The Emerging Role of the Endocannabinoid System in the Sleep-Wake Cycle Modulation

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Abstract: The endocannabinoid system comprises amides, esters and ethers of long chain polyunsaturated fatty acids. *N*-arachidonoylethanolamide (anandamide; ANA) and 2-arachidonoylglycerol (2-AG) are endogenous cannabinoids (endocannabinoids) ligands for the cannabinoid family of G-protein-coupled receptors named CB_1 and CB_2. Endocannabinoids are released upon demand from lipid precursors in a receptor-dependent manner and behave as retrograde signaling messengers, as well as modulators of postsynaptic transmission, interacting with other neurotransmitters systems. The two principal enzymes that are responsible for the metabolism of ANA and 2-AG are fatty acid amide hydrolase and monoacylglycerol lipase, respectively. Pharmacological experiments have shown that the administration of endocannabinoids induce cannabimimetic effects, including sleep promotion. This review will focus on some of the current evidence of the pharmacological potential of the endocannabinoid system on sleep modulation.

Keywords: Anandamide, cannabinoids, cannabidiol, rapid eye movement sleep, cannabinoid receptors, VDM-11.

INTRODUCTION

Exogenous Cannabinoids

During centuries, *Cannabis sativa* has been used in diverse cultures for mystical ceremonies, social interaction as well as for treatment of diseases [1-6]. The principal active compound of this plant, delta-9-tetrahydrocannabinol (Δ^9-THC), was discovered by Gaoni and Mechoulam in 1964 [7]. It has been shown that *Cannabis sativa* can be used for therapeutic purposes, such as decreasing intraocular pressure in patients with glaucoma [8], and the treatment of muscle dysfunction in people suffering with multiple sclerosis [9]. Also, it reduces pain and nausea produced by both, chemotherapy in patients with terminal can

Despite the positive effects reported about the use of *Cannabis sativa* in several diseases, the administration of either *Cannabis sativa* or Δ^9-THC induces negative effects such as DNA fragmentation and apoptosis [1, 3, 11-16]. Behaviourally, it is known that injection of Δ^9-THC facilitates hypomotility, hypothermia, and antinociception [1, 3, 13, 17, 18]. It is accepted that most of the cellular and behavioural effects caused by the cannabinoids are *via* the activation of the cannabinoid receptor system.

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CANNABINOID RECEPTORS

The cannabinoid receptors are G-protein coupled proteins composed of seven transmembrane spanning helices interconnected by three intracellular loops and three extracellular loops. The family of the cannabinoid receptors includes the CB_1 and CB_2 subtypes [19].

The CB_1 Cannabinoid Receptor

The description of the presence of the CB_1 cannabinoid receptor in the central nervous system (CNS) was achieved by Herkenham *et al*., using quantitative radiography, these authors described that the distribution of the CB_1 cannabinoid receptor includes areas such as cortex, hippocampus, striatum, limbic system, cerebellum, and brainstem [20]. The results were confirmed by Matsuda and co-workers (1990) as well as by further studies [21-29]. Noteworthy, the neuroanatomical distribution and density of the CB_1 cannabinoid receptor in a human brain has brought tentative perspectives about the role of the endocannabinoid system modulating diverse behaviours [22, 26, 28, 30]. For example, brains of patients that suffered from Huntington's disease showed a decrease in density of CB_1 cannabinoid receptors (97%) compared to healthy controls [31].

Regarding the mechanism of action of the CB_1 cannabinoid receptor, it includes the inhibition of cAMP formation [19, 32, 33] as well as a modulation in the neurotransmitters release. For example, the activation of the CB_1 cannabinoid receptor inhibits of calcium (Ca^{2+}) channels types P, Q and N and activates of the potassium (K^+) channels [34-38]. The intracellular mechanism of action of the CB_1 cannabinoid receptor is shown in Fig (**1**).

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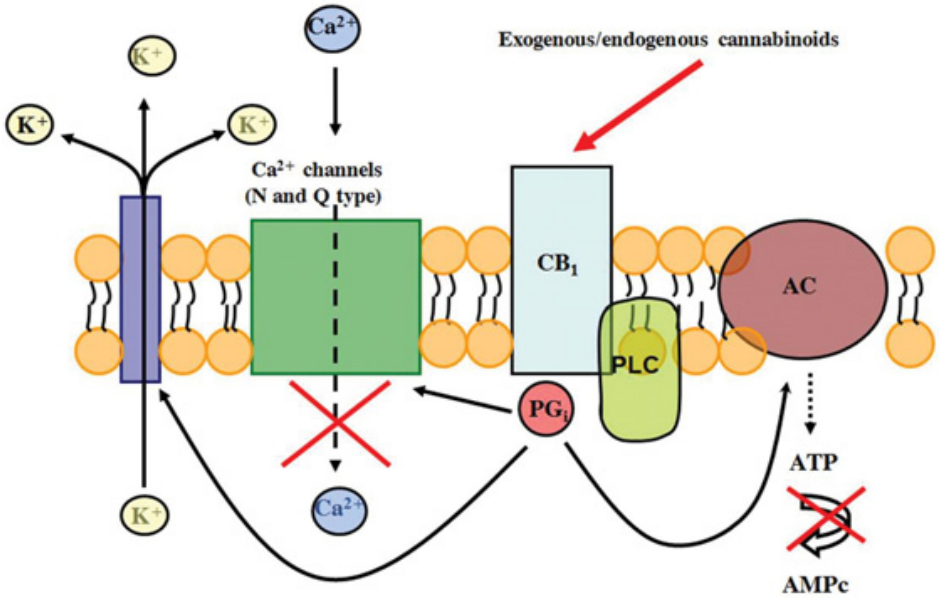

Fig. (1). Activation of the CB_1 cannabinoid receptor leads to the blockade of calcium (Ca^{2+}, N and Q type) and activates potassium (K^+) channels. Exogenous or endogenous cannabinoids induce an inhibition of the activity of the adenililcyclcase (AC) decreasing the synthesis of the cAMP whereas activates a PLC as well. This might be the molecular basis of the behavioral effects induced by exogenous/endogenous cannabinoids. Abbreviations: AC, adenylate cyclase; CB_1, CB_1 cannabinoid receptor; PG_i, G_i coupled protein; PLC, phospholipase C.

It is known that the activation of the CB_1 cannabinoid receptor modifies the activity of diverse neurotransmitter systems. In this regard, several reports indicate that CB_1 cannabinoid receptor diminishes the glutamatergic neurotransmission [39-41], enhances the release of acetylcholine (ACh) [42, 43] and potentiates the activity of the serotonergic (5-HT) system [44-47].

The CB_2 Cannabinoid Receptor

Cloned in 1993 by Munro *et al.* the CB_2 cannabinoid receptor was localized in cells of the immune system and was apparently and absent in the CNS [48]. These observations were confirmed by Brown *et al.* describing the presence of the CB_2 cannabinoid receptor in liver, lung, and testicles but complete absence in the CNS [49]. Despite that the pioneer studies described that the localization of the CB_2 cannabinoid receptor was restricted to immune cells, Van Sickle and co-workers (2005) reported the presence of this receptor in areas of the CNS such as brainstem [50]. Additionally, the intracellular mechanism of action of this receptor is similar to that the activated by the CB_1 cannabinoid receptor [19, 51].

GPR55, the CB_3 Cannabinoid Receptor?

Recently, the orphan G protein-coupled receptor 55 (GPR55) was identified as a putative cannabinoid receptor. The GPR55 is a G-protein coupled receptor, identified in 1998 after a screen of a human genomic library [52] and it has been referred as the novel cannabinoid receptor 3 (CB_3) since it potentially explains the physiological effects that are non-CB_1/CB_2 cannabinoid receptor mediated [53-55]. In this regard, Andradas *et al.* reported that GPR55 promotes cancer cell proliferation in cell culture [56]. Whether GPR55 responds to the endocannabinoid ligands described so far or the exogenous cannabinoids is an issue to be explored.

THE ENDOCANNABINOIDS

The discovery of cannabinoid receptors triggered a search for their endogenous ligands. *N*-arachidonoylethanolamide also known as anandamide (ANA) was the first molecule endogenously synthetized, known to bind cannabinoid receptors [57] whereas 2-arachidonoylgly-cerol (2-AG) was identified 3 years later by the same laboratory [58].

Since the discovery of ANA, several endogenous compounds with cannabinoid-like properties have been described as well, such as the sleep-inducing lipid oleamide [59-69], noladin ether [70-73], *O*-arachidonoylethanolamine, also known as virodhamine [74-76] and *N*-arachidonyldopamine [77, 78]. The neurobiological role of the new members of the endocannabinoid family remains to be described. Further studies will be aimed to describe the pharmacological effects of these compounds on diverse experimental tasks as well as the description of their potential mechanisms of action.

Biosynthesis and Degradation of the Endocannabinoids

Biochemically, the release of the endocannabinoids is different from classical neurotransmitters since they are not stored in synaptic vesicles. For example, ANA and 2-AG are synthesized from lipid precursors, and then further they are released from postsynaptic neurons in an activity-dependent way or "on demand" [79-82]. The ANA precursor is an *N*-arachi-donylphosphatidylethanolamine (N-ArPE), which has been suggested as the origin of the transfer of arachidonic acid from the sn-1 position of 1,2-sn-di-arachidonyl-phosphatidyl-choline to phosphatidylethanolamine which is catalyzed by a calcium-dependent N-acyltransacylase (NAT). Thus, N-ArPE is cleaved by an *N*-acylphosphatidylethanolamine (NAPE)-specific phospholipase D (PLD) which releases AEA and phosphatidic acid [83, 84].

Regarding the degradation mechanisms, it has been postulated different routes. For instance, ANA is transported to the interior of the cell *via* putative transporters. Despite the apparent lack of molecular evidence for a carrier-mediated transport of ANA across the membrane (ANA membrane transporter, AMT) and the debate on its existence, particularly in view of the fact that the lipophilicity of ANA would allow it to cross the plasma membrane by passive diffusion, experimental evidence suggest indeed, the neurobiological role of the putative AMT [85, 86].

While the transporter of ANA is still in debate, the mechanism of degradation of this endocannabinoid and 2-AG has been studied in detail. Current evidence suggest that fatty acid amide hydrolase (FAAH) is the principal ANA-hydrolyzing enzyme whereas monoacylglycerol lipase (MAGL) is responsible for approximally 85% of the hydrolysis of 2-AG [81, 87-91].

To obtain an understanding of the neurobiological role of FAAH and AMT, several compounds have been developed to study the activity of these elements For instance, drugs that block the activity of the AMT, such as (5 Z,8 Z,11 Z,14 Z)-N-(4-hydroxy-2-methylphenyl)-5,8,11,14-eicosatetraenamide (VDM-11) [92] or cyclohexyl carbamic acid 3′-carbamoyl-biphenyl-3-yl estercyclohexyl carbamic acid 3′-carbamoyl-biphenyl-3-yl ester, named URB597 (a FAAH inhibitor) [93] have shown to enhance the endogenous levels of ANA. Additionally, these compounds display pharmacological positive properties since they provide an improvement in pathological conditions, such as anxiety or tumor growing [94-96].

ENDOCANNABINOIDS AND SLEEP MODULATION

Regulation of the sleep-waking cycle is complex and involves multiple neurological circuits and diverse endogenous molecules. The interplay among assorted neuroanatomical and neurochemical systems such as acetylcholine (ACh), dopamine (DA), 5-HT, noradrenaline, histamine, and hypo-cretin maintain wakefulness (W) state whereas the sleep-onset is governed by the interacting forces of the sleep drive, which steadily increases with duration of waking, and circadian fluctuations. Sleep-promoting neurons located in the anterior hypothalamus release GABA and inhibit wake-promoting regions in the hypothalamus and brainstem and participate in the generation of slow wave sleep (SWS). During rapid eye movement (REM) sleep, brainstem regions typically inhibited during W and SWS become active. In this regard, ascending projections from cholinergic neurons in the brainstem activate the thalamus which in turn increases the firing of the neurons in the cortex [97-104].

The role of the endocannabinoid system on sleep modulation has been suggested based in experimental evidence. For instance, classical experiments reported that marijuana and Δ^9-THC modulate the sleep-wake cycle [105-109]. More recently, the very first approach showing the role of the CB_1 cannabinoid receptor on sleep modulation was achieved by Santucci and co-workers in 1996. These authors injected systemically the CB_1 cannabinoid receptor antagonist, SR141716A, (0.1, 0.3, 1, 3, and 10 mg/kg, ip) to rats finding a dose-dependent enhancement of W as well as a diminution in SWS and REMS [110].

Later, in 1998, our group reported that intracerebroventricular (icv) injections of ANA in rats during the lights-on period produced the opposite effect observed to that by Santucci and colleagues. We found a significant diminution in W as well as an increase in SWS and REMS. Additionally, the effects caused by ANA on sleep were more evident if injected into the pedunculopontine tegmental nucleus (PPTg), a sleep-related brain area [111].

Next, it was demonstrated that administration of SR141716A before the injection of ANA either icv or into the PPTg blocked the sleep-inducing effects of ANA [112]. Furthermore, if activity of PLC, which is coupled to the CB_1 cannabinoid receptors [113, 114] was prevented using U73122 (a PLC inhibitor) [115, 116] the sleep-promoting properties of ANA were also blocked [112].

Due to that ANA facilitates the activity of several neurotransmitter systems, it was hypothesized that this endocannabinoid could induce sleep *via* the recruitment of a sleep-inducing molecule such as adenosine (AD). Systemic administrations of ANA (10mg/kg, ip) enhanced the extracellular levels of AD as well as the sleep time whereas the injection of SR141716A significantly blocked these effects. We conclude from these studies that ANA promotes sleep by enhancing the levels of the sleep-inducing molecule AD [117].

Circadian Fluctuations of the Endocannabinoid System

The brain distribution of ANA suggests a neuromodulatory role of this lipid in regions such as cortex, hippocampus, striatum, cerebellum, and brainstem [118-121]. Since several behaviours display diurnal variations, including the sleep-wake cycle it was hypothesized that ANA might be also showing circadian fluctuations. In this regard, it was reported that this endocannabinoid showed a significant enhancement in its contents in cerebrospinal fluid (CSF) during the lights-on period whereas its concentration diminished across the lights-off period. Moreover, in sleep-related brain regions, ANA also showed diurnal fluctuations. For example, in pons, it was found a maximum values during the dark phase. We speculate that ANA is likely accumulated in parenchyma during the lights-off period (when the rodents are awake) and then, released into the CSF to reach out specific target regions in the CNS to modulate sleep [118-121].

The circadian variation of the endocannabinoid system includes also fluctuations of the CB_1 cannabinoid receptor. It has been reported that the highest peak for this protein in the brainstem occurs at 13:00h, whereas for the mRNA the zenith was described at 21:00h. Furthermore, the lowest expression for the protein was detected at 01:00 whereas the mRNA lowest levels were found at 09:00h [122]. These results suggest that the expression of the CB_1 cannabinoid receptor is linked with a circadian component.

Additionally to the circadian variation, the CB_1 cannabinoid receptor displays behavioural state-dependent variations. In this regard, the mRNA and protein of this receptor were increased in sleep-deprived rats compared to control animals. Taking together, the data suggest that the CB_1 cannabinoid receptor could modulate sleep homeostasis [123].

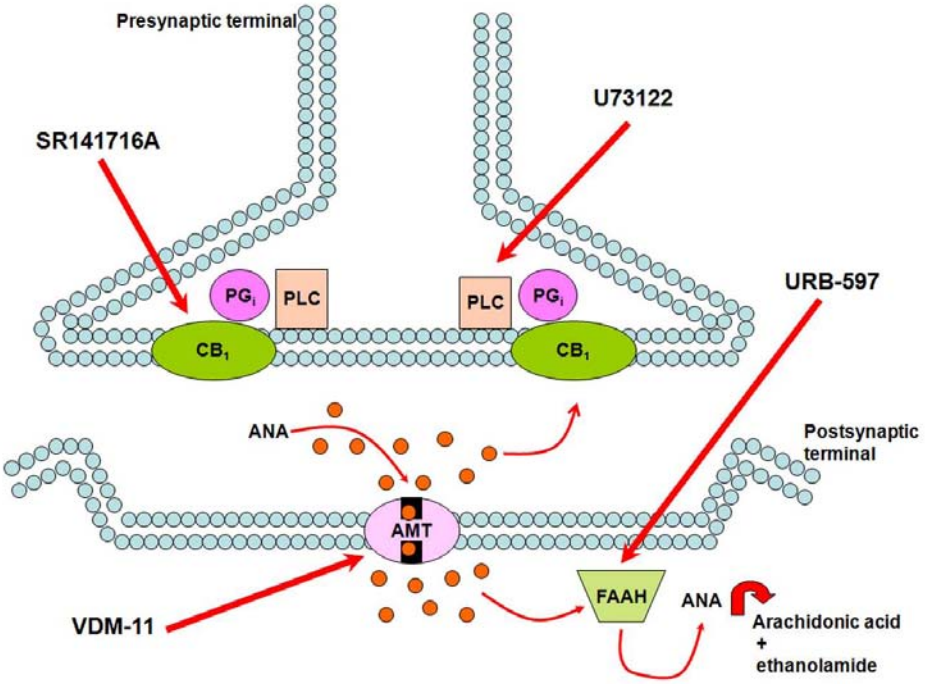

Fig. (2). Schematic representation of the hypothetical mechanism of action of the endocannabinoid system modulating sleep. Pharmacological blockade of the CB_1 cannabinoid receptor using SR141716A increases alertness whereas microinjection of the ligands either anandamide or cannabinoids enhances sleep. U73122, a selective PLC inhibitor, blocks the anandamide´s sleep-inducing effects. Similar results have been observed using VDM-11, an AMT blocker whereas inhibition of the activity of FAAH via URB-597 diminishes sleep. Abbreviations: AMT, anandamide membrane transporter; CB_1, CB_1 cannabinoid receptor; FAAH, fatty acid amide hydrolase; PG_i, G_i coupled protein; PLC, phospholipase C.

Sleep Modulation after the Blocking of FAAH or AMT

Although incipient, the experimental evidence suggests that AMT and FAAH participate in the modulation of the sleep-wake cycle. For example, it has been reported that icv administrations in rats of the FAHH inhibitor URB597 (10 or 20µg/5µL) during the lights-on period, enhance alertness whereas SWS and REMS are diminished. Furthermore, *c*-Fos immunoreactivity in hypothalamus and dorsal raphe nucleus was found increased in rats that received URB597. Finally, extracellular levels of DA are increased after the administration of the FAAH blocker. The findings indicate that inhibition of the FAAH, *via* URB597, facilitates waking [124].

As mentioned previously, VDM-11 is commonly used as an inhibitor of ANA cellular uptake, and thereby to potentiate its actions. When assayed alone in rats, VDM-11 (10 or 20µg/5µL; icv) at the beginning of the lights-off period, diminished W and promoted SWS and REMS. This sleep-inducing effect of VDM-11 was accompanied with a *c*-Fos expression in sleep-related brain areas such as the anterior hypothalamic area, paraventricular thalamic nucleus, and pedunculopontine tegmental nucleus [125]. Fig. (**2**) describes the potential mechanism of action of the endocannabinoid system on sleep.

Despite the lack of experimental evidence about the role of the endocannabinoid system in sleep disorders, some studies have suggested the potential role of this neurobiological system. Although levels in plasma and CSF of ANA were not found statistically different between patients with sleep apnea and control subjects [126], it suggests that the endocannabinoid system may be linked with sleep diseases. Further studies are needed to explore the role of the endocannabinoid system on sleep disorders.

POTENTIAL MECHANISM OF ACTION OF THE ENDOCANNABINOID SYSTEM ON SLEEP MODULATION

Pharmacological blockade of the CB_1 cannabinoid receptor using SR141716A facilitate waking whereas microinjection of ANA promotes sleep. Additionally, administration of U73122 (a selective PLC inhibitor) blocks the ANA sleep-inducing effects. Opposite to this, microinjection of VDM-11 induces sleep whereas URB597 enhances waking. Taken together the evidence described previously, we have hypothesized that the CB_1 receptor localized in pons and basal forebrain, as demonstrated by others [23, 24], could activate cholinergic neurons placed in the same brain regions [127-129]. Experimental evidence indicates that activation of the CB_1 cannabinoid receptor promotes the release of ACh [42]. It is worthy to note that ACh levels are higher in brainstem as well as basal forebrain during sleep [130-133]. Thus, it can be inferred that if CB_1 cannabinoid receptors are expressed in cholinergic neurons (in PPTg as well as basal forebrain), and they are activated by ANA, then a release of ACh could be taking place to promote sleep. The involvement of different sleep-related neuroanatomical and neurochemical factors in the sleep-inducing properties of ANA remains to be described.

DISCUSSION

The discovery of the endocannabinoid system, composed of endogenous lipids, receptors and metabolic enzymes, has brought information on its significance in multiple neurobiological processes, including sleep modulation. The sleep–wake cycle is maintained by different neurotransmitter systems [98, 101, 103, 134, 135], including the endocannabinoid system [110-112, 117, 124, 125].

From the pharmacological and pharmaceutical perspective, the endocannabinoid system might be considered in the near future to treat diverse pathologies, including sleep disorders. Novelty strategies for developing drugs considering the elements of the endocannabinoid system could be useful as an effective approach to the prevention and management of sleep disturbances such as insomnia or excessive diurnal somnolence. For example, the CB_1 cannabinoid antagonists, such as SR141716A, could be considered to treat narcolepsy, whereas the ANA or VDM-11 could be included in the managing of insomnia. The next step would be to describe and integrate the mechanism of action of the endocannabinoid system in sleep modulation and its relevance in sleep disorders.

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