, 51). Conversely, cannabinoids appear to have a predominant anti-allodynic/ antihyperalgesic effect (52, 53). One possible mechanism for the antihyperalgesic actions of cannabinoids in neuropathic pain is suggested by study of Hofmann et al. (54) that states the cannabinoid-induced suppression of noxious stimulus is induced by central sensitization.

Electrophysiological and neurochemical studies provide incontestable evidence that cannabinoids suppress nociceptive transmission *in vivo* (54). Alternatively, the actual literature established that cannabinoids are effective analgesics suppressing nociceptive transmission especialy trough a non-opiate mechanisms dominating, having benefits in relieving of the bone and joint pain, migraine, cancer pain, menstrual cramps, and labor. In chronic neuropathic pain 1′, 1′-dimethylheptyl- D8-tetrahydrocannabinol-11-oic acid (CT-3), at a dose of 40mg/d of THC-11-oic acid analogue, has shown to be more effective than placebo with no major unfavourable side effects (55). Cannabinoids decrease ascending pain messages within an important nociceptive path, the spinothalamic tract (56). Specifically, cannabinoid agonists have been shown to suppress noxious stimulus-evoked activity in the ventral posterolateral nucleus of the thalamus, and are thereby thought to decrease pain sensitivity (56, 57, 58).

In the same time, there are significant reports suggesting that cannabinoids have been used for a variety of symptoms in patients who have **cancer**. Whereas, increasing evidence showed a direct antitumor activity of cannabinoid agonists in a plethora of tumor cells including breast, brain, skin, thyroid, prostate and colorectal. This effect was due to the inhibition of tumor growth, mediated by cell-cycle arrest or apoptosis, as well as by reduction in neovascularization and metastases. Therefore, it is evident that when these findings will be supported by *in vivo* studies, beside their therapeutically implication, they might open new insight on endogenous mechanisms of tumour suppression. For example, human glioblastoma and meningioma showed elevated levels of AEA in glioblastoma, and increased levels of 2-AG in meningioma, findings that might indicate endogenous antitumor actions (59).

The efficacy of cannabinoids in treating pain from cancer is identical to codeine, but is limited by the dose related adverse effects. Surprisingly, palmitoylallylamide produce analgesia with no adverse side effects typically linked with direct cannabinoid receptor activation. Neuropathic pain is generally chronic in nature, and highly unresponsive to traditional analgesics (56, 60). Hallmark symptoms of neuropathic pain include hyperalgesia (the lowering of pain threshold and an increased response to noxious stimuli) and allodynia (the evocation of pain by non-noxious stimuli). Both peripheral and central pathophysiological mechanisms may be involved, including an overstimulation and hyperexcitability of nerve paths (60). Acute pain resulting from stimulation of sensory neurons (nociceptors) can progress to chronic pain, although neuropathic pain does not always involve nociceptors (61). Chronic pain may also be maintained by persistent inflammatory reactions, which can lead to potentiat of nociceptors activation (56, 60). Extensive research supports the role of endocannabinoids and CB1 receptors in the control of nociception and **chronic inflammatory pain** (62). From a clinician point of view, it is harder to ignore the statement of Campbell et al. which concludes that cannabinoids have the same efficacy as codeine in controlling pain but their depressant effects on the central nervous system limit their use. In particular, they also recommend not to use cannabinoids into clinical practice for pain management or in acute postoperative pain, as further valid randomised controlled studies are

1. Gabapentinoid (gabapentin, pregabalin) ± Opioid/opioid rotation **or**
2. Antidepressant (TCA, duloxetine, venlafaxine) ± Opioid/opioid rotation **or**
3. Gabapentinoid + antidepressant + Opioid/opioid rotation; in addition, may consider trials of one or more of the following adjuvants when clinically appropriate:
   - Topical therapies for cutaneous allodynia/hyperalgesia.
   - Anti-inflammatory drugs (corticosteroids for acute inflammatory neuropathic pain).
   - IV bisphosphonates for cancer bone pain or complex regional pain syndrome.
   - Non-gabapentinoid antiepileptic drugs: carbamazepine or oxcarbazepine or lamotrigine ± baclofen for intermittent lancinating pain due to cranial neuralgias.
   - N-methyl-D aspartate antagonists (dextromethorphan, methadone, memantine, amantadine, and ketamine).
   - Mexiletine.

TABLE 2. Analgesic scheme for obscure pain syndromes with moderate to severe pain/functional impairment; pain with a score of > 4 on the on the brief pain inventory (45,55)

needed, but may be an alternative for treating spasticity and neuropathic pain.

Cannabinoids have been used for mild anxiety, increasing appetite, and preventing nausea. **Nausea** and **emesis** occur under a diversity of conditions, including viral illness, cancer, cancer chemotherapy and radiotherapy. Both are produced by excitation of one or a combination of trigger(s) located in the gastrointestinal tract, brain stem, and higher cortical and limbic centers (63). Cannabinoids are thought to exert their therapeutic effects via action on CB1 cannabinoid receptors in all three of these regions, with the best evidence being for effects in the brain (23, 63). Chemotherapy-induced nausea and vomiting are the most distressing side-effects of cancer treatment. Not surprisingly, animal experiments have shown that the cannabinoid agonists suppress opioid-induced retching and vomiting by activation of the cannabinoid CB1 receptor (64). Moreover a systematic review of the use of cannabinoids for control of chemotherapy related nausea and vomiting showed that cannabis derivatives were slightly better than were conventional antiemetics, although they were associated with mixed psychological effects (65). One form of a synthetic tetrahydrocannabinol (dronabinol) has been tested for use in chemotherapy-induced nausea and vomiting. Although it is effective against mild to moderately emetogenic chemotherapy agents, the neuropsychologic side effects of dronabinol may limit its usefulness. Therefore it is considered a fourth-line therapy (66). If these psychologic effects could be excluded, there may be a role for cannabinoids in the treatment of cachexia, emesis, and pain (20). More than 30 studies investigated the role of cannabinoids in management of emesis, although most of them have not assessed their effect on chemotherapy-induced nausea and vomiting. These studies compared the use of various cannabinoid preparations with standard antiemetics including prochlorperazine, metoclopramide, haloperidol, and domperidone. A systematic review (65) found that oral nabilone, dronobinol, and intramuscular levonantradol were more effective in control of emesis than were conventional antiemetics such as prochlorperazine and metoclopramide, after mild to moderate emetogenic chemotherapy. However, these agents have not been shown to be effective after highly emetogenic chemotherapy compared with metoclopramide (67, 68).

Regardless of the mechanisms, cannabinoids are also effective as **appetite stimulants**. Cachexia or wasting is a common feature of the later stages of diseases such as metastatic cancer and AIDS. The significant loss of body weight that occurs, is due to a reduction in appetite, as well as abnormalities in lipid and glucose metabolism. Unlike starved individuals, patients with cachexia do not respond to the negative energy imbalance with a compensatory increase in motivation to eat (69). Cannabinoids are known to lead to robust increases in food intake and can promote body weight gain (70). Curiously, cannabinoids improves insomnia, anxiety and depression. Therefore, the most cases diagnosed with AIDS, stated that smoking cannabinoids improves appetite, decrease nausea, diminishes anxiety, reduces aches and pains, enhances sleep and inhibits oral candidiasis. Indeed, cannabinoids are "very effective anxiolytic deserving of further study", and preliminary data also suggest that cannabinoids are effective hypnotic, and the antidepressant properties in cancer patients and others are consistent. In particular, cannabinoids inhibit primary tumor growth and increase survival in animal tumor models by the unknown mechanisms. Cannabinoids also showed antipyretic and anti-inflammatory activity (71).

Cannabinoids appear to have a **peripheral anti-inflammatory action** (45). It has been shown that cannabinoids act to CB1 and CB2 receptors both locally and centrally; they modulate release of neuropeptides from primary afferent receptors, and inhibit the release of calcitonin gene-related peptide (CGRP) from sensory neurons, minimizing local inflammatory response. In addition, cannabinoid action on CB2 receptors located on non-neuronal cells (primarily immune cells) in surrounding tissues is thought to inhibit the release of inflammatory mediators that excite nociceptors (56, 58). Specifically, cannabinoids have been proposed to inhibit release of prostaglandins and the production of pro-inflammatory cytokines by immune cells, and to inhibit the release of histamine from neighboring mast cells (58).

The anti-emetic, analgesic, anxiolytic, hypnotic and antipyretic properties recommend cannabinoids for improving symptoms in patients diagnosed with cancer or AIDS.

Synthetic cannabinoids are licensed in the UK mainly for the treatment of nausea and vomiting caused by cytotoxic chemotherapy. Randomized control trials in patients with cancer, resistent to usual anti-emetics, already showed that cannabinoids (THC) are statistically superior in relieving the emesis manifestations. Apart from the fact that all cases may develop euphoria or sedation, most oncologists from USA encouraged the legal administration of cannabinoids as an alternative therapy for emesis caused by cancer (72). Currently, the major active component of marijuana – Δ9-tetrahydrocannabinol (THC), has been licensed for clinical use as palliative treatment for cancer patients, in two preparations, dronabinol and its analogue nabilone (73). Given their sites of action and positive findings in animals, cannabinoids may also be useful as pretreatments to avoid establishment of conditioned nausea and anticipatory emesis associated with chemotherapy. Moreover, further studies of cancer-cachexia pathophysiology and the role of endocannabinoids will help us to develop cannabinoids without psychotropic properties, which may help cancer patients suffering from cachexia and improve outcomes of clinical antitumor therapy (74). ❑

Obesity and cardiometabolic risk – cannabinoids may be useful?

Obesity is a major public health problem being associated with increased morbidity and mortality, increased risk of coronary heart disease, type 2 diabets mellitus, cerebrovascular emergency, certain cancer, and arthritis. Predicting the magnitude of these changes, the novel reports suggest that 40% of children in Europe will be overweight by 2010 (75). The appetite-stimulating effects of cannabinoids, in particular of marijuana (Cannabis sativa), have been established for centuries (28). Increasing data proved the significance role of the endocannabinoids system in the control of energy balance, food intake, lipid and glucose metabolism through both central and peripheral mechanisms (27).

Moreover, studies indicate that weight gain associated with CB1 receptor stimulation is caused not only by food intake but also by metabolic processes, independent of food intake (28). It is harder to ignore, that the blockage of CB1 receptors decrease appetite and increase peripheral energy utilization resulting in weight loss (1). Based on the strength of evidences, Gonthier et al (76) proposed a new exciting theory, that some compounds may participate in the efferent signalling from adipocytes, and contribute to the wide range of biological roles attributed to cannabimimetic compounds at both central and peripheral levels. These results support the role of endocannabinoids in the development and maintenance of obesity and suggest a role for CB1 receptor antagonists as a potential new therapeutic approach for obesity and associated cardiometabolic risk factors (77,78). In addition, some data show that the endocannabinoid system also act peripherally in discrete tissues to adjust hepatic lipogenesis (78), glucose homeostasis, and adipose tissue metabolism (28).

Remarkably, the recent studies point out an obvious effect of endocannabinoid action on genes involved in the controll of skeletal muscle metabolism. It seems that blocking of the CB1 receptors, triggers the increases of AMPKa1 mRNA expression in myotubes from both lean and obese persons, supporting the direct role of CB1 on fat oxidation (79). Moreover, fat cell function measured as lipogenesis and lipolysis plus various levels of ADIPOQ expression were not associated with adipose CB1 mRNA. Consequently, these data do not provide evidence for a consistent role of CB1 in human adipocytes function. Activation of CB1 receptors affects fat metabolism, not only through regulating Acrp30 levels but also through increasing fatty acid synthesis in the liver (78). Consequently, the increased adipocytes lipoprotein lipase activity (28) and reduced adiponectin, ADIPOQ, mRNA expression and effects on lipolysis and energy expenditure (80) upon CB1 receptor activation also suggest a fat-cell-specific role of the endocannabinoid system. In this regard, the human CNR1 gene is expressed in both omental and sc adipocytes at both the mRNA and protein levels and found to mediate an increase in intracellular cAMP levels after stimulation (81). In recent studies, obesity was found to be associated with increased levels of endocannabinoids but decreased amounts of CB1 mRNA (82, 83).

Moreover, hypothalamic endocannabinoids which are also modulated by leptin, stimulate the neuropeptide Y neuronal activity and inhibit pro-opiomelanocortin neuronal activity. Leptin is an essential circulating satiety factor that originates in adipocytes and exerts an anorectic

effect in the hypothalamus. Hypothalamic leptin receptors are located in the arcuate nucleus on neuropeptide Y and pro-opiomelanocortin neurons. The overall effect of leptin and insulin is to decrease food intake. Shortly, leptin and insulin inhibit neuropeptide Y/agouti-related protein neurons via leptin and insulin receptors, thereby increases the release of corticotrophin-releasing hormone and cocaine-and-amphetamine-regulated transcript via the paraventricular nucleus. According to these findings, cannabinoid and serotonin systems are both involved in modulation of hypothalamic melanocortin and neuropeptide Y feeding systems. In particular, hypothalamic endocannabinoid levels fluctuate with nutritional status, whereas administration of CB1 agonists causes hyperphagia, and CB1 antagonists cause hypophagia, respectively (84).These changes are under partial negative control of the hormone leptin (28). Thus, as leptin levels decrease, endocannabinoid levels increase resulting in increased appetite, and vice versa (28). More striking is the fact that leptin has well-established pro-inflammatory and immunostimulatory actions; therefore, it has a physiological activity looking to the down-regulation of palmitoylethanolamide. Otherwise, leptin reduces hypothalamic endocannabinoid levels, whereas CB1 blockage causes inhibition of melanocortin and stimulation of neuropeptide Y pathways with definitive hypophagia.

Serum endocannabinoid levels are elevated in obesity (83), which also implies a role for CB1 activation in weight gain and the development of cardiometabolic risk factors. It has been postulated that an unregulated endocannabinoid system with increased central and peripheral activation may be relevant to the pathogenesis of obesity. In support of this theory, Engeli et al. (82) documented elevated peripheral levels of 2 endogenous cannabinoids, anandamide and 1/2-arachidonoylglycerol, which were increased by 35% and 52%, respectively, in obese versus lean women ($p < 0.05$). Furthermore, assessing of endocannabinoid activity from visceral fat mass suggested that abdominal fat accumulation is correlated with dysregulation of the peripheral endocannabinoid system in human obesity (81). Patients with obesity or hyperglycemia caused by type 2 diabetes exhibit elevated levels of 2-AG or of both endocannabinoids in visceral fat or blood, respectively (83, 85). Thus, both central and peripheral CB1 receptors are potential therapeutic targets. Not surprisingly, central and peripheral administration of anandamide increases food intake. This effect is attenuated by coadministration of the CB1 receptor antagonist. Moreover, circulating levels of both endocannabinoids were also shown to be higher in obese compared with lean women. As we mentioned, both cannabinoid receptors CB1 and CB2 are expressed in human preadipocytes and in mature adipocytes from subcutaneous and omental fat (81). Unfortunately, the direct production of endocannabinoids by human adipocytes had never been demonstrated. (76).

There are several potential goals of pharmacologic therapy for obesity, all based on the concept of sustained negative energy balance. The earliest and most studied treatment alternatives were: 1) inhibition of appetite by centrally active medications that modify monoamine neurotransmitters; and 2) decreasing of the fat absorption from the gastrointestinal tract. However, the selective blocking of the endocannabinoid system has recently been recognized (86, 87). Therefore, pharmacologic CB1 blockade with rimonabant improved metabolic factors, increasing insulin resistance, and lowering plasma leptin, insulin, and free fatty acid levels. **Rimonabant is the first selective** CB1 receptor blocker developed for clinical practice, discovered in 1994. Moreover, rimonabant is currently licensed in UK (88) and recently in the European Union for the treatment of obesity (89). Rimonabant traverses the blood-brain barrier with a long duration of action, around 6-8 hours. Experimental studies showed that rimonabant is effective in antagonizing the orexigenic effect of D9-tetrahydrocannabinol and suppressing appetite when given alone in animal models (28). On the other hand, the results of the RIO-NA (79), RIO-Europe (90), RIO-Lipids (91), and RIO-Diabetes (92) studies are highly consistent in terms of efficacy and tolerability/safety outcomes. These large prospective, randomized controlled trials demonstrated the effectiveness of rimonabant as a weight loss agent (79, 90, and 91). The 20-mg per day dose of rimonabant produced significantly greater improvements in waist circumference, high-density lipoprotein (HDL), triglycerides, insulin resistance, and prevalence of the metabolic syndrome than placebo (90). Furthermore, the

cardiometabolic benefits achieved with rimonabant treatment were sustained for up to 2 years. Thus, rimonabant therapy could represent a promising method, in addition to lifestyle modifications, for improving multiple cardiometabolic risk factors in overweight and obese patients, in clinical practice. The above mentioned studies reported side effects as mood changes, nausea and vomiting, diarrhoea, headache, dizziness, and anxiety (90). ❑

Cannabinoids and "the shaping of central nervous system"

Other significant feature of ongoing studies also revealed (a growing evidence) that endocannabinoids "shape" the induction and patterning of the central nervous system, being innately involved in organogenesis, in the configuration of cell–cell contacts and in the onset and modulation of intercellular communication (11). Overall, this concept is supported by the long-term of intrauterine cannabis exposure on excitatory and inhibitory neurotransmission in brain areas that perform learning, memory formation and motor control (11). In contrast, maternal marijuana consumption may affect neurodevelopment because of sustained CB1 receptors activation with disturbing of the right location, postsynaptic target selectivity, and functional differentiation of developing axons (93). A substantial benefit of cannabinoids had not been demonstrated, however low or pharmacologically doses of CB receptor agonists improve electrical brain stimulation reward. The effects of CB1 receptor activity in the regulation of stress are complex. The activation of CB1 receptor increases extracellular dopamine overflow in terminal regions of the reward circuit, the effect being reversed by CB1 receptor blockade (94). As we mentioned above, CB1 receptor activation "stress", whereas CB1 receptor blockade decreases the rewarding effects of sweet and appetizing foods. Anorexia nervosa and binge-eating disorder showed increased blood levels of anandamide, and therefore it may participate in reward aspects of the aberrant eating behaviors typical of these disorders (95).

IV. FUTURE POSSIBLE THERAPEUTIC TRENDS FOR CANNABINOIDS

Cannabinoids are the most commonly used illicit drugs in the world and about 2.5% of the world population consume cannabis annualy. However, ongoing studies support the roles of cannabinoids in the next neurodegenerative or neuromotor disorders as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy and neuronal excitotoxicity, and neuropathic pain, but large randomized clinical trials are necessary.

An important physiological role of cannabinoids seems to be neuroprotection. Current evidence supports that CB1 receptor activation is also involved in the control of neural cell fate, and exerts neuroprotective action on *in vivo* models to brain injury, including excitotoxicity and ischemia. Ischemia and hypoxia in the central nervous system induce abnormal glutamate hyperactivity and other processes that cause neuronal damage. These processes also participate in chronic neurodegenerative diseases such as Parkinson's and Alzheimer's disease and multiple sclerosis. Anandamide and 2-AG are neuroprotective mediators released during ischemia and hypoxia (96). Recent studies have shown that the endocannabinoid signaling system, expressed in neural progenitors, participates in the control of progenitor cell proliferation and differentiation (29) in the normal brain. Endocannabinoids are produced by neural progenitors leading to intracellular calcium increase, through CB1 receptor activation and triggering of hippocampus neural progenitors proliferation and neurogenesis (29). Thus, the CB1 cannabinoid receptor plays a neuroprotective role against brain excitotoxicity and stroke and in different neurodegenerative (29). In this context, chronic pharmacological administration of the synthetic cannabinoid induces neurogenesis. Dexanabinol is a synthetic cannabinoid analogue devoid of psychotropic activity, with strong neuroprotective potential. The drug differs from other neuroprotective drugs because it targets various pathophysiological mechanisms, including glutamate excitotoxicity, free-radical damage, and inflammatory response. Dexanabinol was shown to be highly neuroprotective in an animal model of traumatic brain injury. Overall, the capacity of cannabinergic drugs to modulate neurogenesis after brain damage may open new approaches to improve the insufficient neurogenic response of endogenous neural progenitors caused by excitotoxicity or ischemia mechanisms.

It is important to point out that endocannabinoid system was identified as a potential target for the treatment of several disorders of the central nervous system, including epilepsy and excitotoxicity (8). The researches data looking for the efficacy of the cannabinoids in treatment of epilepsy are still scarce. Disruption of CB1 receptor signaling had been shown to increase excitotoxic and seizure susceptibility, as well as to attenuate neuronal protection (8). Regardless of this, endocannabinoids are elevated following seizure induction, possible being produced and released to prevent excitotoxic development (8).

Among these, the cannabinoids appear to play an important role in the regulation of the endocrine system. On average, it has been demonstrated that endocannabinoids modulate hypothalamus-pituitaryadrenal axis function (97). The CB1 receptor is expressed in the hypothalamus and the pituitary gland, and the activation of CB1 receptor can modulate all of the endocrine hypothalamic-peripheral endocrine axes. In particular, earlier studies demonstrated that CB1 receptor blockade potentate self-control stress-induced hypothalamus-pituitary-adrenal axis activation and neuronal activity in the paraventricular nucleus of the hypothalamus (97).

By definition, the main findings of multiple sclerosis, cerebral palsy and spinal cord injury is spasticity. On the other hand, cannabis was often used to treat pain, muscle spasm, cramps and ataxia in the 19th century, and many modern sufferers have reported benefits. There have been sporadic hypotheses regarding the association between cannabis use and schizophrenia for over 3 decades. A meta-analysis of prospective studies focused on the association between "prior cannabis use" and "the later development of psychosis" showed an estimated odds ratio of 2.1 (95% confidence interval (CI) 1.7-2.5), that clearly advocates that cannabis is a (component) cause in the development and prognosis of schizophrenia (98).

There is a long history of use of marijuana in **multiple sclerosis (MS),** especially for reducing of spasticity and pain relief. Data offered by clinical trials suggest that cannabinoids successfully reduce pain and spasticity in MS (99). Moreover, it also seems that cannabinoids improve the coordination from MS. On the other hand, other studies showed no improvement in spasticity, but with a trend toward improvement in the treatment group with oral THC plus CBD (100). A randomized control study for the evaluation of the effect of the oral synthetic dronabinol (delta-9-tetrahydrocannabinol) on the central neuropathic pain in patients who had multiple sclerosis showed a moderate analgesic effect (101). In conclusion, it seems that exocannabinoids administered to patients with MS improves relieving of spasticity and muscle pain, night leg pain, depression, tremor, anxiety, spasms on walking, paraesthesiae, leg weakness, trunk numbness, facial pain, impaired balance, constipation, or memory loss.

Basic research indicates that cannabinoids components inhibit opioid withdrawal. Moreover, some studies point out a key role of cannabinoid CB1 receptors in the behavioral and biochemical processes underlying drug addiction. In summary, sensitization is defined as the phenomenon that is characterized by the increased response to the subsequent drug challenge after the repeated administration regimen is discontinued, being supposed to mediate "drug wanting" (102). The undergoing studies show that antagonists of cannabinoid CB1 receptors reduce the maintenance of drug self-administration and its relapse, finding that may be efficacious in the drug cessation processes from nicotine, opioid, cannabinoids, while the specific blockade of cannabinoid CB1 receptors is a new therapeutic option to treat cocaine relapse (103). Currently, the study of Malgorzata et al. (104) revealed that cannabinoid CB1 receptors play a role in cocaine sensitization and relapse, while an endogenous tonic activation of CB1 receptors is not required for cocaine reinforcement and discrimination. At this time, there is insufficient evidence, but newly evidences showed that CB1 receptor antagonists (for example rimonabant) inhibit the further effects induced by Δ9-THC in humans, therefore it may prevent relapse to smoking (103).

Clinically, all these data could have implications for changes in motivation that occur in human neuropsychiatric disorders, such as posttraumatic stress disorder, major depressive disorder, drug abuse, and schizophrenia (96), but further randomized controls trials are necessary. Abnormal endocannabinoid levels and excessive activity at CB1 receptors might

be a factor to hepatic fibrosis that surprisingly is characterized in humans by overexpression of CB1 receptors in fibrogenic cells (105).

Also, the gastrointestinal disorders are interlinked with cannabinoid system. Therefore, the roles of cannabinoids in control of colon inflammation are supported by the elevated anandamide levels from the biopsies of patients with ulcerative colitis (106). Patients with diverticular disease have increased anandamide levels in colon strips, supporting the role of cannabinoids in modifications of neural control of colon motility (107). In addition, the higher colonic endocannabinoid levels observed in patients with ulcerative colitis might cause CB1-mediated anti-inflammatory and motility inhibitory actions (92).

In addition to their classical known effects on analgesia, impairment of cognition and learning, or appetite enhancement, cannabinoids have also been related to the regulation of cardiovascular responses and implicated in cardiovascular pathology. Elevated levels of endocannabinoids have been related to the extreme hypotension associated with shock as well as to the cardiovascular complications due to cirrhosis. It also influences the cardiovascular and respiratory systems by controlling heart rate, blood pressure, and bronchial functions (108). Moreover, cannabinoids have been associated with beneficial effects on the cardiovascular system, such as the protective role in atherosclerosis progression and in cerebral and myocardial ischemia. In addition, it has also been suggested that the pharmacological manipulation of the endocannabinoid system may offer a future approach to antihypertensive therapy. Rimonabant is a selective central and peripheral CB1 blocker that reduces body weight and improve metabolic syndrome in obese patients by raising HDL-cholesterol and adiponectin blood levels as well as diminishing LDL-cholesterol, leptin, and C – reactive protein concentrations.

Summary

Cannabis is the most commonly used of the illicit drugs internationally. A substantial proportion of cannabis users develop cannabis-related problems, including abuse and dependence. The adverse psychological effects of cannabinoids comprise cognitive and psychomotor impairment, anxiety and panic attacks, and also acute psychosis and paranoia. The most common related side-effects are somnolence, dry mouth, ataxia, dizziness, dysphoria, palpitations, and orthostatic hypotension. Drugs acting as agonists to CB1 receptors are now proposed for evaluation as drugs for treatment neurodegenerative disorders (Alzheimer's and Parkinson's diseases), epilepsy, anxiety, and of stroke. Thus, the future of the endocannabinoid system might be full of revelations more than ever supposed before.

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