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Review Article

Pharmacodynamics of cannabinoids

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"Pharmacodynamics of cannabinoids "(i.e. a set of biological effects elicited in the living organism by interaction with its biochemical and biophysical functions up to the cellular level) is studied for a long time during both, physiological and pathological conditions. Cannabinoids received their names according to their natural occurrence as constituents of Cannabis sativa L. (marijuana). The species was classified in the "Linnaeus's Species Plantarum (1753)", the word "sativa" means things that are cultivated [1]. For ages, people have used cannabis-based preparations for healing and pain suppression until the discovery (in 1897) of aspirin (acetylsalicylic acid) which contemporary medicine uses until today. Chemical investigation of marijuana confirmed various cannabinoid-type components called cannabinoids (presently estimated at about 150). Regarding their possible pharmacodynamic effects, tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most explored. The determination of THC structure by means of nuclear magnetic resonance imaging increased sharply the number of professional scientific reports dealing with the studies of THC pharmacodynamic mechanisms of action [2]. Thus, it has been possible to verify THC specific binding sites in the vertebrate organisms including humans named "cannabinoid receptors" [3]. Subsequently, discoveries of endogenous cannabinoid receptor ligands were of high significance. The first such N-arachidonoyl-ethanol amide was isolated from the brain of a pig and called anandamide [4]. Subsequently, other endocannabinoids with various stimulatory, i.e. "agonistic" receptor activity were discovered: 2AG (arachidonoyl glycerin ether) [5], NADA (N-arachidonoyl dopamine) [6]. The last endocannabinoid identified virodhamine (O-arachidonoyl-ethanolamine), shows on the contrary, an "antagonistic" effect on the first discovered cannabinoid receptors, now called CB1 receptors [7]. The cannabinoid CB1 receptor was originally discovered in the central nervous system (in the cortex, basal ganglia, hippocampus, hypothalamus, cerebellum, spinal cord, spinal cord ganglia), then also in the enteric nervous system and on cells of fat, endothelial cells, liver, gastrointestinal tract.

Gradually, various scientific laboratories identified a number of other differential subtypes of cannabinoid receptors with various control functions in vertebrate tissues including humans:

- CB2 receptors on immune cells as well as in the CNS (especially on activated glial cells during neuropathies) [8].

- the orphan "**G P**rotein-coupled **R**eceptors": GPR55, GPR18, GPR119 [9].

- TRPV1, TRPV2, TRPA1, TRPM8 receptors ("**T**ransient **R**eceptor **P**otential" ion channels) with similar effects as capsaicin [10,11].

- PPAR receptors ("**P**eroxisome **P**roliferator-**A**ctivated **R**eceptors" nuclear receptors) [12].

All the findings mentioned above have induced further intensive research of the

physiological and pathophysiological roles of the system consisting of endogenous cannabinoids, enzymes involved in their synthesis and biodegradation and specific sites for their binding (receptors). This system named as the "Endocannabinoid System" [13] is active not only in the central nervous system but also in a wide variety of other tissues of vertebrates including humans. The physiological or potential pathophysiological activities of the Endocannabinoid System is intensively investigated, in particular, by the administration of specific cannabinoid receptor ligands (agonists, partial agonists, antagonists, inverse agonists) or by pharmacokinetic studies of biosynthesis and biodegradation of endocannabinoids. For example, biosynthesis of anandamide and 2-AG depends on the activity of N-acyl phosphatidyl ethanolamine-selective phospholipase D (NAPE-PLD) and diacylglycerol lipases (DAGLα and DAGLβ). Fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are involved in their release and degradation [14].

Endocannabinoids show neuromodulatory effects on the activity of other neurotransmitter receptor systems such as opioidergic, serotonergic, dopaminergic, nicotinic-acetylcholinergic, NMDAergic [15,16]. One possible explanation for such actions is the formation of "heterodimers" of specific receptors [17].

A comprehensive set of present knowledge on molecular pharmacological mechanisms of endogenous cannabinoids, biochemical pathways of their metabolism and subtypes of cannabinoid receptors, led to the proposal of new naming of these phenomena as "Endocannabinoidome" and "Phytocannabinoidome" respectively, in evaluating phytocannabinoids and their pharmacological properties [18].

Both experimental preclinical research and clinical studies (the "translational research") are investigating simultaneously all the findings described above. The attention is paid to the physiology and pathophysiology (e.g. during pain, inflammation, immune disorders, obesity and other metabolic disorders, cardiovascular and gastrointestinal diseases, neurodegenerative changes), as well as to possibilities of new therapeutic approaches using both, cannabinoids as well as substances with indirect effects on the endocannabinoid activities (e.g. endocannabinoid degradation inhibitors and others).

The substances of cannabinoid type are:

a) Endocannabinoids present in the vertebrate body, including humans.

b) Phytocannabinoids of plant origin.

c) Synthetic cannabinoids of various chemical classes with different activity at cannabinoid receptors (e.g. also blockers).

d) Endocannabinoid Like Molecules (ELMS) which do not bind to CB1 and CB2 receptors but activate GPR receptors or ion channels or nuclear receptors or affect endocannabinoid metabolism [19].

The findings achieved show that the physiological and pathophysiological activities of the endocannabinoid system are ubiquitous in the vertebrate organism, including humans [20]. The subject of scientific interest is, of course, the possibility of therapeutic use of plant and synthetic cannabinoids or other substances or mixtures of substances, which may affect endocannabinoid functions [21]. It is important to pay attention to the possible, repeatedly confirmed interactive synergism of cannabinoids, terpenoids, and flavonoids present in the cannabis which is called the "entourage effect" [22-25]. In other words, "entourage effect" means that the potential of the pharmacological action of the whole cannabis plant may be greater than that of the individual phytocannabinoids. The final effect may be the result of either "the pharmacodynamic" or "the pharmacokinetic" interactions of marijuana components.

The pharmacodynamic interactions may occur if some of the components have the same or at least similar influence on activities of the endocannabinoidome receptors. In the pharmacokinetic interactions, some of the plant components may improve the absorption or distribution of the therapeutically effective cannabinoids or reduce their biodegradation. Thus, to assess the therapeutic efficacy and potential adverse effects of cannabinoids, it is also important to evaluate the effect of the application method, the dosing as well as the combination of cannabinoids [19]. This was also the reason for the publication of a review on available clinical evaluations of the effects of THC, CBD, or THC+CBD applications in epilepsy, cancer, chronic pain, Parkinson disease, pediatrics, with concomitant opioids, and in relation to driving and hazardous activities [26]. The results of clinical trials described confirmed that the combined treatment reduced the psychoactive effect of THC and the development of tolerance to cannabinoid therapy. The review thus clarified how important is the ratio of THC and cannabidiol in cannabis preparations used for their therapeutic efficacy.

As regards the pharmacodynamics of individual plant cannabinoids, tetrahydro-cannabinol (THC) and cannabidiol (CBD) are probably the most explored.

Pharmacodynamics of tetrahydrocannabinol

(THC; delta-9-tetrahydrocannabinol; synthetic: dronabinol)

Examination of pharmacological mechanisms of THC confirms its binding to cannabinoid receptors CB1 and CB2 with partial agonistic activity. The CB1 receptor is present at a high density on the presynaptic level of the neuronal synapses, where its stimulation activates potassium channels and on the contrary, inhibits calcium-dependent channels, what results in inhibition of the neurotransmitter release. Concerning this mechanism of action mentioned, endocannabinoids are also called as the "Retrograde Synaptic Messengers" [13]. Even just partial agonistic action of THC on CB1 receptors may modulate a number of neurotransmitter systems, what can be a source of its psychoactive and analgesic effects [27]. Activation of CB2 receptors inhibits adenylyl cyclase and THC as a partial agonist of these receptors can elicit such an effect. Furthermore, also other pharmacological THC effects can be of receptor-mediated origin [28-31]:

a) Partial agonistic activity at the cannabinoid receptors GPR18 and GPR55;

b) Negative allosteric modulation of serotonergic 5HT3 receptors and opioid receptors μ and δ;

c) Inhibition of adenosine receptors END1;

d) Positive allosteric modulation of glycine receptors;

e) Agonistic activity at the TRPV2, TRPV3, TRPV4, TRPA1 ion channels;

f) Antagonism at the TRPM8 transient ion channel;

g) Agonistic influence at the PPARγ nuclear receptor.

Molecular pharmacological effects of cannabidiol

(CBD)

The exact chemical structure of cannabidiol isolated from cannabis oil [32] was determined by chemical methods in 1963 [33] what enabled an estimation of its potential therapeutic effects.

CBD influences the tone of the endocannabinoid system as well as of some other receptor systems due to its following pharmacological activities [30,34,36].

a) CBD acts as a negative allosteric modulator of the CB1 receptors, thereby reducing the efficacy of its agonists, e.g. of endogenous anandamide or THC (CBD itself does not have a psychoactive effect);

b) CBD acts as an antagonist/inverse agonist at the CB2 receptors;

c) CBD is an antagonist of cannabinoid receptors GPR18c;

d) CBD increases levels of anandamide due to its inhibitory influence on FAAH inactivating hydrolase;

(e) CBD acts at serotonergic receptors as an agonist of the 5HT1A subtype, a partial agonist of the 5HT2A subtype and a non-competitive antagonist of the 5HT3A subtype;

f) CBD may also activate adenosine A1A receptors; GABAergic GABAA receptors; nuclear PPARγ receptors; glycine ion channels;

g) CBD displays antagonist-like activity toward opioid sigma receptors (σ1R) what disrupts their regulatory association with the NR1 subunit of NMDA receptors

h) CBD may act as a non-selective inhibitor of the voltage-dependent sodium channels

Endocannabinoidome in health and disease, and the therapeutic use of cannabinoids

The endocannabinoid mechanisms in humans take part in a number of physiological processes, such as functions of the immune and cardiovascular systems, food intake control, fertility, pain modulation, memory, neuroprotection [37]. Thus, experimental studies focus also on the endocannabinoidome pathophysiology and possible therapeutic benefits of cannabinoid therapies.

The knowledge of the endocannabinoidome pathophysiology with findings of possible therapeutic interventions is the subject of interest of so-called "translation medicine" which deals with using knowledge gained from both the preclinical experimental studies and clinical trials [38,39]. Results of such scientific approach, narrowing the gap between the bench and bedside, provide practical applications for new treatments, development of drugs and health politics.

Attention, of course, still is also paid on the possibility of dependence development in the case of repeated use of cannabis or individual psychotropic cannabinoids (especially THC) with loss of control over their intake and psychic changes. These changes correspond in particular to the proven increase in activities of the so-called reward pathway in the dopaminergic ascending mesocorticolimbic system and a cascade of neuroadaptations in the central nucleus of the corticotropin-releasing factor (CRF), amygdala and glutamatergic changes in the corticostriatal projections of the CB1 receptors [40,41]. The withdrawal of psychotropic cannabinoid intake is then associated with opposite effects in the CNS followed by classical withdrawal symptoms such as impaired mood, irritability, anxiety, nausea, and craving after another dose, which also contributes to "down-regulation" of cannabinoid receptors CB1 [42]. Thus it is also important to control the above mentioned pharmacological mechanisms of cannabinoids in clinical trials that currently investigate the effects of different cannabinoids in more than 50 indications [43-45].

In clinical trials the most frequently tested were phytocannabinoids (D9-tetrahydrocannabinol, Δ9-tetrahydrocannabivarin, cannabinol, cannabidiol, cannabidivarin, cannabigerol, cannabichromene). It is important to take into account that the choice of a method of their extractions from the parent herb can have an impact on their pharmacological activity and therapeutic efficacy [30,45].

The Final Reports from the "lege artis" provided clinical trials with the participation of a high number of patients in the period of 1975-2015 reported positive cannabinoid therapeutic effects in a significant number of cases evaluated. The summery was published in the journal "Critical Reviews in Plant Sciences (Impact Factor 6.825; in the year of publication) which is devoted to the current results of a wide variety of disciplines dealing with the various scientific perspectives of plant research [43]. This report confirmed the positive evaluation of the therapeutic effects of marijuana and cannabinoids in indications: nausea and vomiting during chemotherapy and radiotherapy; support of appetite HIV/AIDS positive in patients or suffering from cancer; neuropathic or other chronic pain; spasticity in multiple sclerosis.

The available large meta-analyses of clinical studies aimed at evaluating the therapeutic potential of cannabinoid substances brought, for example, the following conclusions:

a) The results of 79 randomized placebo-controlled clinical trials (6 462 patients) evaluating the effects of cannabidiol, dronabinol, nabilone, and nabiximols (THC / CBD) confirmed the therapeutic efficacy in the following indications [46]:

- chronic pain; spasticity (with the best effects);

- nausea and vomiting during chemotherapy; Tourette syndrome; sleep disorders; weight control in HIV/AIDS positive patients; psychoses (with the lower effects);

- anxiety; glaucoma (with the lowest effects).

On record were the following side effects: dizziness, dry mouth, nausea, fatigue, sleepiness, elation, vomiting, disorientation, confusion, loss of balance, hallucinations.

b) Also the review of results obtained from the "lege artis" clinical studies published in the year 2016 confirmed the therapeutic potential of cannabinoid therapies in: multiple sclerosis and epilepsy; pain and spasticity; nausea and vomiting; eating disorders; glaucoma; epilepsy; stress and anxiety; schizophrenia; carcinoma; neuro-protection [47].

An important criterion in assessing the results of clinical trials is also the safety of patients included in diagnostic and screening treatment interventions. For example, the international open access journal "Drug, Healthcare and Patient Safety" published a review dealing with the evidence-based analysis of the cannabinoid therapeutic potential; the authors stated that cannabinoids are a suitable alternative to classical treatments for patients suffering from epilepsy, movement disorders, and pain. As a further possible choice are mentioned patients with multiple sclerosis, digestive tract disorders, anorexia, and multiple myeloma [48].

Further meta-analysis using the methodology "Grading of Recommendations Assessment, Development and Evaluation" compared the efficacy, tolerability, and safety of cannabinoid palliative treatment with herbal Cannabis, plant-based or synthetic cannabinoids, or placebo In nine studies, patients (a total of 1561) received either cannabinoid or placebo therapy because of cancer, or HIV–AIDS, or dementia, heart disease, lung disease, and liver disease. The results did not provide a clear recommendation for the use of palliative cannabinoid treatments in patients with cancer, HIV–AIDS, or dementia. Thus, the authors recommend urgent further clinical research to obtain evidence-based data on the efficacy and safety of cannabinoids utility in palliative care [49].

In addition to assessing the possible risks of using marijuana and cannabinoids on psychosocial relationships and human health, a 16-member team of experts selected by the National Academy of Sciences, Engineering and Medicine (http://www.nationalacademies.org/) controlled also their possible therapeutic effects. The conclusions of this expert report published state [34]:

a) The sufficient availability of evidence of cannabinoid efficacy for treatment in adults suffering from chemotherapy-induced nausea, for the therapeutic efficacy of cannabinoids in the treatment of adult pain, chemotherapy-induced nausea and vomiting, and spasticity associated with multiple sclerosis.

b) The average evidence of cannabinoid treatment in secondary sleep disorders.

c) The limited availability of evidence for application in indications of anorexia, Tourette's syndrome, anxiety, post-traumatic stress, cancer, irritable bowel syndrome, epilepsy, and various neurodegenerative disorders.

Besides the human medicine, also veterinarians investigate the potentiality of the therapeutic use of cannabinoids in order to protect the health and wellbeing of the animals. (http://www.veterinarycannabis.org/) [50,51].

The further development of methods enabling research of the physiological and pathophysiological endocannabinoidome processes in both translational animal models and in clinical trials can provide further answers to questions dealing with the possible therapeutic use of cannabinoid therapy, its efficacy, tolerability, and safety. This, for instance, is also a part of the program, of the International Cannabinoid Research Society (http://icrs.co) and the International Cannabis and Cannabinoids Institute in Prague (https://icci.science/).

Declaration

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