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The Relationship between Ultradian Rhythm and Rapid Eye Movement (REM) Sleep

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ABSTRACT

Most of the mammals have nerve networks that generate rhythmic activities in their central nervous system. These systems produce ultradian rhythms which change between a few minutes to a few hours, and can regulate subconsciously the automatic functions such as, walking, breathing, sleep, wakefulness, arousal, motivation, addiction, and memory consolidation. The networks contain pacemaker neurons with the intrinsic ability to generate rhythmic activity in the form of action potentials. The most known rhythmic activity-produced by pacemaker cells, in the tegmental area of the brainstem, are the pre-Botzinger cells of the respiratory system. Pre-Botzinger cells change their activity level due to norepinephrine which is adjusted by changes in environmental and behavioral conditions. Norepinephrine not only modulates the respiratory network, but is in fact one of the most prominent neuromodulators in the mammalian nervous system. The ultradian rhythm that affects all the bodily functions is claimed to be shifting due to cerebral dominance and the activation of the sympathetic or parasympathetic systems, and it continues with NONREM and REM phases of the sleep. It can be asserted that pontin-geniculo-occipital (PGO) waves in REM sleep can be triggered by increased Ca^{2+} conductivity of pontine tegmental neurons, during sympathetic activity of the brain, as seen in the dominance of right hemisphere.

INTRODUCTION

Daily biologic rhythms

The sleep-wake cycle of mammals is controlled by a 'circadian clock' within the brain, which is synchronized to the day–night cycle. However, other physical or mental properties of mammalians such as activity levels, alertness, appetite, body temperature, blood pressure; fluctuate in cycles that repeat every few hours in a day. These cycles are known as ultradian rhythms, and they support the survival for many species [1]. Circadian rhythms are life's response to cycles of light and darkness and are regulated by clock genes. Ultradian rhythms on the other hand, last from half an hour to a few hours depending on basic metabolic changes. Some neurons generate action potentials by themselves in a periodicity which affects the brain activities, especially the autonomic functions. These rhythmic activities, generated in many parts of the mammalian nervous system, produce some very important physiological functions such as the control of breathing, walking, sleep, wakefulness, arousal, movement, motivation, addiction, memory consolidation, cognition [2]. The rhythm-generating networks are thought to be found in the spinal cord, brain stem, neocortex, thalamus, locus coeruleus, ventral tegmental area, hippocampus, and amygdala [3]. These rhythm-generating neurons have the intrinsic capacity to produce periodic spiking in the absence of synaptic inputs and are considered as autonomous spiking pacemakers [2,4-8].

Rhythm-generating neurons in the brainstem

The most known network, having pacemaker cells in pons and bulbus and generating spontaneous activity, seems to be pre-Botzinger complex which is essential for the generation of the respiratory rhythm. Apart from the brainstem, respiration also includes areas such as the spinal cord, neocortex, cerebellum, and amygdala [4]. Pre-Botzinger neurons exhibit pacemaker potentials that would enable them to discharge with an inspiratory rhythm. Respiratory neuroscientists suggest that respiratory neurons may be activated by cellular processes similar to that of heart-pacemaker cells [9]. Several other known neuronal networks referred to as 'central pattern generators (CPGs), have been identified in the spinal cord. They control rhythmic motor functions such as locomotion, ejaculation, micturition, and scratching. Thus, they may theoretically have their own spinal ‘‘command centers’’ [10-12]. Although the activating mechanisms of these CPGs are not definitively determined, the ultradian rhythm of the body has been examined in broad body functions.

Ultradian rhythm and hemispheric lateralization

Ultradian rhythms, having infra low frequencies (ILFs) in the millihertz-range (0.001Hz), and lasting for 90 minutes to 2 hours or more; are easily observed in electroencephalogram (EEG). They reflect cortical excitability and plasticity cycles, and subsequent activity reduction. For example, 0.18 mHz corresponds to a 90-minute cycle and 0.14 mHz to 2 hours [1,13]. Ultradian studies show that left or right EEG power is closely related with the autonomic, cardiovascular, neuroendocrine and energetic systems [14]. EEG studies of lateralized ultradian rhythms during wakefulness reveal a correlation between hemispheric dominance and the nasal cycle. Right nostril dominance, correlated with the left brain produces sympathetic activity; and left nostril dominance, correlated with the right brain produces parasympathetic activity [15]. The lateral shifts in sympathetic tonus are associated with lateral shifts in catecholamine concentrations in the peripheral circulation, such as differences in adrenal blood flow and cortisol secretion rates over a period of approximately 90 minutes [15]. Debra Werntz (1981) showed the relatively large integrated EEG values in the right hemisphere, are related to a dominant airflow in the left nostril and vice versa [16].

Relationship between ultradian rhythm and sleep

In our nightly sleep (rapid eye movement, REM and non-rapid eye movement, NON-REM sleep) we have phases similar to our daily ultradian rhythms [16,17]. Changes in laterality of the nasal cycle frequently coincide with switches in posture and tend to occur in REM sleep. It never occurs in slow-wave sleep, and may be absent in subjects with severe nasal septal deviations [18]. Numerous experimental and theoretical reports, suggested that the ponto-geniculo-occipital (PGO) wave-generating cells were involved in the formation of REM sleep and are also associated with cognitive functions. [19]. PGO waves occur in the nucleus subcoeruleus, which are in the dorsal part of the pons. The most important outputs of PGO-generating neurons are the brainstem nuclei, thalamus, hypothalamus, entorhinal cortex, piriform cortex, amygdala, hippocampus, occipital cortex, and many other cortical areas that participate in the generation of REM sleep. These active fields enable random memory engrams to be matched and create dream scenarios [20]. The projection of these PGO-producing cells into the entorhinal cortex, piriform cortex, amygdala and hippocampus; indicates that they are also involved in the modulation of cognitive functions [21]. Since the 1950s, it has been discovered that approximately 20 minutes of sleep cycles per 90-120 minutes have been spent in REM sleep in which dreaming occurs. In recent years, it has been assumed that this 90-120 minute rhythm may be an extension of the ultradian rhythm of the brain / body cycle. This high and low level cortical excitability, due to ultradian rhythm, is probably a response to the underlying metabolic changes and continues as REM and non-REM sleep cycles overnight [19]. For the entire EEG delta and alpha bands, right hemisphere dominance was found during NON-REM stage, and left hemisphere dominance was found during REM stage. Although we know the start and end stages of sleep, we do not know the triggering factors of PGO waves and REM sleep.

Probable mechanism in generation of PGO waves

Considering that the ultradian rhythm is composed of the brain stem for 24 hours, we can speculate that PGO waves too can be produced from the dorsolateral tegmental region of the brainstem following daytime ultradian rhythm. We know that there are ‘respiratory rhythm generator cells’ in pons called pre-Bцtzinger complex [22]. Thus, it can be asserted that PGO waves can be started by some ionic regulations, similarly as seen in the pre-Botzinger cells. Fieldman JL (2015) suggested that, “neural circuit controlling breathing by the pre-Botzinger cells may inspire general mechanisms for elucidating of other neural microcircuits” [23]. In the pre-Botzinger cells, voltage dependent ionic currents, such as the persistent sodium current INaP or the calcium-activated cation current, play key roles in mediating respiratory rhythm [22,24]. There are some clues that; most dopaminergic neurons in the midbrain fire spontaneously usually in a highly rhythmic “pacemaker” fashion. For example, in the ventral tegmental area (VTA) the pacemaker cells have non-voltage dependent back ground sodium conductance, which results a resting membrane potential only 10-15 mV hyperpolarized and is very near to firing level of action potential. Thus, these neurons can reach the threshold of (-55mV) and fires easily

by the entering of positive ions such as Na^+ or Ca^{2+} [22-26]. The triggering activation of the PGO waves during the right hemisphere dominancy may be similar with these respiratory pacemaker cells.

CONCLUSION

Since pacemaker cells in the tegmental area of the brainstem create triggering activities to produce ultradian rhythm in the right or left hemisphere and activate sympathetic or parasympathetic systems, they may induce the formation of PGO waves following sympathetic activity at nights. Sympathetic activity increases the Ca^{2+} conductivity to the cells, and may trigger the action potentials in some cells, such as pacemaker cells of heart and pre-Botzinger cells of the respiratory network. Norepinephrine is known to induce burst properties by a calcium-dependent mechanism. Therefore, PGO waves forming REM sleep associated with sympathetic activation can be considered to be activated by calcium-activated cation current in some pacemaker cells in the pons tegmental area.

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