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Review article

Endocannabinoids and sleep

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ABSTRACT

Sleep is regulated by several brain structures, neurotransmitters and neuromodulators. Endocannabinoids (eCBs) are a group of lipids with modulatory activity in the brain and bind mainly to cannabinoid receptors CB1R and CB2R, thereby modulating several brain functions, (memory, mood, food intake, pain perception). Oleoylethanolamide and palmitoylethanolamide belong to the *N*-acylethanolamides (NAEs) family, another type of active endogenous lipids. They bind to the peroxisome proliferator-activated receptor α but not to CB1R, thereby modulating food satiety, inflammation and pain. Both eCBs and NAEs seem to be regulating the sleep-wake cycle. Our objective is to analyze the experimental evidence published in the literature and to discuss if eCBs and NAEs are actually sleep modulators. Studies suggested 1. eCBs and NAEs are under circadian control. 2. NAEs promote wake. 3. eCBs promote non-rapid-eye movement. 4. eCBs also promote rapid-eye-movement sleep by interacting with melanin-concentrating hormone neurons in the lateral hypothalamus. 5. The pharmacological blockade of the CB1R reduces sleep while increasing wake. 6. eCBs restore sleep in a model of insomnia in rats.

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1. Background

The sleep-wake cycle is a complex process that includes at least three states. Waking (W): this is a state in which different levels of alertness occur, depending on the behavior the subject is performing. The general brain electrophysiological activity in this stage, as recorded by a standard electroencephalogram (EEG), is mainly β (13.5–20 Hz) and α (8–13 Hz) when the subject closes his/her eyes. In this stage, the subject is aware of what he is currently thinking, what emotion he is experiencing and what sensations he is perceiving. The subject is also aware of his surroundings. During waking, several cognitive processes are taking place, i.e. attention, learning, decision making, among many others (Edelman, 2005; Hobson and Voss, 2011). Waking is modulated by neurons located mainly in the lateral and posterior hypothalamus (Fig. 1a), that

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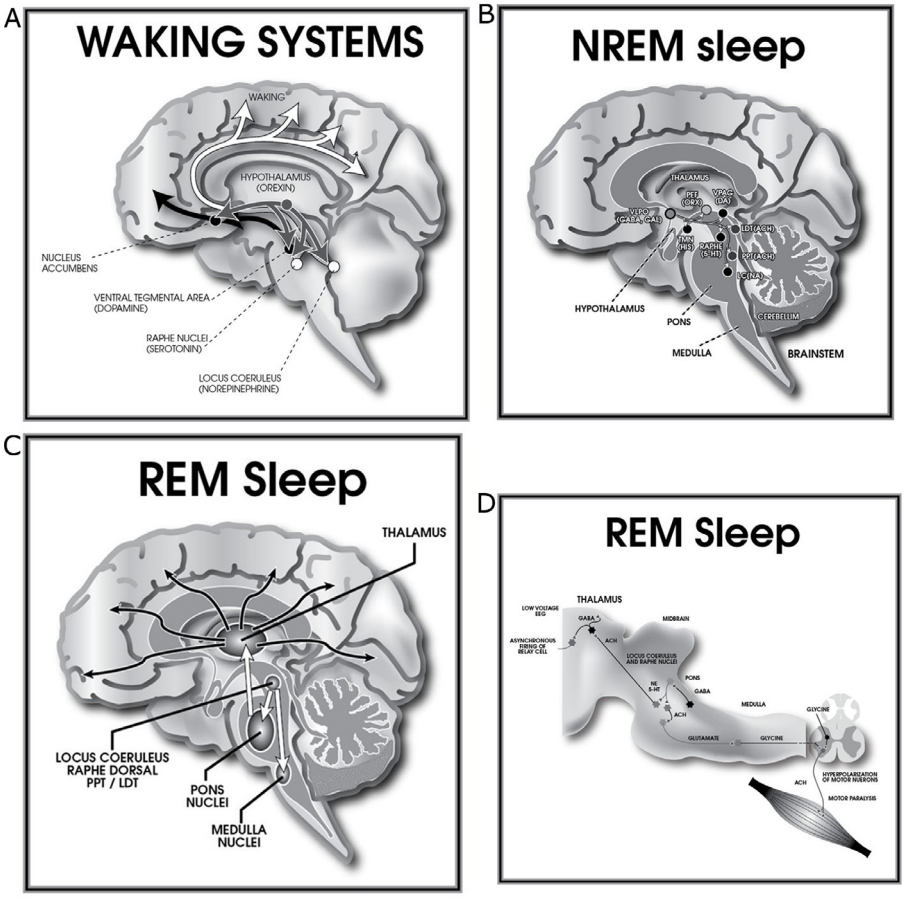

Fig. 1. a) Wake systems. This is a simplistic view of the major brain wake systems. It can be observed that orexinergic neurons are playing a crucial role in orchestrating the executive systems for wake promotion. b) In this illustration, the crucial system promoting NREM sleep is depicted. MPOA and VLPO play a crucial role in turning off the wake systems. c) Some of the REM sleep mechanisms are illustrated in this figure. d) Crucial mechanisms for postural atonia.
Not all the systems involved in REM sleep generation are included in this figure.

synthesize neurotransmitters, such as orexins/hypocretins (ORX), and histamine, and brainstem neurons synthesizing noradrenaline (Locus coeruleus), serotonin (dorsal raphe nucleus), and acetylcholine (peduncle pontine tegmental nucleus) (Siegel, 2009; Luppi and Fort, 2011). Non-rapid-eye-movement (NREM) sleep: This is not a homogeneous state. In humans it is divided into three stages: N1, N2 and N3 (American Academy of Sleep Medicine, 2015), while in rats it is frequently divided into slow-wave sleep 1 (SWS1) and SWS2. The EEG of humans exhibits several waves, i. e., vertex sharp waves (N1); spindles and K-waves (N2), and δ waves (N3). Although several processes take place during these stages, i.e., some dreaming activity, one of the major processes is the consolidation of declarative memory, particularly during N3 (Stickgold, 2013). NREM sleep is promoted by the anterior hypothalamus (medial and ventrolateral preoptic area) (Fig. 1b). GABA, a major inhibitory neurotransmitter, adenosine, a nucleoside and PGD2, a prostaglandin, participate in its regulation (Siegel, 2009; Luppi and Fort, 2011; Kumar et al., 2013). Rapid-eye-movement (REM) sleep: The EEG mainly shows β waves. It may also exhibit α (paradoxical α) and saw tooth waves (very infrequently). In the hippocampus of rats and cats θ waves can be recorded (Siegel, 2009; McCarley, 2011). The subject also exhibits eye movements and postural atonia. In this stage, humans have their more vivid dreams. One of its most studied functions is to facilitate contextual memory and creativity (Cai et al., 2009; Stickgold, 2013; Boyce et al., 2016). REM sleep is promoted mainly by nuclei located in the brainstem, i.e., peduncle pontine tegmental (PPT), laterodorsal tegmental (LDT), and pontis oralis nuclei (PON), among others (Fig. 1c and d) and neurotransmitters, such as acetylcholine and glutamate and neuropeptides, such as melanin-concentrating hormone (MCH) (Siegel, 2009; Luppi and Fort, 2011).

Table 1
eCBs and NAEs and sleep.

Endocannabinoid	W	NREM	REM
Oleamide	↓	↑	↑
Anandamide	↓	↑	↑
2-AG	↓	↑	↑
Oleoylethanolamide	↑	↓	↓
Palmitoylethanolamide	↑	↓	↓

In the last 20 years, experimental evidence has been supporting the notion that endocannabinoids may be also modulating the sleep-wake cycle.

Endocannabinoids (eCBs). eCBs are a family of bioactive lipids, most of them derived from arachidonic acid, i.e., anandamide (*N*-arachidonoylethanolamide, AEA) and 2-arachidonoyl glycerol (2-AG), 2-arachidonoyl-glyceryl ether (AGE), O-arachidonoyl-ethanolamine (virodhamine), *N*-arachidonoyl-dopamine (NADA) and the oleoylglycine derivative oleamide (*cis*-9-10-octadecenoamide, ODA) (Table 1). eCBs interact directly with the cannabinoid receptors 1 and 2 (CB1R and CB2R), but they also interact with other receptors, i.e., transient receptor potential vanilloid type 1 (TRPV1) and G protein-coupled receptor 55 (GPR55) (Iannotti et al., 2016). ODA also interacts with serotoninergic 5HT2c receptors, and with the peroxisome proliferator activating receptor α (PPARα) and gap-junctions (Takao et al.,