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The effectiveness and persistence of LTP on synaptic plasticity during sleep and sleep deprivation

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Abstract. The synaptic strength, which is crucial for memory and cognition function, is significantly influenced by sleep. According to earlier research, sound sleep is crucial for promoting connections between neural networks that are necessary for memory consolidation in the hippocampus. On the other hand, sleep deprivation can seriously impair the plasticity of our synapses. Sleep deprivation will disrupt LTP in region CA1 of the hippocampus, causing damage to neural connections. LTP has been proven to improve the connection between synapses, which will promote synaptic plasticity and so influence cognition function favorably. We also take a deeper look at LTP from a cellular and genetic perspective. In this review, we explore the detrimental effects of sleep deprivation on LTP stimulation and how they weaken synaptic plasticity and impair memory and learning performance. By studying LTP we can unravel the mysteries of brain function and the ability to learn and memory, and it can also give implications for understanding neurological disorders and advancing our knowledge of neurol system.

Keywords: Sleep, LTP, NMDA, AMPA, protein synthesis.

1. Introduction

In the past decade, there has been a growing body of evidence linking sleep to cognitive ability [1]. Sleep is an indispensable aspect of life, and sleep deprivation has been shown to diminish the biological capacity for information processing and memory consolidation. Numerous experiments have corroborated the significance of this effect in both animals and humans. In mammals, including humans, sleep patterns can be categorized into REM (rapid eye movement) sleep and non-REM sleep. It is believed that these two distinct sleep patterns exert differential influences on information processing and synaptic plasticity in the brain.

The consolidation and enhancement of memory during sleep primarily arise from synaptic modifications, with synaptic plasticity being closely associated with long-term potentiation (LTP) and long-term depression (LTD). This association stems from the synthesis of new proteins and synapses related to LTP. When individuals or animals experience sleep deprivation, LTP stimulation in the hippocampus becomes impaired, subsequently leading to reduced protein production as well as diminished synaptic plasticity—ultimately impacting memory formation and cognitive abilities.

However, it remains unresolved that which specific sleep pattern predominantly governs LTP induction and synaptic plasticity? whether it involves the forming of new NMDA receptors or AMPA receptors? Furthermore, how does LTP influence new protein synthesis? Is this process intricately linked

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to protein synthesis? These questions persist unanswered. In order to solve these questions, multiple practical experimental methods will be used, including animal model and different tests. By using these methods the empirical and unbiased results will be acquired to better understand the function of LTP.

2. Part I experiment introduction

The first portion of the experiment will examine whether hippocampus long-term potentiation (LTP) will be hampered by REM or NREM sleep deprivation. In order to better understand how sleep deprivation, namely NREM and REM sleep loss, affects the brain's capacity to create and maintain connections in the hippocampus—a vital area for learning and memory—this study will assist. The goal of this article is to acquire a greater knowledge of how various sleep phases affect cognitive functions by looking at how these two forms of sleep deprivation affect LTP. NREM and REM sleep both have been demonstrated to be crucial for memory consolidation in earlier research, but it is still unclear how each of these sleep cycles contributes specifically to the process.

2.1. Methodology of Part I experiment

2.1.1. Animal Model. To conduct this study, Animal models was chosen such as mouse. Mice will be individually housed in cages under 12h light-dark cycle at room temperature (26℃). Then mice will be divided into three groups, labelled control group, REMSD (REM sleep deprivation) group and NREMSD (NREM sleep deprivation) group and will be implanted with devices to test hippocampal EEG signal. After the experiment begin, the mice in control group will remain normal sleep and wake up time, mice in REMSD group will be immediately waken up when they enter REM sleep stage, and mice in NREMSD group will be immediately waken up when they enter NREM sleep stage, and this will be repeated during night cycle (mice will be first exposed to light to live normally for 10 hours then start experiment).

2.1.2. Multiple Platform Method (REM sleep deprivation). To accomplish sleep deprivation on mice, the modified multiple platform approach was used [2]. Mice were kept separately in cages with 12 tiny, cylindrical platforms that sized 3.5 cm in diameter and 3 cm in height, submerged in water that was 1 cm deep. Animals were kept on platforms with free access to water and food pellets. They were startled by falling into the water as REM sleep progressed as a result of muscular atonia [3].

2.1.3. Gentle Handling Model (NREM sleep deprivation). Partial SD models provide a practical way to abruptly abolish portions of the sleep cycle for brief periods of time, despite the fact that it is almost difficult to deliberately block one particular phase or stage of sleep without impacting the other. When animals enter a certain sleep phase (REM or NREM), which is being tracked by EEG recordings or ocular observation, the gentle handling paradigm comprises providing tactile, olfactory, or visual stimulation [4]. Because it needs constant monitoring by the researchers, this paradigm is only helpful for brief periods of time.

2.1.4. Passive Avoidance Test. The passive avoidance test, which makes use of a shuttle box avoidance system, was used to examine mice's capacity to learn and retain stimuli like foot shock. The shuttle box had sections that were both light and dark, as well as a grid floor that was connected to an electric shock source. Mice were placed in the bright compartment after the experiment started, and the door between the two compartments was left open for 10 minutes while the mice explored the box. As soon as the animal entered the dark chamber, the door between the two compartments was shut, and a single electric foot shock (0.7 mA, 1 s) was administered for the purpose of measuring learning. In order to help the mouse connect the dark compartment with fear (foot shock), the mouse was remained there for an additional minute before being taken back to its cage at home. The mouse was placed back in the light room an hour after the initial foot shock, and the step-through latency (the amount of time it took the mouse to enter the dark chamber) was timed. Each set of mice had a retention time to step-through that

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was recorded. After the mice entered the dark compartment, a second electric shock was administered. Mice were once more placed in the lit compartment after another hour in order to assess the step-through latency maximum of 300 s [5]. Compared to longer latency intervals, shorter latency durations signify poor memory recall.

2.1.5. MWM Test. In order to help the mouse connect the dark compartment with fear (foot shock), the mouse was remained there for an additional minute before being taken back to its cage at home. The mouse was placed back in the light room an hour after the initial foot shock, and the step-through latency (the amount of time it took the mouse to enter the dark chamber) was timed. Each set of mice had a retention time to step-through that was recorded. After the mice entered the dark compartment, a second electric shock was administered. Mice were once more placed in the lit compartment after another hour in order to assess the step-through latency maximum of 300 s. Compared to longer latency intervals, shorter latency durations signify poor memory recall. Visible platform training was used for the pre-training water maze exam. At the intersection of the four quadrants, 0.5 cm above the water's surface, a white, cylindrical platform with a diameter of 6 cm was positioned. After being released at random into each of the four quadrants, mice were given two minutes to swim to the platform. Days 1 through 5 (P1–P5) of concealed platform training involved moving the platform to a random place and submerging it 1 cm beneath the water's surface. Each mouse was launched randomly and in a different direction. Every day, training sessions were run with a 30-min break in between, and the latency to each platform was recorded. The platform was taken out of the concealed platform test the day after the last day (day 6), and mice were given 60 seconds to investigate the pool as part of a probing trial. The platform's former location's opposite quadrant saw the discharge of mice. Time spent swimming in each of the four quadrants was noted. To assess memory retention, it was calculated the proportion of time spent in the target quadrant [6].

2.2. Results and discussion of Part I experiment

Using the multiple platform method and gentle handling model, the paper successfully induced REM sleep deprivation and NREM sleep deprivation on mice and then used passive avoidance test and MWM test to measure the effects of SD on mice's ability to learn and remember and their spatial memory. As the results shown, mice with REMSD entered the dark chamber with shorter retention time compared to control group and mice with NREMSD. In the first session of the MWM test, mice from all three groups arrived at the escape platform at around the same times. In sessions 2, 3, 4, and 5, the REMSD group took longer to reach the escape platform since the escape latency time significantly reduced with the number of sessions. As a result, we can say that REMSD primarily hinders animals' learning and memory functions. It can also reduce LTP. As was mentioned in one article, REM sleep plays a role in maintaining synaptic plastic changes in the PP-DG circuit, whereas REMSD after LTP induction severely hinders the maintenance of LTP in the PP-DG pathway [7].

3. Part II experiment introduction

In the second part, the paper will continue to investigate the relationship between sleep and LTP, and my exploration will extend to focusing on NMDA receptors and AMPA receptors and their impact on sleep. These two types of glutamate receptors are fundamental components of synaptic plasticity, which underlies learning and memory processes in the brain, and also are indicators of LTP stimulation. Due to limitation of our lab equipment, the paper will only test on the enhancement of NMDA receptors on sleep. By examining how NMDA receptors impacts sleep, insights into the mechanisms can be acquired through which sleep promotes synaptic strengthening.

3.1. Methodology of part II experiment

To conduct this study, the participants were divided into two groups, one as control group. Both groups were assigned to a learning and memory task at 10p.m. and they will be taught for 1.5 hours. Two groups of participants were advised to retire to bed at 11:30, and the experiment group was given D-cycloserine

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(DCS), a coagonist at the NMDA receptor's glycine binding site that helped declarative memory encoding [8], just before the lights went off. Both groups were awakened up after 7.5 hours of sleep, and their memory functions were then assessed.

The declarative word-pair association task was used to evaluate the participants' memory and capacity for learning after sleeping [9]. First, the participants had to recall a list of 40 word pairings. Performance was evaluated utilizing a cued-recall approach following the display of the whole list, which included feedback of the right word. The cued-recall process was repeated until the individual met the 60% accurate response threshold. The same cued-recall approach used throughout the learning phase was used to measure retrieval at the conclusion of the experimental session. As a gauge of nighttime retention, the absolute disparities between word pairs that were remembered during retrieval testing and on the criterion trial during learning were used.

3.2. Results and discussion of part II experiment

By using this memory test, the paper demonstrated the influence of NMDA receptors on synaptic plasticity during sleep. Experiment result showed that DCS administration before sleep distinctly improved the recall of word pairs at the last session of experiment, and this was essential evidence for the importance of NMDA receptor in consolidation of memory. During REM sleep when brain engages in consolidating newly acquired information into solid memory, the activation of NMDA receptors within hippocampus facilities this process by strengthening synaptic connections between neuron, more specifically speaking, by enhancing LTP.

4. Part III experiment introduction

In the third part, the relation of LTP and new protein synthesis will be discussed. LTP is a cellular model for many forms of learning and memory in hippocampus, and to ensure its stabilization and persistence, the synthesis of novel proteins becomes essential [10]. These newly synthesized proteins are involved in gene expression and contribute to the structural changes at synapses necessary for long-term memory formation. They will also play other important roles such as modulating neurotransmitter release and receptor trafficking during LTP expression, so we can say to some extent LTP is protein-synthesis dependent [11].

4.1. Methodology of part III experiment

Transverse hippocampus slices from rats were cut using a Mcllwain tissue cutter to demonstrate this theory. Following 20 minutes of steady recording, LTP was generated by two 100 Hz, 1 s strand, 20 s apart, at a current strength to elicit field excitatory postsynaptic potentials (EPSP), which were recorded using glass microelectrodes soaked in saline solution and positioned in the stratum radiatum. Then, one set of the test slices was kept in rapamycin, an inhibitor of growth-related protein synthesis, throughout the duration of the recordings [12]. To investigate if LTP is dependent on novo protein synthesis, the intensity of EPSPs will be continually measured.

4.2. Results and discussion of part III experiment

During stable recording, EPSPs of both groups were almost the same, and the readings were around 100% baseline. When LTP was induced, ESPS of both groups increased rapidly to 150%, but after incubating experiment slices into rapamycin, ESPS of experiment group decreased gradually to 110% in 80 min, however ESPS of control group stayed at 150%. This result gave us evidence that LTP in hippocampus require new protein synthesis to remain its persistence.

5. Conclusion

In general, this review explored the connection between sleep, long-term potentiation (LTP), NMDA receptors and protein synthesis, providing an overall view of how these factors intertwine to impact cognitive function and memory. Sleep, which is an indispensable process of life, play a pivotal role in consolidating memories and strengthening synaptic connections, primarily through LTP and LTD. On

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the contrary, sleep deprivation has detrimental effects on LTP, and the results from first part demonstrated that REM sleep deprivation prominently impairs learning and memory processes, suggesting a critical linking between REM sleep and LTP, which also in accord with previous research that REM sleep is important in maintaining high synaptic plasticity. After that, NMDA receptors were proved to strengthen consolidation of memory and enhance LTP function, and LTP was closely dependent on new protein synthesis. From this review we know adequate sleep supports memory consolidation, while sleep deprivation hinders LTP function and thus impair synaptic connections. NMDA receptors and protein synthesis mechanisms provide us cellular and genetic view of this process and give us a deeper understanding of how our brain encode and retain information. This research advances our knowledge of fundamental neurobiology and also highlights the importance of healthy sleep patterns to our cognitive function and memory retention. However, this paper still maintains some deficiency, such as lack of repeated experimentation or limited experiment methods and research targets. For example, the paper only used mouse as model to perform the experiment and all the results were acquired from this single animal model. For future experiments, more models are expected and the results from different models can be analyzed and a more comprehensive conclusion can be made. The future research directions in the field of LTP has been evolved since then, and I think the potential areas of interest may focus on the mechanism of LTP induction, and the relation of LTP to disease. By examining the mechanism of initiation of LTP and the role of LTP in many neurological disorders such as Alzheimer's Disease and Depression, we can better know our brain and advance medical development.

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