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

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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

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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).

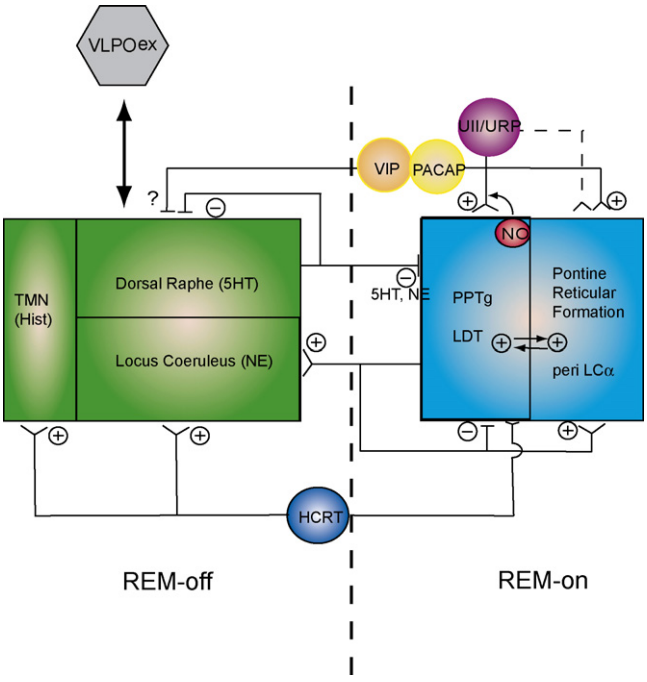

Fig. 1 – A peptide-centric view of the reciprocal interaction model. The original reciprocal interaction model proposed that monoaminergic REM-off cells inhibit the activity of cholinergic REM-on neurons in the pontine reticular formation. Different revisions of the model have added GABAergic inhibition 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

REM sleep [69,76]. The REM-off component includes the monoaminergic cells in the locus coeruleus (LC) and in the dorsal raphe (DR) that are silent during REM sleep and are known as REM-off neurons. According to the reciprocal interaction model, connections between aminergic and cholinergic mesopontine neurons, including those in the LDT and PPT, result in alternation of REM and NREM sleep [39]. In this model, REM-on cells are excited by cholinergic afferents and are excitatory at their terminals ending in both REM-on and REM-off nuclei (Fig. 1). Monoaminergic REM-off cells are inhibitory and originate in the DR (serotonin), in the LC (noradrenergic) and the tuberomamillary nucleus (TM, posterior hypothalamus, histamine). Neurons of all three systems are silent during REM sleep, and pharmacological inhibition or gene abolition of histamine synthesis results in an increase in REM sleep. During waking, the aminergic systems are tonically activated and inhibit the pontine cholinergic system. During NREM sleep, aminergic inhibition decreases as cholinergic excitation decreases. A REM sleep bout is generated when monoaminergic inhibition permits the excitation of cholinergic REM-on cells. Revised versions by the authors [59] include recent data showing excitatory cholinergic–non-cholinergic interactions that involve ACh and glutamate, which enhance the firing of mesopontine REM-on cells [44]. This latter study also reported the existence of recurrent inhibitory inputs to the cholinergic neurons in PPT/LDT which completes the interactive circuitry. In vivo extracellular recordings of cholinergic REM-on cells revealed increased firing before the onset of REM sleep, therefore suggesting a role in the triggering of REM sleep episodes [70].

In a different model of REM sleep regulation, the transitions between sleep states are controlled by ''sleep switches'' that consist of bi-stable systems that prevent intermediate states [45]. Based on anatomical tracing and lesion studies as well as c-fos immunoreactivity [45], Saper and co-workers suggest that the extended VLPO inhibits REM-off cells to promote wakefulness. Also, according to this model, REM-on areas are divided into two glutamatergic populations: one that projects to the basal forebrain and accounts for the changes in EEG activity, and another that controls muscle tone. The transitions between NREM and REM states would be modulated by peptidergic systems in the hypothalamus, such as the hypocretins or MCH [45]. Lesions in the pre-coeruleus and subcoeruleus regions result in decreased REM sleep, suggesting that these areas are also important components of the REM-on cell group. Interestingly, this area contains a subset of glutamatergic neurons that produce Neuropeptide S, a recently described peptidergic system that increases wakefulness and reduces anxiety [79]. Other peptidergic systems, acting directly on REM-on neurons in the mesopontine tegmentum, i.e. UII, vasoactive intestinal peptide (VIP) or pituitary adenylate cyclase activating polypeptide (PACAP), might also have a prominent role in stabilizing the switches.

2.1. *Peptidergic modulation of REM sleep*

Over the years, multiple peptides have been shown to impact REM sleep after icv administration. Here we will only address the role of three sets of peptides in the context of the reciprocal model. Other peptidergic systems such as substance P, the opioid peptides, as well as cytokines, may also have a modulatory role in different aspects of the transitions between sleep states, which is addressed elsewhere [42,64].

2.1.1. *VIP/PACAP*

PACAP and VIP belong to a family of structurally related peptides including secretin, glucagon and growth hormone releasing factor. Both peptides increase the intracellular content of cyclic AMP and act through activation of common specific receptors [38]. PACAP and VIP have long been proposed as putative modulators of REM sleep by studies reporting REM sleep enhancement following intracerebroventricular (icv) administration [33,50,65]. In rats, local intracerebral infusion of the peptides allowed the identification of brain areas involved in their REM sleep promoting effect, i.e. the dorsal raphe (DR) for VIP [32] and PRF for VIP and PACAP [1,10,13].

More remarkably, a single microinjection of PACAP or VIP into the REM sleep induction areas within the PRF promotes REM sleep for several days, up to 12 days providing the first model of long-term induction of REM sleep in rats ([1,10,13]. VIP has been shown to excite PRF neurons inducing a longer-lived depolarization than that evoked by carbachol. The enhancement of REM sleep for several days requires reciprocal PACAPergic/muscarinic receptor interaction [1,2,10] since (1) in vivo REM sleep promotion was prevented by a previous infusion of cholinergic or PACAP antagonist into the same site; (2) in vitro, by quantitative autoradiography, the muscarinic binding sites were increased in presence of PACAP (and also at the level of receptor-coupled G protein using the same technique to quantify the GTP-γ-S binding in presence of peptide and muscarinic ligand). Quantitative autoradiography revealed the presence in the PRF of specific binding sites with high affinities for the two forms of PACAP, but very low affinity for VIP, suggesting that PAC1 receptor may mediate this long-term action of PACAP on REM sleep [1]. More recently, immunocytochemical data showing the presence of PACAPergic cell bodies and fibers in the PRF, but no VIP labeling, support the idea that PACAP, rather than VIP, within the PRF plays a critical role in long-term regulation of REM sleep [3]. Conversely, a dense network of VIPergic cell bodies and fibers is observed in the DR [3,62]. Thus, VIP and PACAP, two related peptides, impact the balance of the REM-NREM alternation model on different sides and in a different manner, i.e. short-term for VIP and long-term for PACAP.

2.1.2. *The hypocretins*

The hypocretins (Hcrt-1 and Hcrt-2), also known as orexins [28,67], have a key role in stabilizing the sleep wakefulness cycle, and the initial observation that infusion of hcrt-1 suppresses REM sleep [12,63] placed these peptides as important regulators in this reciprocal interaction circuitry. The fact that deficiencies in the hypocretin system lead to sleep fragmentation with direct entries in REM sleep or REM component during waking make it more likely that action at REM-on structures by hypocretin occurs only during waking periods. This is supported by recent juxtacellular recordings of hypocretin cells in vivo [43,49] that revealed an almost absence of hypocretin activity during REM sleep. The role of hypocretin in regulating the REM gate is a complex one in that hcrt is

known to modulate both components of the REM-on REM-off model. Paradoxically, the REM-on structures receive both indirect hypocretin-initiated inhibitory signals from REM-off cells and direct projections from the hypocretin neurons themselves and therefore must decide on how to respond to this push–pull pressure in different scenarios.

Regarding the REM-off system including LC, DR and TMN Hcrt neurons innervate and depolarize neurons of these latter structures to promote wake; and repress REM sleep when applied to the LC. Considering the REM-on component, Hcrt-containing neurons project to the pontine tegmentum as well as the PRF, eliciting an inhibitory action [58]. Local injection of Hcrt1 peptide into the LDT of freely moving cats increases wakefulness and decreases the number of REM episodes, but does not influence episode length [78], suggesting that the hypocretin system influences the gate (or switch) to REM. Conflicting results have been obtained in REM sleep after local administration into the PRF of Hcrt-1 [78] or hcrtr2 antisense [73] into the PRF. Hcrt application into the PnO inhibits the firing rate of PnO neurons in a dose-dependent manner [58].This inhibitory effect is blocked by prior application of the GABAA receptor antagonist, bicuculline, suggesting it is a consequence of activating GABAergic receptors, and possibly increasing the release of GABA from interneuron terminals. Hcrt causes an ACh release within the PRF [7]. Hypocretin-1 has been shown to cause a concentration-dependent increase in PnO GABA levels. Taken together, these findings are consistent with the interpretation that hypocretin promotes arousal, in part, by increasing ACh release in the reticular formation. Finally, it is possible that hypocretin acts presynaptically at the synapses between the REM-off and REM-on neurons and, hence, facilitates the indirect inhibitory inputs [72].

2.1.3. *Urotensin II*

Huitron-Resendiz et al. [40] showed that UII might be another important regulator in the circuitry that regulates REM sleep. These authors showed that intracerebroventricular administrations of UII caused a dramatic increase in REM sleep sustained for several hours, and at a lower degree a wake promotion observed during the first hour following the injection. The observation of a strong REM promoting activity of the peptide is also supported by the anatomical distribution of UII receptor that is preeminently localized in the brainstem REM-on and REM-off areas. To allow the identification of brain areas involved in the REM promoting effect of UII, Huitron-Resendiz et al. [40] locally injected the peptide into the PPT and LC in the rat. Local infusion of UII in the PPT induced a significant increase in REM sleep of 90.0, 59.0, and 69.8%, respectively, 2, 3, and 4 h after treatment, compared with vehicle. This increase was blocked by pretreatment with a UII receptor antagonist [6]. No significant effects were observed in the other states of vigilance (wake or NREM), or when UII was injected in areas adjacent to the PPT nucleus. Interestingly, the EEG qualitative analysis of UII effects revealed increase in theta and gamma activities during wakefulness and REM sleep after icv or local injection into the PPT, suggesting that the action of the peptide has a prominent effect on the ascending pathway that controls EEG activity.

Conversely, UII injected locally into the LC was not efficient in modifying REM sleep amounts. In spite of a large distribution of UII receptors, including all components of the REM-on/off model, autoradiographic studies revealed binding of the peptide only in the REM-on LDT and PPT [41]. This result added to the lack of effect of UII injection into the LC raise the question of the functional significance of the presence of UII receptors in other areas, such as the DR, an area with high concentration of UII receptor. Indeed, among other possible systems targeted by UII, the serotoninergic system is an obvious candidate.

Altogether, these observations suggest that the behavioral effects of UII are consistent with increases in cholinergic tone, which in general increases cortical excitability (see model in Fig.1). The lack of UII receptor mRNA and UII binding sites in the cholinergic basal forebrain suggest that the modulatory effect of UII on the cholinergic tone affects mainly the mesopontine tegmentum. This observation is also consistent with the behavioral effect of icv administration of UII that modulates selectively REM sleep. Moreover, whole-cell recordings from rat brain slices show that UII selectively excites cholinergic PPT neurons via an inward current and membrane depolarization that were accompanied by decreases in membrane [19]. This effect does not depend on action potential generation or fast synaptic transmission because it persisted in the presence of TTX and antagonists of ionotropic glutamate, GABA, and glycine receptors. The mesopontine (LDT/PPT) cholinergic neurons are known to be involved not only in REM generation, but also in cortical activation both during waking and REM sleep through their ascending projections to the thalamus and posterior hypothalamus [26,27]. Since both hypocretins and UII excite directly these cholinergic cells, a cholinergic mechanism in the wake-promoting and behavioral effects of both peptides could be important. Another possible point of convergence between UII and the hypocretins is the ventral tegmental area (VTA), a dopaminergic nucleus long known to be involved in brain reward [35]. Hypocretin induces dopamine release [54] and enhances glutamatergic responses in dopaminergic neurons [9]. Similarly, Clark et al. have shown that microinfusion of UII into the VTA produces a sustained increase in dopamine efflux in the nucleus accumbens, as measured by in vivo chronoamperometry [19]. Thus, activation of UII receptors may have an effect on motivation and hyperarousal associated with drug addiction. A recently described UII-diphtheria toxin, which selectively acts on mesopontine cholinergic neurons [18], could serve as an invaluable tool to test these hypotheses.

Another key question that remains unanswered is the origin and the nature of the endogenous UII receptor ligand. Based on the current immunohistochemical, pharmacological and electrophysiological data it is still unclear which of the two peptides (UII or URP) could both serve as modulators of REM sleep.

2.2. *Vasoactive vs. neuronal activity*

The hypnogenic properties of some putative sleep factors could be related to changes in blood pressure [34]. Vasoactive substances such as nitric oxide (NO) or UII, could affect blood pressure and regional blood flow in the brainstem, as shown in

imaging studies [14], and indirectly affect cholinergic activity. NO is produced by LDT/PPT neurons, and might help to maintain the cholinergically mediated REM sleep state in the pons and thalamus [77]. The level of extracellular NO is elevated when the activity of LDT cholinergic neurons increases, and NO modulates the release of ACh in the basal forebrain [75]. Therefore, UII could affect REM sleep directly, through activation of LDT/PPT neurons, or indirectly, through its vasoactive properties and/or enhancing NO release from cholinergic mesopontine neurons. Huitron-Resendiz et al., monitored regional cerebral blood flow after icv and local UII infusion in the PPT. UII infusion in the ventricles dramatically affected cerebral blood flow as compared with saline treatment. However, local injection of UII in the PPT caused a dramatic increase in REM sleep amounts, but did not elicit changes in blood flow. The proof-of-concept demonstration that UII affects neuronal activity came from intracellular recordings of PPT neurons. Whole cell recordings under voltage clamp conditions showed an inward current in bNOS positive neurons, but not in bNOS negative cells. Current clamp recordings indicated that UII produced membrane depolarizations, even in the presence of tetrodotoxin, strongly suggesting a postsynaptic effect [40].

Collectively our data strongly suggest that UII can function to modulate REM sleep by enhancing the excitability of mesopontine cholinergic neurons, independent of its effects on the cerebral vasculature. Following the concepts originating from the hypocretin work [29], peptidergic systems might integrate a variety of physiological signals, including metabolic, circadian, limbic and other variables, and convey this information into a coherent output that results in stable states of vigilance. UII, VIP/PACAP and other peptidergic systems may all contribute to the stability of the neuronal networks responsible for REM sleep generation.

Consequently, alterations of mesopontine tegmentum in humans could be responsible for REM-related disorders such narcolepsy and REM sleep behavior disorder (RBD). A robust association of idiopathic narcolepsy and RBD has been confirmed [55] and, remarkably, a recent paper reports the case of a subject who developed both medical disorders as a result of a lesion of the dorsomedial pontine tegmentum [48], suggesting that this might be a common pathway for both disorders. Dysfunction of UII system within the mesopontine tegmentum may thus participate in the pathogenesis of REM-related disorders.

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