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Activation of inactivation process initiates rapid eye movement sleep

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ABSTRACT

Interactions among REM-ON and REM-OFF neurons form the basic scaffold for rapid eye movement sleep (REMS) regulation; however, precise mechanism of their activation and cessation, respectively, was unclear. Locus coeruleus (LC) noradrenalin (NA)-ergic neurons are REM-OFF type and receive GABA-ergic inputs among others. GABA acts postsynaptically on the NA-ergic REM-OFF neurons in the LC and presynaptically on the latter's projection terminals and modulates NA-release on the REM-ON neurons. Normally during wakefulness and non-REMS continuous release of NA from the REM-OFF neurons, which however, is reduced during the latter phase, inhibits the REM-ON neurons and prevents REMS. At this stage GABA from substantia nigra pars reticulate acting presynaptically on NA-ergic terminals on REM-ON neurons withdraws NA-release causing the REM-ON neurons to escape inhibition and being active, may be even momentarily. A working-model showing neurochemical-map explaining activation of inactivation process, showing contribution of GABA-ergic presynaptic inhibition in withdrawing NA-release and dis-inhibition induced activation of REM-ON neurons, which in turn activates other GABA-ergic neurons and shutting-off REM-OFF neurons for the initiation of REMS-generation has been explained. Our model satisfactorily explains yet unexplained puzzles (i) why normally REMS does not appear during waking, rather, appears following non-REMS; (ii) why cessation of LC-NA-ergic-REM-OFF neurons is essential for REMS-generation; (iii) factor(s) which does not allow cessation of REM-OFF neurons causes REMS-loss; (iv) the association of changes in levels of GABA and NA in the brain during REMS and its deprivation and associated symptoms; v) why often dreams are associated with REMS.

Contents

Abbreviations: α, alpha; ACh, acetylcholine; CRF, caudal brain stem reticular formation; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; FTG, gigantocellular tegmental field; GABA, gamma amino butyric acid; LC, locus coeruleus; LDT, laterodorsal tegmentum; MRF, midbrain reticular formation; NA, noradrenalin; Na–K ATPase, sodium potassium adenosine triphophatase; NREMS, non-REMS; PeF, perifornical area; PGO, ponto-geniculo-occipital waves; PnO, pontine nucleus oralis; POAH, preoptico-anterior hypothalamic area; PPT, pedunculopontine tegmentum; PrH, prepositus hypoglossi; REM-OFF, REMS-OFF neuron; REM-ON, REMS-ON neuron; REMS, rapid eye movement sleep; REMSD, REMS deprivation; SNrPr, substantia nigra pars reticulata; TH, tyrosine hydroxylase.

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1. Introduction

Sleep and waking are expressed in animals relatively higher in evolution. The closest analogous states in animals lower in evolution are rest and activity. By and large, although animals have species-specific sleeping posture(s), experimental studies towards our understanding on the brain regulation of sleep could systematically progress only after these states could be objectively defined and quantified by the presence or absence of associated electrophysiological signals recorded from the brain, the electroencephalogram (EEG), eye movements, electrooculogram (EOG) and muscle tone, electromyogram (EMG). These electrophysiological recordings have finally helped us to set aside the earlier belief that sleep is a homogenous state and paved the way towards our present understanding that sleep is an active, non-homogenous state. Based on such objective electrophysiological criteria sleep has been broadly classified into rapid eye movement sleep (REMS) and non-REMS (NREMS); the REMS has also been referred to as active sleep, paradoxical sleep, desynchronized sleep or dream state of sleep.

Based on the electrophysiological criteria, although REMS has been objectively characterized since 1953 (Aserinsky and Kleitman, 1953), behaviourally, dream state of sleep has been known to humans since ancient times. Different states of consciousness and sleep including those of dream stage of sleep are mentioned in the oldest philosophical scripts associated to *the original inhabitants of the Indus valley civilization of the Indian peninsula, the Vedic and the Upanishadic literatures* written between 11th and 16th century BC (Datta and Maclean, 2007), in *Chinese* and *Greek* literatures (Barbera, 2008; Shapiro et al., 2009) as well as in other relatively lesser ancient documents, stories, paintings, etc. (Shapiro et al., 2009). However, very few attempts have been made to offer neuro-physio-anatomo-pharmacological correlation of those older philosophical concepts in light of the present knowledge especially based on experimentally derived neuro-biological data (Mallick and Mukhopadhyay, 2011).

Our understanding on the neurobiological mechanism of REMS regulation also has undergone significant revisions and modifications. **In this review we will focus on the control and responses of locus coeruleus (LC) noradrenalin (NA)-ergic neurons for REMS-regulation**. In brief, it will be shown that the NA-ergic neurons in the LC normally continue firing during all states except REMS, and they continue firing upon REMS deprivation (REMSD). Any factor, that would keep these neurons active or essentially would not allow them to cease activity, would prevent appearance of REMS and result in associated increased level of NA. Furthermore, this elevated level of NA is a primary factor responsible for underlying cellular changes inducing expression of REMS loss-associated signs and symptoms and patho-physio-behavioural changes.

2. REMS—an overview

Based on classical characteristic electrophysiological parameters until now REMS in some form has been detected at least in birds and mammals (www.bu.edu/phylogeny). Since EEG desynchronization during sleep is one of the most important characteristic features for objective identification of REMS, it can be observed only in species higher in evolution with a phylogenetically evolved and ontogenetically developed brain. Therefore, based on the existing criteria our definition will be limited and we cannot expect to observe classical REMS in species without a phylogenetically evolved brain and in the foetus until the brain has developed sufficiently. Thus, it is premature to conclude that REMS does not exist in lower species and consequently there is a need to find a fundamental and possibly a molecular marker for REMS detection. Notwithstanding the above, following arguments support that REMS serves as a fundamental physiological process and that its presence in higher animals cannot be a vestigial remnant.

Scientific community at large is yet to be convinced upon one or a defined set of critical functions of REMS. Although reasonably strong arguments in favour and against the necessity of REMS have been put forward, the arguments in favour out weigh the other. Since REMS has retained its character through generations and evolution across species, one may argue that it is likely that it would serve one or more important physiological process(es) in the body, although there may be species variations, adaptive and compensatory modifications and so on. The amount of REMS varies with ageing and it is never absent throughout life in all species where it has been identified. It has also been reported that upon its loss, REMS recovers with a rebound increase (Everson et al., 1989). The primary physiological expressions characterizing REMS, e.g. EEG desynchronization, eye movements, muscle atonia, although are apparently unrelated to each other, in normal subjects they are precisely regulated in a well orchestrated manner, while their dissociation suggests pathological condition(s). Further, at least in humans the episodic duration of REMS increases with the depth of sleep. Also, REMS is likely to serve important function(s) because its central control is essentially located at the core of the brain stem, the site responsible for regulation of other autonomic functions essential for survival, e.g. cardio-vascular and respiratory regulations. Like most other patho-physiological and neuro-behavioural processes regulated by the brain, the brain mechanism of REMS regulation as such is undoubtedly very complex at the same time extremely well regulated process. As far as brain stem mechanism of REMS regulation is concerned isolated studies have reported that most of the neurotransmitters, e.g. NA, serotonin, histamine, dopamine, orexin, acetylcholine (ACh), GABA, glutamate have been shown to modulate REMS as shown in Tables 1 and