The Role of Endocannabinoid System

Subjects: Pharmacology & Pharmacy

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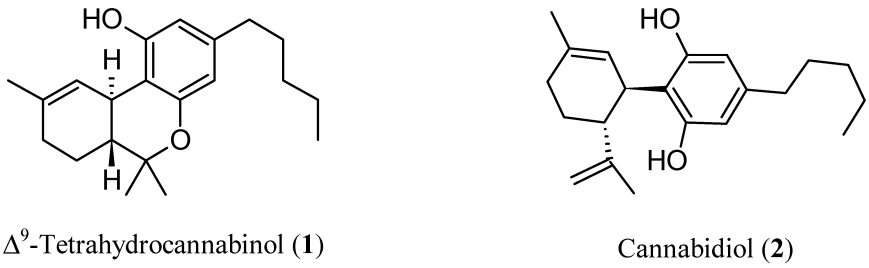
The endocannabinoid system (ECS) is one of the most relevant neurotransmitter systems in the brain and plays a pivotal role in the regulation of cognitive abilities, mood, stress, and sleep.

endocannabinoid system FAAH inhibitors MGL inhibitors repositioning

1. Introduction

The endocannabinoid system (ECS) is one of the most relevant neurotransmitter systems in the brain and plays a pivotal role in the regulation of cognitive abilities, mood, stress, and sleep [1]. Relatively fewer explored targets for antipsychotic treatment could be found in ECS. Thinking about cannabinoids, the minds run to the well-known pro-psychotic properties of Δ^9-tetrahydrocannabinol (THC, **Figure 1**), the main psychoactive ingredient of cannabis, which acts as an agonist on cannabinoid (CB) receptors (CBRs). In addition to its pro-psychotic potential, THC causes an undesirable behavioral tetrad, that is, analgesia, catalepsy, hypothermia, and hypolocomotion. THC synthetic analogs, both agonists and antagonists [2][3], or recreational drugs—the so-called NPS (new psychoactive substances) [4][5]—are generally tainted with severe side effects. The worst is that the activation of CBR of type 1 (CB_1R) in the central nervous system (CNS) by xenobiotics can lead to irreversible effects [6]. On the other hand, (−)-trans-cannabidiol (CBD, **Figure 1**), one of cannabis' main secondary metabolites, seems to be endowed with antipsychotic properties useful to protect against the pro-psychotic effects of THC: depending on its composition, cannabis would act either as Mister Hyde (i.e., a risk factor for psychosis) or as Doctor Jekyll (i.e., an antipsychotic). The hypothesis has been formulated that CBD could be an antipsychotic, with benefits in preventing psychotic disorders, whatever the cause (endogenous or THC-induced) [7].

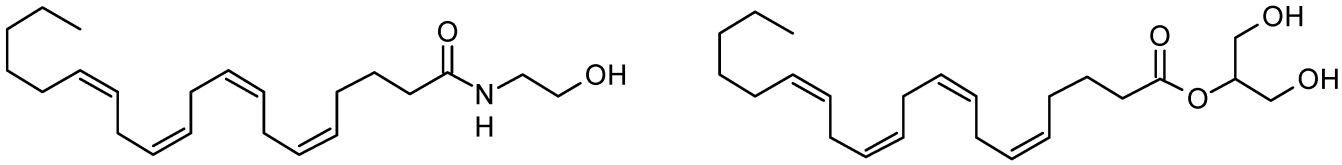


Δ^9-Tetrahydrocannabinol (**1**) Cannabidiol (**2**)

Figure 1. Chemical structures of Δ^9-tetrahydrocannabinol (THC, **1**) and cannabidiol (CBD, **2**).

In a randomized, double-blind controlled clinical trial, CBD exerted antipsychotic properties comparable to the reference drug amisulpride [8][9]. Interestingly, the reduction of psychotic symptoms was significantly associated

with an increase in the serum concentrations of *N*-arachidonoylethanolamine (anandamide, AEA, **Figure 2**), which is the most important endogenous ligand of CBR, and this outcome was found only in patients treated with CBD. The results indicated that, at least in part, the antipsychotic activity of CBD was due to the inhibition of the enzymes physiologically devoted to the degradation of AEA [10], thus acting as an indirect agonist. This finding agrees with the observation that both increased availability of CB_1R and upregulation of AEA seem beneficial, although the underlying mechanisms are mostly elusive. The evidence supporting the possible protective role of AEA in schizophrenia has been reviewed [11].



N-Arachidonoylethanolamine (**3**) 2-Arachidonoylglycerol (**4**)

Figure 2. Chemical structures of *N*-arachidonoylethanolamine (anandamide, AEA, **3**) and 2-arachidonoylglycerol (2-AG, **4**).

The inhibition of enzymes responsible for the degradation of the ECS endogenous ligands might overcome the above obstacles to the systemic use of exogenous substances acting on ECS. EC degradation inhibitors would provide focused action, where and when necessary, by acting as endogenous CBRs ligand modulators.

2. Endocannabinoid System

The exhaustive description of ECS architecture and functioning is beyond the scope of this work; more details can be found elsewhere [12][13]. The right functioning of the ECS is related to the natural balance established between its main components, which are CBRs, the endogenous ligands binding them, and the enzymes involved in the synthesis, transport, and degradation of ECs. A disruption of the physiological activity of this system (i.e., modifications in the expression of receptors or the functions of enzymes) is associated with various pathologies. This situation, therefore, is the basis for therapeutic pharmacological opportunities founded on drugs able to interact naturally with ECS [14][15][16][17][18].

The discovery of CBRs and the main endogenous ligands is relatively recent, as the first one, CB1R, was identified in the second half of the 1980s [19], while the second receptor, namely CB_2R, was discovered a few years later [20]. The two targets differ in their corresponding main functions, signaling processes, and structural aspects [21][22]. Their signal neurobiology and tissue distribution are also different, being the CB_1R mainly expressed in the CNS (mostly in the basal ganglia, cerebellum, cortex, and hippocampus), whereas CB_2R is particularly present in the immune system (mostly in B-cells and natural killers) [23]. Overall, it is demonstrated that CBR, through their activation, performs a key role in inducing activation or depression of neurotransmission by the inhibition of adenylate cyclase, which determines a decrease in cyclic adenosine monophosphate levels, or, only in the case of CB_1R, by the coupling with ion channels [23][24]. A careful analysis of the above characteristics, in particular those

related to the different tissue distribution, is important when envisioning a pharmacological therapy aiming at a selectivity of action and the consequent reduction of undesired effects.

The main and most studied CBR endogenous ligands are AEA [25] and 2-arachidonoylglycerol (2-AG) [26][27] (**Figure 2**).

Both ligands are produced on demand from membrane phospholipids to satisfy contingent physiological needs due to intense neuronal activation [28][29]. AEA and 2-AG act through a retrograde or non-retrograde signaling pathway. Their half-life is short (a few minutes) as a rapid carrier-mediated diffusion occurs in the cells where they are metabolized [28][29]. It is very interesting to consider that ECs-mediated retrograde signaling is involved in the excitatory or inhibitory processes related to the modulation of neurotransmitters, such as glutamate or γ-aminobutyric acid [29][30][31][32], through short-term and long-term neuroplasticity (taking some seconds and some minutes, respectively) physiological processes [33][34]. The first is involved in processes such as depolarization-induced suppression of inhibition and depolarization-induced suppression of excitation through the inhibition of voltage-gated Ca^{2+} channels, whereas the second one leads to the long-term depression phenomenon through a CB_1R repeated stimulation of these brain circuits. Consequently, CBR has to be considered a potential drug target for the prevention and treatment of neurologic pathologies, in particular, in the case of CNS involvement [35].

AEA is biosynthesized by the *N*-acyl phosphatidylethanol-selective phospholipase D [36]. It acts as a total or partial agonist of the CB_1R and has low activity toward CB_2R [37]. AEA comes up against rapid degradation due to its capture by a transporter [38][39], as occurs in the extracellular space of brain neurons and astrocytes [17], which is followed by the degradative action mainly carried out by fatty acid amide hydrolase (FAAH) [40][41][42][43], a homodimer integral membrane protein. The functional component of the enzyme consists of a catalytic triad formed by the amino acids Lys142-Ser217-Ser241, with the latter determining the nucleophilic attack on the electrophilic carbonyl group of AEA through the hydroxy group [44].

The biosynthesis of 2-AG begins with diacylglycerols and hydrolysis operated by the diacylglycerol lipase isoform α or β [45][46]. It acts as a full agonist of both CB_1R and CB_2R [47]. In addition, in the case of 2-AG, therefore, the molecule is captured by a transporter with characteristics identical or similar to those shown by AEA [48], which causes internalization and subsequent hydrolysis mainly by monoacylglycerol lipase (MGL) [49][50][51], an enzyme belonging to the α/β hydrolase superfamily. The mechanism involves the participation of various amino acids, which contribute to the initial preparatory phase aimed at catalytic activity by the Ser122-Asp239-His269 triad, where the serine residue is responsible for the nucleophilic action towards the carbonyl group of the substrate [52][53].

Taken together, the ECS certainly constitutes a reference model for drug discovery endeavors aimed at finding ideal molecules without the undesirable effects caused by the direct activation of CBRs [54].

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