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Neuropeptide interactions and REM sleep: A role for Urotensin II?

Luis de Lecea [a,*], *Patrice Bourgin* [b]

[a] *Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 701 B Welch Road, Palo Alto, CA 94304, United States*

[b] *Department of Biological Sciences, Stanford University, Palo Alto, CA, United States*

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ABSTRACT

Urotensin II (UII) is a peptide with structural similarity to the somatostatin family with potent vasoconstrictor activity. UII receptor is expressed broadly in the periphery, and most notably in the heart and microvessels. In the brain, the UII receptor can be detected in the spinal cord and in cholinergic nuclei in the brainstem known to be involved in REM sleep regulation. Recent data suggest that, in addition to their vasoactive properties, UII receptor ligands may have excitatory activity on a selective group of neurons that modulate REM sleep. This review focuses on the implications of these findings for the neurobiology of REM sleep regulation and discusses the possible impact of UII and other neuropeptides on the balance of the alternation between sleep states.

1. Introduction

The states of vigilance (wakefulness, NREM and REM sleep) are the result of thalamocortical interactions and are modulated by different subcortical circuits. The states of vigilance are defined based on electroencephalogram (EEG), electrooculogram (EOG) and muscle tone (EMG) signals. Fast, low amplitude desynchronized activity during wakefulness is followed by high amplitude slow waves during non-REM sleep (NREM). Rapid eye movement (REM) sleep is characterized by high level of cortical and hippocampal activation (theta rhythm in rodents), rapid eye movements and loss of muscle tone. The transitions between sleep states are modulated by discrete nuclei in the hypothalamus and in the mesopontine tegmentum. Models for the neurobiology of REM sleep underlie NREM–REM alternation as a consequence of a reciprocal interaction between cholinergic and monoaminergic circuits at the brainstem level. In the present review, we

* *Corresponding author*. Tel.: +1 650 736 9039.
E-mail address: llecea@stanford.edu (L. de Lecea).

Abbreviations: EEG, electroencephalogram; EOG, electrooculogram; EMG, electromyogram; FTG, gigantocellular tegmental field; Hcrt, hypocretin; LC, locus coeruleus; MCH, melanin concentrating hormone; NPS, neuropeptide S; NREM, non-rapid eye movement; periLC alpha, peri-locus coeruleus; PnO, pontis nucleus oralis; REM, rapid eye movement; RPO, nucleus reticularis pontis oralis; subCD, nucleus subcoeruleus dorsal; TSH, thyroid stimulating hormone; UII, Urotensin II; URP, Urotensin-related peptide; VTA, ventral tegmental area.

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will focus on Urotensin II (UII) as a possible modulator of the reciprocal model of REM regulation.

UII belongs to a growing collection of neuropeptides identified in fish and lower vertebrates that subsequently have been shown to exhibit relevant roles in mammalian physiology. Initially isolated from urophysis extracts of several species of fish [60], UII is a cyclic peptide with a core structure (a hydrophobic tetrad FWKY) that bears some similarity with somatostatin and cortistatin and that is conserved through mollusks to mammals [15,21–24]. The cyclic core is essential for its activity, since disruption of any of the flanking cysteines results in loss of receptor binding and biological activity [25]. A closely related peptide, named URP for Urotensin related peptide, shares the core structure, although it is synthesized from a different precursor, and probably arose as a gene duplication [17,71]. The UII peptide precursor is distributed widely in the peripheral vascular tissue and in the heart [4,30]. In the central nervous system, UII-like immunoreactivity has been detected in spinal motor-neurons [16,31,61], which probably include both UII and URP.

UII and URP bind with high affinity to a single G-protein coupled receptor, previously known as GPR14 [52,53,57]. Within the central nervous system, UII can be detected in the olfactory system, hippocampus, olfactory and medial amygdala, hypothalamus, epithalamus, several tegmental nuclei, locus coeruleus, pontine nuclei, motor nuclei, nucleus of the solitary tract, dorsal motor nucleus of the vagus, inferior olive, cerebellum, and spinal cord [41]. UII receptor mRNA colocalizes with choline acetyltransferase in the mesopontine tegmental area, including the pedunculopontine tegmental (PPT) and the lateral dorsal tegmental (LDT) nuclei [20]. In contrast, no UII peptide, UII receptor mRNA or UII binding sites have been detected in cholinergic neurons in the basal forebrain.

In mammals, UII has potent vasoconstrictor activity in the periphery [8,30,66]. Intracerebroventricular (icv) injection or intraarterial injection of UII induces hypotensive and brady-cardiac effects in rats [37]. Icv administration of UII increases rearing and grooming, and increases motor activity in a familiar environment. Further, UII increases plasma prolactin and thyroid stimulating hormone (TSH) but does not affect levels of corticosterone [36]. UII plays a role in cardiovascular homeostasis through its specific receptor (UII-R) in blood vessels and in the central nervous system [4,53,57]. However, it should be noted that the cardiovascular effects of UII are not uniform across species [56].

The distribution of UII receptor message in the cholinergic PPT and LDT neurons suggests that, in addition to its vascular actions, the UII system may be involved in the regulation of the sleep–wake cycle, and in particular, in the generation of REM sleep.

2. Reciprocal interactions between cholinergic and monoamines regulate REM sleep

In a landmark paper, Alan Hobson and Robert McCarley proposed a reciprocal interaction model of REM sleep, in which connections between neurons of the LC and neurons of the FTG (gigantocellular tegmental field) in cats result in a sleep cycle oscillation [39]. According to this model, REM episodes are under the control of a balance between a REM-on and a REM-off component, respectively, active and silent during REM sleep (Fig. 1).

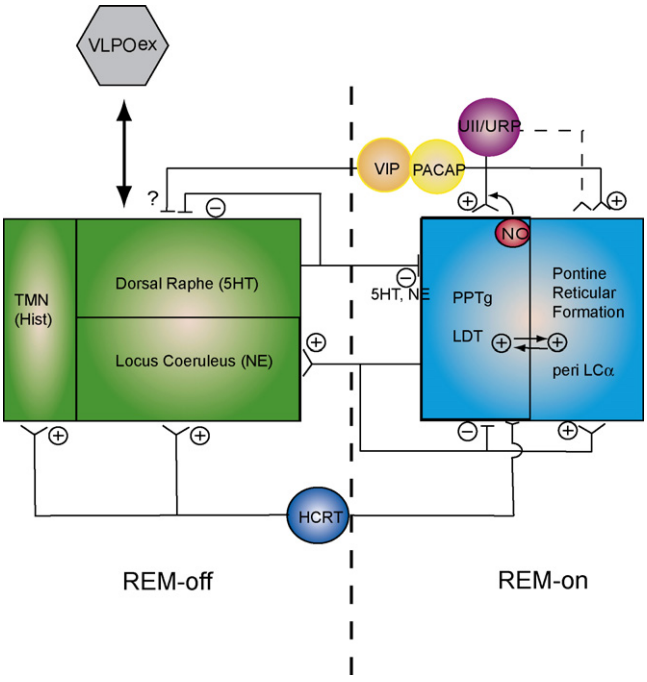

Fig. 1 – A peptide-centric view of the reciprocal interaction model. The original reciprocal interaction model proposed that monoaminergic REM-off cells inhibit the activity of cholinergic REM-on neurons in the pontine reticular formation. Different revisions of the model have added GABAergic inhibition to these reciprocal interactions and modulation of the REM-off component by the extended VLPO. The discovery of the role of the hypocretins in narcolepsy and stability of wakefulness suggested that peptides could also play a relevant neuromodulatory role in this model. In this review we discuss the role of VIP, PACAP and Urotensin II as putative neuroregulatory elements of REM on neurons.

Since 1975, this model has been updated several times with inclusion of additional systems, especially the cholinergic REM-on structures. Indeed, 10 years later, Shiromani et al. [68] and independently McCarley and his group [51] gave one of the first evidence supporting that PPT/LDT are the suppliers of acetylcholine to the pontine reticular formation. Finally, the REM-on component contains the cholinergic PPT and LDT cells that project to cholinoceptive neurons in the pontine reticular formation (PRF), known as REM-on, that are active during REM sleep and whose activity appears to be required for the generation of REM sleep. Local infusion of cholinergic agonists into the PRF allowed the identification of a restricted area within the PRF, also named REM sleep induction zone. This REM sleep induction zone has been defined (i) in cats as RPO [5,46] or peri-LC alpha [74], and (ii) in rats [11] and mice [47] as the caudal part of PnO and adjacent subCD. However, lesions of PPT/LDT do not suppress REM sleep, or the phasic events of