INTERNATIONAL JOURNAL OF HEALTH & MEDICAL RESEARCH

ISSN(print): Applied, ISSN(online): Applied

Volume 01 Issue 01 April 2022

Page No.- 36-40

A Review of on the Psychobiological Differences among Tetrahydrocannabinol, Cannabinol, Cannabidiol and Cannabigerol

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ABSTRACT: The endocannabinoid system plays a physiological natural anti-infiammatory anticancer role and the pharmacological effects of cannabinoids from Cannabis plant simply reflect the action of the endogenous ones. Therefore, from a therapeutic point of view Cannabis plant cannot be understood without taking into consideration the physio-pathological role of the endocannabinoid system. Despite the great number of potentially therapeutic molecules with the Cannabis plant, they may be synthetized within four archetypic molecules, which consist of tetra-hydro-cannabinol (THC), cannabinol (CBN), cannabigerol (CBG) and cannabidiol (CBD). All molecules play a similar anticancer activity, whereas their psychological effects are different. THC is the only psychotropic psychedelic cannabinoid, whereas the other three cannabinoids have no psychotropic effect, but exert an important anxiolytic activity. Moreover, only THC acts as a direct enzyme responsible for cannabinoid degradation, by enhancing the endogenous cannabinoid content. Unfortunately, despite the great number of experimental studies, the clinical use of cannabinoids in the treatment of systemic human diseases is still at the beginning.

KEY WORDS: Cannabidiol, Cannabigerol, Cannabinol, Cannabis plant, Cannabis therapy, Tetrahydrocannabinol

INTRODUCTION

Cannabis plant has been proven to contain more than 100 potentially active principles in terms of both psychological and biological effects. Moreover, the main Cannabis plant are represented by Cannabis Sativa and Cannabis Indica, which differ in relation to the different concentrations of each single principle. However, despite the great number of alkaloid compounds, from a synthetic point of view, it is possible to identity within the Cannabis plant four major archetypic principles consisting to tetrahydrocannabinol (THC), cannabinol (CBN), cannabidiol (CBD) and cannabigerol (CBG) (1,2), which differ for their neuropsychological effects on anxiety, mood, appetite, mind concentration, motor coordination and mainly psychedelic activity in terms of sensorial and pleasure amplification, and expansion of consciousness. On the contrary, the biological effects are similar among them, including the anti-inflammatory, the neuroprotective, the antalgic effects, and in particular the anticancer activity, which is due to both direct cytotoxic action and antiangiogenic effects (1,2), and at present only very few data are available about a possible different antitumor potency played by the various cannabinoids (3,6). On the other side, from a pharmacokinetic point of view, the major differences existing among the different cannabinoids from Cannabis plant regards the mechanisms of actions, which are substantially represented by a direct stimulatory action on cannabinoid (CB) receptor, or by the inhibition of the fatty acid amide hydrolase (FAAH), the enzyme responsible for cannabinoid degradation, with a consequent increase in the endogenous cannabinoid content. At present, there are known two main CB receptors, CB1 and CB2.CB1 receptor is responsible for the psychotropic psychedelic effects of Cannabis, and it is widely expressed by most cellular types, while CB2 receptors is only expressed by the various immune cells, since it is involved in the neuro-immuno-modulatory processes (1, 2). THC is the only CB1-CB2 receptor agonist from Cannabis. CBN is a partial CB receptor agonist (7), as well as CBG (8), even though in an apparent less manner, while CBD would act only as FAAH inhibitor, and as a vanilloid receptor agonist for its antalgic activity. Then, CBN may be considered as an intermediate molecule between the CB receptor agonist THC and the FAAH inhibitors, such as CBD. The main characteristic of Cannabis Indica with respect to the Sativa specie consists of its greater THC concentrations, generally more than 20%. Moreover, it is important from a physiopathological point of view to correlate the cannabinoids from Cannabis to those produced by human brain and body. The main andogenous cannabinoid agonists are represented by arachidonyl-ethanol-amide (AEA), also termed as anandamide for its psychedelic effects, and 2-arachidonyl-glycerol (2-AG), which are respectively produced during the dark and during the light phases of the day (8). On the other side, the most know endogenous non-cannabinoid agent, which act as FAAH inhibitor, is the palmitoyl-ethanol-amide (PEA) (9). From a clinical point of view, the evaluation of the functional status of the CB system may be simply realized by detecting the blood concentrations of FAAH, and the evidence of abnormally high FAAH levels is the expression of an endocannabinoid deficienct because of FAAH-induced degradation of the cannabinoid agents.

THE PSYCHIC EFFECTS OF THE DIFFERENT CANNABINOIDS

An evident psychedelic effect in terms of expansion of consciousness and all sensorial perceptions is exerted by the only THC from Cannabis plant, as well as by their endogenous equivalent AEA and 2-AG (1). Moreover, there are some differences between the psychic effects of AEA and 2-AG. In fact, it has been shown AEA plays an important role in the modulation of memory consolidation, whereas 2-AG is not involved in memory processes (10). It is interesting to observe that the expansional action of THC regards two generally opposite conditions from the point of view of the actual culture, consisting of the expansion of the spiritual sensitivity and of the sexual fancies, by realizing simultaneous aphrodisiac and spiritual effects. The undesirable effects of THC are represented by its anxiogenic activity and its tachycardic effects, which are due to an inhibitory action on muscarinic cholinergic receptor (1). The 11-hidroxy-THC would be more psychoactive than THC itself (1). CBN plays a modest anxiolytic effect, which, however, is lower than that played by both CBD and CBG. Finally, as far the influence on appetite is concerned, THC is the most stimulatory of the appetite, CBN has a lower action, while CBD tends to reduce the appetite, mainly that related to the anxiety. CBG also would be a molecule intermediate between THC and CBD. Moreover, CBG would be the only cannabinoid agent which interacts with alpha2-adrenoceptors and serotonin-1A receptors (11).

THE ANTICANCER ACTION OF CANNABINOIDS

The endogenous CB system represents a fundamental anticancer structure within the human body (3-6). All tumour histotypes may be potentially inhibited by cannabinoids, including breast cancer, lung cancer and gastrointestinal tumours (3-6). Then, it has been suggested that cancer progression may depend at least in part on an endocannabinoid deficiency (1). This finding would not be surprising, since it has been already shown that cancer progression is associated with a progressive decline in the pineal function and in the nocturnal secretion of its most known indole hormone, melatonin (MLT) (12). Because of the well demonstrated connection between pineal gland and CB system (13), the pineal deficiency could allow a concomitant diminished function of the CB system. In fact, it has been shown that cancer progression is characterized by low levels of AEA in association with increased values of 2-AG, and this evidence would reflect an altered function of the endogenous CB system (14). As far as the anticancer potency of the different cannabinoids, the CB receptors agonists would be superior with respect to the FAAH inhibitors (1), particularly in the presence of CB receptor-expressing tumours (15), even though no experimental randomized study has been performed to compare the anticancer activity of the various cannabinoid agents. Moreover, the anticancer activity of CBN would be superior to that of CBD (16). Other studies, however, showed different results, and particularly it has been observed that CBD and CBG are more active than THC in the treatment of brain tumours, including glioblastoma (17). Another question regards the efficacy of cannabinoid association with respect to each single agent. Preliminary results would suggest that the association of cannabinoids may allow better results than the single cannabinoid (17). Unfortunately, despite the great number of experimental studies confirming the anticancer activity of cannabinoids, cannabinoid therapy of cancer is still at the beginning (18-20). In fact, at present the therapeutic use of cannabinoids is generally limited to the treatment of pai and other cancer-related symptoms, as well as with chemotherapy-induced side-effects. Moreover, along with cannabinoids, Cannabis plant contains several other potentially anticancer agents, including flavonoids and terpenes. Finally, it has to be remarked that at present it is still unclear whether the anticancer actions of cannabinoids may be a dose-dependent phenomenon (18-20).

IMMUNOMODULATORY EFFECTS OF CANNABINOIDS

The immunomodulatory effects of cannabinoids are still controversial, since they are the results of the different effects on macrophage system and on the different lymphocyte subsets. All studies agree to confirm the inhibitory action of cannabinoids on the inflammatory activity of macrophages, with the following inhibition on the secretion of their inflammatory cytokines, including IL-6, IL-1 beta and TNF-alpha, the main responsible for the onset of cachexia in the systemic diseases (1,2). The most controversial results regard the action of cannabinoids on TH1 lymphocytes, since their inhibitory action on lymphocyte proliferation (21) has not been confirmed by other studies (22). On the contrary, all authors confirm the inhibitory action of cannabinoids on the release of IL-17 from TH17 lymphocytes (23, 24). Then, the inhibitory action of cannabinoids on IL-17 secretion would constitute the main mechanism responsible for the anti-inflammatory action of cannabinoids, including CB agonists and FAAH inhibitors (1, 2, 23).

Moreover, the inhibitory action of cannabinoids on IL-17 secretion would already justify the employment of cannabinoids in the treatment of both cancer and autoimmune diseases, since IL-17 has been proven to directly stimulate cancer cell proliferation and angiogenesis (25), and to inhibit regulatory T lymphocytes (T reg), with a following predisposition to the development of autoimmune processes (26). Further studies, however, will be required to differentiate the effects of each cannabinoid agent on the cytokine network and cytokine secretion. CBD has appeared to inhibit the secretion of the immunosuppressive cytokine IL-10 and stimulate that of IL-12 (27). CBD has been proven to stimulate the secretion of IL-37 (28), which would represent one the three main antitumor cytokines in humans (29) in association with IL-2 (30) and IL-12 (31).

THE NEUROINFLAMMATORY ACTION OF CANNABINOIDS IN NEURODEGENERATIVE DISEASES

The endocannabinoid system plays a fundamental role in the inhibitory control of the neuroinflammation, which represent the common mechanisms responsible for the different neurodegenerative diseases (32), including Alzheimer's and Parkinson's diseases (33-36). Then, cannabinoids could be effective in the treatment of the neurodegenerative pathologies. Contrarily to the neoplastic diseases, for whom it is yet unclear whether the anticancer action of cannabinoids may be a dose-dependent phenomenon, as well as whether the combination of cannabinoids may enhance the efficacy of the single cannabinoid agent, in the case of neurodegenerative diseases it seems that the efficacy of cannabinoids may be a dose-dependent phenomenon (33-36), and that the combination of cannabinoid may allow better therapeutic results (28).

THE NEW PSYCHIATRY FOUNDED ON CANABINOID THERAPY

Despite the evidence of the psychotropic effects of cannabinoids in terms of modification of both consciousness and sensorial perception, as well as for their influence on mood and anxiety, very few clinical data are available about the pathological involvement of the endocannabinoid system in the psychiatric disorders, and the possible therapeutic use of cannabinoids in the treatment of anxiety, depression, and schizophrenia. Recently, one of the first mechanisms responsible for the depressive disease would consist of an enhanced production of IL-17 at brain level (37) as a consequence of a diminished activity of ACE2-angiotensin 1-7 brain axis (38), which plays a fundamental role in the modulation of mood and sense of force. On the other side, schizophrenia has appeared to be characterized by an enhanced endogenous cannabinoid production (39), which could be antagonised by the administration of cannabinoid anatagonists. At present, the only preliminary studies regard the therapeutic use of CBD, which has appeared to be effective in the treatment of anxiety and depression (40, 41). Moreover, it has been proven to reduce the hallucinatory experiences in patients with schizophrenia (41). Finally, some human unclear pathologies with both somatic and psychic disturbances, such as fibromyalgia, may achieve some benefits from CBD therapy (42).

CANNABINOIDS IN THE MEDIATION OF PLEASURE AND THE SPIRITUAL EXPERIENCE

CBD, CBN, CBG from Cannabis plant, and PEA from human body have no psychotropic activity, but on the contrary they may be effective in the treatment of anxiety and at least in part of depression. On the contrary, YJC from Cannabis and AEA and 2-AG from human body may exert psychotropic effects, consisting of amplification of both pleasure, including appetite and sex, and consciousness states. However, the use of cannabinoid psychotropic agents would require a mental preparation ant he eventual association with spiritual practices, such as yoga and other forms of spiritual meditation and devotion, since the modulation of the effects of cannabinoid psychotropic agents is not automatic but it need adequate psychospiritual preparation and education.

CONCLUSIONS

Because of the involvement of the endocannabinoid system in the regulation of the biological system and their pathologies, a real systemic and holistic medicine cannot exclude the employment of cannabinoid in the treatment of systemic human diseases, including cancer, autoimmunity and neuropsychiatric diseases, obviously not only in a palliative use, but also to influence the physiopathology of human diseases after a more complete investigation of the pathological role of the endocannabinoid system.

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