Hypothesis

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Possible Role of the Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels in Memory Consolidation during Slow-Wave Sleep

Mahshid Tahamtan, Mohammad Shabani*, Vahid Sheibani*

Neuroscience Research Center, Neuropharmacology Institute, Kerman University of Medical Sciences, Kerman, Iran

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*Corresponding authors:
Mohammad Shabani
Vahid Sheibani,
Neuroscience Research Center,
Neuropharmacology institute,
Kerman University of Medical
Sciences, Kerman, Iran
shabanimoh@yahoo.com
vsheibani2@yahoo.com

Abstract

Over more than a century of research has demonstrated that sleep is necessary for the retention of memory. The current review aim to discuss the functional brain network connectivity is important during slow-wave sleep (SWS) for memory consolidation. While several evidences indicated the importance of SWS for memory consolidation but information to understand the main mechanisms of it are not enough. Although there is the likely involvement of various factors in this phenomenon, we hypothesize the key role of Ih current arising memory consolidation during SWS by generation of neuronal oscillations. Finding the possible mechanism involving in this process may provide lights to suggesting new treatments against memory impairments.

Introduction

The consolidation of memory requires neural reactivation during sleep. The coactivation of hippocampal and neocortical pathways may be important for the process of memory consolidation. During this process memories are gradually translated from short-term hippocampal to longer - term neocortical stores(1), in the other hand projections from the locus coeruleus innervate the hippocampus and cerebral cortex(2) and are capable of releasing norepinephrine (NE) in hippocampal and cortical circuits that process consolidation of memory(3). Hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels are important targets of NE(4).

The activation of HCN channels produces an inward current (Ih) (4). The role of Ih in rhythmogenesis has been examined in several studies and is involved in multiple physiological processes, such as sleep and wakefulness, circadian rhythm, and learning and memory(5-7). Since the exact neural mechanisms of sleep that cause memory consolidations remain unclear, therefore investigating the LC-hippocampal-cortical interaction during memory consolidation in SWS should bring new insights into mechanisms underlying memory formation. Experiments will focus on role of Ih currents on learning and memory.

SWS Sleep and memory consolidation

Mammalian sleep is composed of two prominent types: slow-wave sleep (SWS) and rapid-eye-movement (REM) sleep(8,9) and Both have been shown to be important for long-term consolidation of memory.

Sleep slow wave activity is recognized mainly in the low-frequency, high-amplitude activity (<4 Hz) and referred to deep sleep. SWS are one of the candidate oscillatory mechanisms which are necessary for memory consolidation process. Several studies have demonstrated that markers of synaptic potentiation are associated with an enhancement in sleep slow wave activity in both animals and human (10-12).

Prefrontal–hippocampal circuitry

Consolidation of hippocampus-dependent memories relies on a dialog between the neocortex and hippocampus. Crucial features of this dialog are the neuronal reactivation of new memories in the hippocampus during SWS, which stimulates the redistribution of memory representations to neocortical networks(13).

In hippocampus, SWS is marked by irregular bursts of high frequency activity, known as sharp wave ripples (SWRs), which is thought to be a major mode of processing, during which information is synaptically consolidated within the hippocampus (14). SWR bursts have an impact on neocortical activity and can transfer the stored representations to neocortical areas for longer term storage(15,16).

In contrast to these high-frequency burst patterns in the hippocampus during SWS, neocortical SWS activity is organized into lower-frequency oscillations known as sleep spindles. It has been demonstrated the existence of strong temporal correlations between neocortical spindles and hippocampal ripples can constitute an important mechanism of cortico-hippocampal communication during sleep(1).

Locus coeruleus

The Locus coeruleus (LC) arising catecholaminergic, specifically NE release(17). The LC has been implicated in attentional processes related to orienting behaviors, learning and memory, the sleep-wake cycle. SWS, a state in which activity of LC neurons is normally diminished (18).

NE released in cortex and hippocampus could act through volume transmission to initiate molecular cascades necessary for the formation of a long-term memory trace(19,20). It has been shown that the level of activity of LC neurons, in particular, is of crucial importance for expression of several immediate early genes associated with long-term plasticity(21).

The Ih current

Hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels are important targets of NE to influence neuronal excitability, synaptic transmission, integration and plasticity (4). HCN channels conduct an inward, excitatory current Ih in the nervous system. Ih, a voltage-dependent current that plays a key role in the generation of neuronal oscillation, regulation of oscillatory activity, and is implicated in multiple physiological processes, such as sleep and arousal, learning and memory, sensation and perception(4). Ih can also trigger a rhythmic burst mode firing, delta and spindle oscillations during SWS in thalamo-cortical neurons(22,23). There are some evidences show Ih is required for learning and memory.

Mellor et al (2002) reported that LTP in hippocampal mossy fiber synapses was mediated by presynaptic Ih since the established LTP was blocked and reversed by Ih channel antagonists(24).

Another study reported a dampening of overall neuronal excitability after LTP induction that seemed to result from increased Ih(25). It is in parallel with synaptic potentiation which can promote the ability of pyramidal cells to detect coincident EPSPs(26).

Also, global deletion of HCN1 channels mainly impaired the motor learning, indicating that the integration of Purkinje cells through Ih is essential for motor learning and memory(27).

Hypothesis

Since LC-hippocampal-cortical interaction plays a possible role on memory consolidation in SWS and encouraged by these reports:

1. The role of Ih currents in generation and regulation of neuronal oscillations (4)
2. Neuronal oscillations are characterization of sleep and important for learning and memory (1)
3. The role of Ih currents in sleep, learning and memory (4)

Therefore, our hypothesis is formed based on the possibility of the role of Ih current in the mechanism of memory consolidation during SWS. Through discovering the role of Ih current in learning and memory, we may hope to find a treatment against memory impairments following by sleep disturbances.

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