An Outline of Molecular and Cellular Endocannabinoid Functioning in the Nervous System

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***Abstract* — The endocannabinoid system modulation is already a relevant method used for therapeutic purposes. It has been analyzed extensively in the last two decades, showing promising results and reliable future possibilities. The activity of cannabinoid receptors and their ligands - exogenous, endogenous and synthetic, as well as of the according enzymes has been mapped and described, in order to understand better the physiological mechanisms of the human body, together with the involvement in different illnesses. The studies targeting endocannabinoid system offered new pharmacological opportunities and more facts are proposed for upcoming exploration or medical use. The nervous system has been given a lot of attention by the scientists and the information gathered already serves as basis for treatment and for oriented further investigation. The resultative implications of cannabinoid medicines in numerous pathological conditions are conferring a priority for them in the arising standards. .**

***Index Terms* — Cannabinoid receptors, endogenous ligands, nervous system, therapeutic implications.**

I. INTRODUCTION

Cannabinoids in general are low-molecular-weight lipophillic compounds, with a varying degree of affinity at specific cannabinoid receptors. Researchers T.B Wood, W.T.N. Spivey and T.H. Easterfield isolated the first cannabinoid substance from Cannabis sativa plant, cannabinol, in 1896, in the Agricultural Chemistry Laboratory in Cambridge, UK and R.S Cahn proposed its chemical structure in the 1930s. The major phytocannabinoid, called delta-9-tetrahydrocannabinol (Δ^9-THC), was isolated and described in 1964 by the team of Y. Gaoni and R. Mechoulam in Israel [1,2]. It was the biggest milestone of the direction to that day, and the pharmacology of cannabinoids has been extending since.

R. Mechoulam working together with W. Devane discovered anandamide (named after the Sanskrit 'ananda' meaning bliss or joy), the first human endocannabinoid to be known, in 1992, and 2-arachydonoylglycerol, the second major one, also in his laboratory, in 1995 [3,4]. The first specific receptor, referred CB1 'cannabinoid binding', was discovered in 1988 by A.C. Howlett from US, then cloned in 1990 by japanese team of L.A. Matsuda and colleagues. Afterwards, CB2 has been identified and cloned in 1993 by S. Munro in Cambridge, UK [5,6,7]. These exquisite advancements made in less than 10 years led to acquiring even more information. In such way, unprecedented volume of studies on the topic were conducted and published by now.

The human endocannabinoid system consists of cannabinoid receptors (CB1, CB2 and other non-specific), cannabinoid naturally synthetized human ligands (anandamide, 2-arachydonoylglycerol 2-AG, virodhamine, oleamide OEA and others), plus the enzymes and cofactors taking part in the biosynthesis and degradation characteristic processes. The CB receptors bind the phytocannabinoids, endocannabinoids and synthetic cannabinoids that have analogue or antagonist action with the representatives from the first two groups or the enzymes participating in their cell fate [8].

This article is an introductory review based on the medical literature regarding the endocannabinoid system, focusing within the nervous system and emphasizing the physiological and biochemical mechanisms, consequently the therapeutic values, based on the cellular biology implied.

II. THE CB1 RECEPTOR

The endogenous cannabinoid system includes two major receptors: CB1 and CB2. The CB1 receptors are the most abundant G protein-coupled receptors in the central nervous system. They have a density 10 to 50 times greater than that of dopaminergic and opioidergic receptors. Electron microscopy studies demonstrated CB1 receptors being predominantly on presynaptic terminals [9]. They are found mainly in the CNS in brain areas such as the globus pallidus, the hippocampus, the cerebral cortex, the hypothalamus, the cerebellum, amygdala, the striatum, the mesencephalic periaqueductal gray matter and other regions. Some parts of the brain display a moderate density (neocortex, basal amygdala, medial hypothalamus, solitary nucleus), while others like the thalamus and brain stem exhibit lower levels of CB1 receptors. The CB1 receptors are found at periphery as well, in reproductive, cardiovascular, locomotory and gastrointestinal systems, also lungs, kidney, thyroid gland and adrenal gland, either in nerves or tissue cells [10].

The CB1 receptors are coupled with Gi or Go protein, negatively to adenylate-cyclase (adenylyl-cyclase), thus attenuating the production of cAMP, and positively to mitogen-activated protein kinase (MAP). The CB1R are also coupled to ion channels through Gi/o proteins, positively to A-type and inwardly rectifying

potassium channels, and negatively to N-type and P/Q-type calcium channels and to D-type potassium channels.

Based on these findings, it has been suggested that cannabinoids play a role in regulating neurotransmitter release. Inhibition of presynaptic calcium channels by cannabinoids decreases neurotransmitter release from CB1-expressing presynaptic terminals [11].

Endocannabinoid-mediated activation of CB1 receptors on neurons inhibits neurotransmission in many brain regions, including striatum, hippocampus, cerebellum, cortex, hypothalamus, and nucleus accumbens, and also inhibits release of neuropeptides from CB1 receptor-containing nerve terminals. Inhibition of Ca^{2+} channels and stimulation of K^+ channels both contribute to inhibition of neuronal excitability and suppression of neurotransmitter release [10,12]. A schematic view is presented in *Fig. 1*.

The CB1 receptor expression was detected in regions influencing a number of major functions, among which mood and emotions, motor coordination, autonomic function, memory, sensation and cognition [13,14].

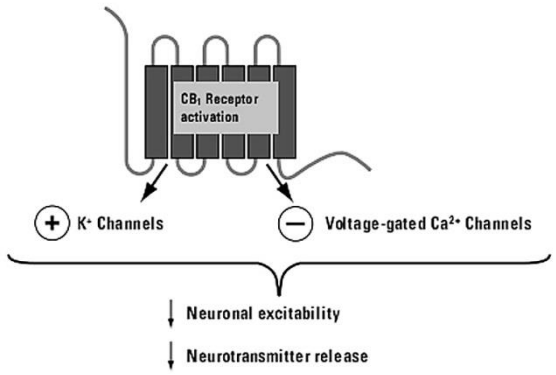

Figure 1. Inhibition of Ca^{2+} channels and stimulation of K^+ channels both contribute to the inhibition of neuronal excitability and the suppression of neurotransmitter release.

CB1 receptor activation leads to inhibition of voltage-gated Ca^{2+} channels, involving decreased neurotransmitter discharge. Inhibition of adenylate cyclase downstreams several signaling. The onset of K^+ channel induces hyperpolarization of the cell with subsequent decrease in neurotransmitter release. Both mediations serve in balancing neuroprotection and neuroadaptation.

The CB1 receptors, among stated, play an important role in the central and peripheral regulation of food intake, fat accumulation, energy metabolism and homeostasis [13,15].

III. THE CB2 RECEPTOR

The CB2 receptor is also coupled to Gi/o proteins and thereby negatively coupled to adenylate-cyclase and the cAMP pathway in various types of cells, and it stimulates mitogen activated protein kinase (MAPK) cascades. Inwardly rectifying potassium channels can also serve as a signaling mechanism for the CB2. This receptor is located principally in peripheric tissues of the immune system, as those of spleen, tonsils and thymus, also on the surface of immune cells like monocytes, macrophages, B-cells, T-cells, besides that in central and peripheral nervous structures as well [9,16].

The most prominent staining for CB2 receptor in CNS was observed in the anterior olfactory nucleus, in the neurons of the piriform, orbital, visual, motor and auditory cortex. Glial cells, also display from moderate to dense CB2 specific immunostaining. Some thalamic nuclei exhibit prominent cell bodies with CB2 markers, and reticular thalamic nucleus contain a dense plexus of CB2 immunoreactive fibres [12].

Moderate density of CB2 immunopositive cell bodies were found in the periaqueductal gray (PAG), substantia nigra pars reticulata, and other nuclear structures of the brain stem, together with Purkinje cell bodies of the cerebellar lobules [17].

The CB2 receptors can modulate immune cell migration and cytokine release in periphery and in the brain. The gathered knowledge about cannabinoid receptors revealed that both of them control central and peripheral functions such as cellular functions, neuronal development, neurotransmission, inflammation, cardiovascular, reproductive and hormonal functions, energy metabolism, antinociception, muscle development, skin protection as well as therapeutic possibilities and osteopathic perspectives in numerous pathological conditions including cancer [11,18].

IV. OTHER TARGETS

Among other endocannabinoids (eCBs) binding structures there are surface non-cannabinoid receptors, ion channels receptors and nuclear receptors. A structure noted GPR55, a new G protein-coupled receptor has been identified as a cannabinoid receptor, which favours neuronal excitability. Moreover, it has also been discovered that anandamide is an endogenous activator of the transient receptor potential, vanilloid sub-type, TRPV1 receptor [8]. TRPV1 is activated by inflammatory factors and nerve growth factors. It is found on dopamine neurons in the substantia nigra, on pyramidal neurons in the hippocampus, the locus ceruleus and several cortical layers [9].

There is a specific interaction between anandamide and an intracellular site of TRPV1. The effect of anandamide on this channel can be diminished or blocked by specific antagonists of TRPV1, whereas it is not affected by antagonists of CB receptors. Noteworthy, 2-AG does not activate TRPV1 receptors. The action of eCBs on dopamine transmission may be mediated via TRPV1 receptors [19]. Anandamide and analogues are full TRPV1 agonists, while Δ^9-THC does not bind vanilloid receptors. Endocannabinoids also interact with nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs), a family divided in three sub-types α, β, γ, all of them expressed in the nervous system. Anandamide activates PPAR α and γ subtypes. In addition, oleamide and anandamide have a high affinity for the binding site of PPAR, which confer them anorexigenic, anti-inflammatory, neuroprotective, anti-

seizure, cognitive enhancing and anti-addictive properties [19,20].

V. BIOSYNTHESIS AND DEGRADATION OF MAIN ENDOGENOUS LIGANDS

The endogenous ligands, like major AEA and 2-AG, are not stored in resting cells but unlike other mediators they are synthesized and released 'on demand', when and where necessary, following physiological or pathological stimuli, in a way depending upon Ca^{2+} influx, either on activated metabotropic and ionotropic receptors. The synthesis of AEA and 2-AG is associated with the formation of non-cannabimimetic, or weakly cannabinoid receptor active compounds, such as N-acyl-ethanolamines and 2-acylglycerols, which have been suggested to potentiate the effects of endocannabinoids, known under the name of 'entourage compounds' or 'entourage effect' [21].

There are several alternative pathways and enzymes for the biosynthesis and inactivation of AEA and 2-AG. Anandamide was suggested to come from phospho-anandamide, a product of the hydrolysis of N-arachidonoyl phosphatidyl ethanolamines (NArPE), catalysed by a phospholipase-C-like enzyme. An tyrosine phosphatase was identified as the most likely enzyme responsible for phospho-anandamide hydrolysis to anandamide. Another possible route for anandamide formation is via the sequential cleavage of the two acyl groups of NArPE, catalysed by a/b-hydrolase, followed by phosphodiesterase-mediated hydrolysis of glycerophospho-anandamide to anandamide. The cellular biosynthesis of endocannabinoid anandamide might also occur via conversion of NArPE into 2-lyso-NArPE by phospholipase A2, followed by the action of phospholipase D [16,22]. A putative endocannabinoid membrane transporter (EMT) involved in the cellular uptake of endocannabinoids may also be involved in their release. Besides that, transportation of anandamide and 2-AG, when present in the extracellular space, can also take place by facilitated diffusion, in neurons or any other cells. However, a specific anandamide transporter protein has yet to be cloned. Regarding the intracellular degradation of anandamide it has been concluded that it is mediated predominantly by fatty acid amide hydrolase (FAAH) that breaks it down to arachidonic acid and ethanolamine [22,23]. The endocannabinoid 2-AG is synthesized in most cases from the hydrolysis of diacylglycerols containing arachidonate in the 2nd position (DAGs), catalysed by a specific DAG lipase known of two forms – DAGLa and DAGLh. The molecule of 2-AG can also be formed in pathways from both phosphatidylcholine and phosphatidic acid by the action of DAG lipase [24,25]. Intracellular 2-AG could be esterified into neutral lipids and is inactivated in a one-step reaction, being catalyzed by monoacylglycerol lipase (MAGL) [25].

Ethanolamine, arachidonic acid and glycerol, the hydrolysis products of AEA and 2-AG are recycled into the membrane, in order to be used again for synthesis of eCBs and for membrane structuring. It was also established that AEA and 2-AG can be enzymatically transformed into prostaglandin ethanolamides (prostamides) and prostaglandin glyceryl esters [26].

Other potential catabolic pathways for the endocannabinoids employ the enzymes of the arachidonate cascade, like cyclooxygenase-2, lipoxygenases and cytochrome p450 enzymes, all reported and reviewed [21,23].

VI. BASIC ENDOCANNABINOID NEURONAL ACTIVITY

The first demonstration of retrograde endocannabinoid signaling came from the discovery that eCBs mediate forms of short-term synaptic plasticity known as depolarization-induced suppression of inhibition (DSI) by Ohno-Shosaku et al. and separately by Wilson et al., both in 2001, and depolarization-induced suppression of excitation (DSE) by Kreitzer in the same year [27]. It was later shown that eCBs also mediate presynaptic forms of long-term depression (LTD) at both excitatory and inhibitory synapses [28]. Endocannabinoids have since emerged as the best characterized retrograde messengers, with numerous examples of short- and long-term synaptic plasticity reported throughout the brain (*Fig. 2*).

Their localization at neuronal terminals strongly suggests that cannabinoid receptors play important roles in regulating synaptic function. The CB1R activation inhibits and controls neurotransmitter release at synapses with glutamate, acetylcholine or noradrenaline communication, through two main mechanisms. For short-term plasticity, in which CB1Rs are activated for a few seconds, the mechanism involves direct G protein-dependent inhibition of presynaptic Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCCs) [30]. For long-term plasticity, the predominant mechanism requires inhibition of adenylyl-cyclase and downregulation of the cAMP/PKA. The expression mechanism for eCB-LTD may involve presynaptic proteins Rab3B/RIM1or a reduction of P/Q-type of VGCCs [29,31].

While 2-AG seems to be the head eCB required for activity-dependent retrograde signaling, the functional crossing between 2-AG and AEA signaling was reported, and recent findings suggest that 2-AG and AEA can be recruited differentially from the same postsynaptic neuron, depending on the type of presynaptic activity [13,28]. Growing evidence indicates that glia participate in eCB signaling. The synthetic machinery for eCB production was observed in oligodendrocytes, astrocytes, and microglial cells [30,32]. Likewise, cultured astrocytes and microglial cells can produce 2-AG or AEA.

Several findings support a role for eCBs signaling to astrocytes and their ability to indirectly mediate synaptic function [31,33]. Astrocytes may have long-distance neuromodulatory effects that are mediated by eCB signaling. Endocannabinoid mediated neuron-astrocyte communication has also been implicated in long-term plasticity [32].

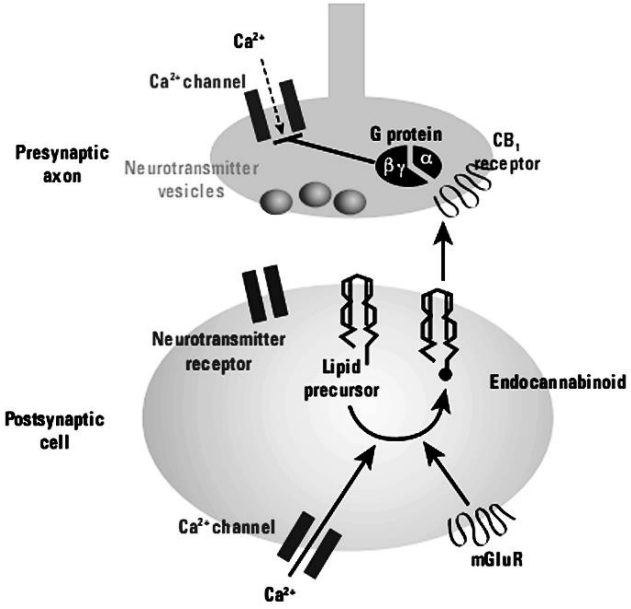

Figure 2. Essentials of retrograde signaling conducted by endocannabinoids.

Endocannabinoid synthesis in response to direct depolarization is strongly dependent on increased intracellular Ca^{2+} influx, which may synergize with the activation of metabotropic glutamate receptors (mGluR) as well as phospholipase C-linked receptors (GPCR) to further stimulate endocannabinoid production. Postsynaptic depolarization opens voltage dependent Ca^{2+} channels that activates enzymes to synthetize eCBs from membrane lipid precursors. Activation of mGluR can also generate eCBs likely by activation of phospholipase C. Endocannabinoids leave the postsynaptic cells and activate presynaptic CB1 receptors. G protein activation liberates Gβγ and inhibits presynaptic Ca^{2+} channels, which decreseas the neurotransmitter release.

Adapted from Wilson RI et al. [29]

In addition to the classical, activity-dependent phasic mode of eCB mobilization, tonic eCB signaling has been reported. Tonic signaling can be observed as an increase in basal synaptic transmission after pharmacological blockade of CB1Rs [34].

The fact that most 2-AG is hydrolyzed by MGL suggested that 2-AG mediates tonic eCB signaling, which is consistent when happening release of 2-AG in cultured neurons. AEA can also contribute to tonic eCB signaling. Chronic inactivity in neuron cultures reduced the AEA tone by augmenting AEA uptake and degradation. Together, these studies suggest that tonic eCB signaling can control in some conditions basal synaptic neurotransmitter release [33].

VII. THERAPEUTIC POTENTIAL OF CANNABINOID MEDICINES

Currently, three synthetized medicines that activate cannabinoid CB1/CB2 receptors are in the clinics of the countries that approved it: Cesamet (or Nabilone; synthetic mixture of THC isomers), Marinol (Dronabinol; also THC) and Sativex (THC with cannabidiol CBD) [35,36]. These can be prescribed for the amelioration of chemotherapy-induced nausea and vomiting (Cesamet and Marinol), stimulation of appetite (Marinol), and symptomatic relief of cancer pain or management of neuropathic pain and spasticity in adults with multiple sclerosis (Sativex), as protocoled examples [37].

Authors provide an up-to-date account of where the field stands and underline additional reliable therapeutic targets for cannabinoid receptor agonists [12,20]. These include other types of pain, like different forms of migraine as well as fibromyalgia, epilepsy, anxiety, depression, Parkinson disease, Alzheimer's, Huntington disease, amyotrophic lateral sclerosis, stroke and ischemia, a variety of cancer types, drug dependence, glaucoma, osteoporosis, sepsis and hepatic, renal, intestinal and cardiovascular disorders [26,37,38].

Therefore, the CB receptors agonist are indicated to be used for medication as potential hypnotics, wide range analgesics, antiemetics, antiasthmatics, antihypertensives, immunomodulatory drugs, anti-inflammatory and neuroprotective agents, antipsychotics, antiepileptics, for treating spasticity and other movement disorders, post-traumatic stress disorder and alcohol or cocaine dependence and withdrawal [17,19,39].

There are several potential strategies for improving the efficacy and benefit-to-risk ratio of these agonists in the standard usage. It is notably used the targeting of cannabinoid receptors in the brain, CBRs located outside the blood-brain barrier, CBRs expressed by a particular tissue, upregulating cannabinoid receptors, together with selective targeting of cannabinoid CB1 or CB2 receptors and/or adjunctive 'multi-targeting' [40].

In conclusion, the medical utility derives either as using agonists and phytocannabinoids stimulating the activity of the endocannabinoid system, or antagonists that are preventing the binding of endogenous ligands and thus inhibiting the activity in certain locations and conditions

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