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The Potential Role of Nicotine in the Treatment of Learning and Memory Impairment after REM Sleep Deprivation.

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Abstract Sleep deprivation has become a contributing factor to the world's health concerns such as cardiovascular disease, mental illness and inattentiveness in occupationand decision making. It can also disturb synaptic plasticity that can lead to learning and memory impairment. Therefore, boosting cholinergic activity using acetylcholine imitator that can be found in the tobacco plant, known as nicotine, is essential in reversing the negative influences of sleep loss in the brain. Thus, studies on the effects of nicotine treatment on molecular mechanisms and structural changes of hippocampal brain cells are vital in order to gain more understanding and to overcome the detrimental consequencesof learning and memory impairment related to sleep divest.

Keywords: Sleep deprivation, Nicotine, Hippocampus, Learning and Memory Impairment

INTRODUCTION

Numerous people in our society today are unable to obtain sufficient sleep on a daily basis. Social and occupational demands cause them additional pressure to sacrifice sleep in order to meet urbanisation lifestyles and to increase productivity. Chronic sleep loss is associated with chronic problem such as heart disease, kidney disease, high blood pressure, diabetes, obesity and mental illness [21, 26, 31, 33, 43, 44, 60]. In addition, the loss of sleep can also contribute to irritability, aggression, inattentiveness and diminished psychomotor vigilance [34, 48, 59]. Therefore, it is critical to understand the

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molecular and cellular impact of sleep loss on the brain especially hippocampus as an effort to identify novel therapeutic approaches to counteract these effects.

Categories of Sleep

Sleep can be categorized as non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep [55]. These states of sleep are identified and classified based on variouselectrophysiological signals electroencephalogram (EEG) recorded from the brain and neck as well as the eye muscles [39]. NREM sleep is known as slow wave sleep (SWS) due to its synchronous slow-oscillation of membrane potentials in neurons of neocortex area [49]. REM sleep, being an important component of sleep, is also known as active sleep, desynchronized sleep, or paradoxical sleep and is characterised by a desynchronised pattern, high frequency low amplitude waves in electroencephalogram, rapid eye movements and atonia in antigravity muscles [39].

REM Sleep Deprivation Models

Three primary techniques that have been employed to deprive laboratory rats of sleep. The first is the platform-over-water, pedestal or known as flower pot method which is the best method to selectively deprive animals of REM sleep for one or multiple days with only minimum monitoring [32]. The animals are placed in a chamber with one or multiple small platforms surrounded by water. REM sleep is prevented by the muscular atonia in which the rats are awakened when their bodies come into contact with water. For the control group, each rat was placed in the same experimental condition as REM sleep deprivation model except that the diameter of the platform was larger which allowed REM sleep to occur.

The second method utilizes forced locomotion, in which the animal is placed in a chamber with a revolving floor or rotating drum that forces the animal to reposition itself with each revolution [15]. Control animals can be manipulated to move as deprived animals but with longer periods of rest in between in order to prevent excessive sleep loss. The third method is based on gentle handling or mild stimulation. Researchers will make noises, gently jostle the animal's home cage, and disturb the animal's nesting material and in some cases stroke the animal [28]. However, the disadvantage of gentle handling technique is, it requires constants vigilance by the researcher and it cannot be performed over a long period of time.

REM Sleep Deprivation and Impairment of Learning and Memory

Previous reports revealed that sleep contributes significantly to the process of memory and neural plasticity [40, 45, 57]. It is also known that adequate sleep is essential for fostering connections among neuronal networks for memory consolidation in the hippocampus [41]. In fact, hippocampal activity is increased during sleep after a learning task [24, 25].

Formation of memoryin the brain consists of at least three stages: encoding, consolidation and retrieval [2]. Sleep is particularly beneficial to the consolidation stage of memory storage. Manipulation of sleep during this stage will affect the consolidation of memory.The process of learning begins with a transient increase in calcium ions and adenylyl cyclase, an enzyme responsible for the production of the second messenger, cyclic adenosine monophosphate (cAMP) [63]. The second messenger cAMP activates downstream kinases such as calmodulin-dependent protein kinase (CAMKII), mitogen activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK1/2) leads to phosphorylation of transcription factor [3,53]. The transcription factor such as cAMP response element binding protein (CREB), promotes up-regulation of gene expression for a protein that will consolidate labile memories into long-term memories [53]. Therefore, hippocampus dependent memory consolidation (formation and working memory) is particularly sensitive to sleep deprivation.

REM Sleep Deprivation and Hippocampal Synaptic Plasticity

Long-term potential (LTP) and long-term depression (LTD) are forms of hippocampal synaptic plasticity. Sleep deprivation has generally been shown to attenuate the LTP in the hippocampus. McDermott and his colleagues [41] reported that the disturbance in NMDA receptor function can lead to the LTP deficits observed after chronic periods of sleep deprivation and administration of glycine, which enhances N–methyl-d-aspartate (NMDA) receptor function, reversed the effects. NMDA receptors belong to ionotropic (ligand-gated ion channel) glutamate receptors. Glutamate (the primary excitatory neurotransmitter in the central nervous system), will bind to the glutamate receptors and permits the flow of positive ions (Ca^{2+}, Na^{+}) into the cell, creating an excitatory postsynaptic potential (EPSP), a temporary depolarization of postsynaptic membrane potential caused by the flow of positively charged ions into the postsynaptic cell [42]. The glutamate receptors can be divided into two broad categories, metabotropic (G-protein-linked) receptors and ionotropic (ligand-gated ion channel) receptors. Ionotropic receptors are further classified into three major subtypes known as NMDA, AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and kainite [37].

In contrast to the attenuation of LTP, REM sleep deprivation for 12 hours using gentle handling has been shown to enhance LTD in hippocampal slice accompanied by elevated expression of γ-aminobutyric acid ($GABA_\gamma$) and metabotropic glutamate 1γ receptors in hippocampus [58]. Compared to the glutamate, GABA receptors exert an inhibitory influence on postsynaptic neurons, and can be categorised into two major types, the $GABA_A$ and the $GABA_B$ receptors. $GABA_B$ (a metabotropic class receptors) are working through second-messenger systems, as they increase the permeability of the ion channels that permit K^+ to exit the cell, reduce the influx of Na^+ and/or Ca^{2+} into the cell, and inhibit the formation of cyclic AMP by inhibiting adenylyl cyclase, the enzyme responsible for converting ATP into cyclic AMP. All these effects are inhibitory in nature [42]. Thus, the function of NMDA and γ-aminobutyric acid ($GABA_\gamma$) receptors in the hippocampus appears to be an important contributor to modulate the hippocampal plasticity after sleep deprivation.

REM Sleep Deprivation and NMDA Receptor

NMDA receptor activity plays a significant role in all three stages of memory, especially the consolidation phase where the memory from the labile form transforms to a more stable permanent form [30]. Sleep deprivation has been shown to impair proper activation of this glutamate receptor type through altering receptor subunit composition, surface expression and reduced calcium influx [17]. McDermott et al., 2006 found that prolonged sleep deprivation for 72 hours reduced the NMDA/AMPA receptor ratio in CA1 pyramidal cells in response to Schaffer collateral stimulation. NMDA receptor mediated currents from the distal dendrites of CA1 cells causing reduced amplitude due to the reduced surface expression of NMDA receptors after sleep deprivation [41]. The disruption ofthe NMDA receptor trafficking to the cell surface and the reduction in NMDA in the receptor mediated current were also observed after 24 hours of sleep deprivation [18]. Thus, NMDA receptor function is needed for plasticity and memory and longer periods of sleep deprivation disrupt NMDA receptor function and impair both plasticity and memory.

REM Sleep Deprivation and DREAM Protein

DREAM protein is a Ca^{2+}-binding protein of the EF-hand subfamily of neuronal calcium sensors. It is multifunctional and has a highly significant role in the various cell compartments [14]. In the nucleus, DREAM acts as a Ca^{2+}-dependent transcriptional repressor that regulates gene expression [16, 35, 36, 50]. While on the outside of the nucleus; it interacts with A-type potassium channels Kv4, which are voltage-gated potassium channels, directing their

traffic to the plasma membrane and regulating channel gating properties [8, 52]. These channels are concentrated at somatodendritcally that act as crucial regulators of postsynaptic excitability and modulators of synaptic plasticity. In this particular context, DREAM is recognized as a potassium channel γ subunit interacting protein (KchIP3).

DREAM protein has been demonstrated to be involved in the mechanism of learning and memory by functioning as a transcriptional repressor for CREB in a Ca^{2+}-dependent manner. Knockout DREAM gene mice have been reported to facilitate the CREB gene transcription and enhance learning and memory performance [22]. A study using transgenic mice overexpressing a Ca^{2+}-insensitive DREAM mutant (TgDREAM) found that DREAM protein played a role in postsynaptic modulation of the NMDA receptor and contributed to synaptic plasticity and also behavioural memory [62]. The mice lacking the DREAM protein were found to facilitate the learning and memory process by decreased potassium A current (I_A). The results were comparable when the mice were treated with 4-aminopyridine (4-AP, 1mg/kg i.p) ($I_A$inhibitor). The decreased potassium A current (I_A) has been shown to require the activation of NMDA receptors containing the NR2B subunit to facilitate the learning and memory process [23]. All these findings suggest that Kv4.2, DREAM protein and NMDAR protein are integral components of interacting complex that regulates the synaptic efficacy mediating synaptic plasticity and learning via NMDARactivation.

REM Sleep Deprivation and Cholinergic Receptor

The cholinergic system has a significant role in memory formation [20] and a major modulator of neuronal activity [12]. It has been reported that REM sleep deprivation for 96 hours increases acetylcholinesterase, an enzyme that breaks down acetylcholine and reduces muscarinic M2 cholinergic receptors in the pons and hippocampus [56]. Sleep depression for 72 hours has also been reported to increase GABA receptors [61] which lead to the increase in GABAergic signaling and a suppression of the activity of excitatory neurons. It's believed that increased GABAergic activity after sleep deprivation reduces the cholinergic activity and impairs the memory formation.

Therefore, many efforts have been made to boost the cholinergic activity with the aim to reverse the effects of sleep deprivation on memory formation. Systemic administration of nicotine has been found to prevent memory deficit in the hippocampus-dependent radial arm maze task after 24 and 48 hours of REM sleep deprivation, using the platform over water method, [4, 6]that were suggested by the activation of nicotinic acetylcholine receptors particularly the γ7nAch receptor. Nicotine treatment has also been shown to reverse the

impairment in hippocampus synaptic plasticity (LTP) in CA1 and dentate gyrus regions [6]. However, in what way nicotine treatment can prevent learning and memory impairment after sleep deprivation is still unclear.

Nicotine

Nicotine imitates the action of acetylcholine (a natural neurotransmitter) and binds to a particular type of acetylcholine receptor, known as the nicotinic receptor. Whether it is ACh or nicotine that binds to the nicotinic receptor, they respond in the same manner, by changing the nicotinic receptors and causes ion channel to open (for few seconds). The yallow Na^+ to enter the neuron, which depolarizes the membrane and exciting the cell [19]. Then, the channel closes again, and the nicotinic receptor becomestemporarilyunresponsive to any neurotransmitters (desensitization) [19].

History, Structure and Metabolites

Nicotine is an alkaloid found in the nigshade family of plants ("solanaceae") which constitutes approximately 0.6-3.0% of the dry weight of tobacco, with biosynthesis taking place in the roots and accumulating in the leaves [1]. It is named after the tobacco plant called "nicotianatobacum" which in turn is named after Jean NicotDevillemain, a French ambassador to Portugal, who sent tobacco and seeds from Brazil to Paris in 1560 and promoted their medicinal use [1]. Nicotine was first isolated from the tobacco plant in 1828 by German chemists Posselt and Reinmann, and its chemical empirical formulas C_5H_7N was described by Melsens in 1843, while its structure was discovered by Garry Pinner in 1893 as $C_{10}H_{14}N_2$, and it was first synthesized by Apictet and Crepieux, in 1904 [1].

Nicotine is distilled from burning tobacco and carried proximally on tar droplets, which are inhaled. Absorption of nicotine across biological membranes depends on pH (better absorbed in the pH of 6.5 and above) [10]. Nicotine is rapidly absorbed when tobacco smoke reaches the small airways and alveoli of the lung (through pulmonary venous circulation, from which it moves quickly to the left ventricle of the heart and to the systemic arterial circulation).Then the nicotine blood concentrations will rise rapidly and peak at the completion of smoking, and reach the brain in 10-20 seconds [10]. Nicotine binds to the brain tissues with high affinity, and the receptor binding capacity is increased in smokers compared with non-smokers [13, 46], owing to a higher number of nicotinic cholinergic receptors in the brain of the smokers [10].

Blood or plasma nicotine concentrations sampled in smokers generally range from 10 to 50 ng per ml, whereas the peak level of blood nicotine

will decline rapidly inthe next 20 min due to tissue distribution. Besides,the plasma half-life of nicotine after intravenous infusion or cigarette smoking averages about 2 hours [10]. Nicotine is extensively metabolized to a number of metabolites by the liver, the most important metabolite in most mammalian species is the lactam derivative, which is known as cotinine (in humans, about 70–80% of nicotine is converted to cotinine) [10, 51].

Cotinine is present in the blood of smokers in much higher concentrations than those of nicotine, averaging about 250–300 ng per ml in the groups of cigarette smokers, and after stopping smoking, the levels decline in a log linear fashion with an average half-life of about 16 hours [10]. The presence of cotinine in biological fluids indicates exposure to nicotine, due to the long half-life it has been used as a biomarker for daily intake, both in cigarette smokers and in those exposed to second-hand tobacco smoke [9]. Based on the work of Jarvis and his co-workers, who measured cotinine levels in individuals attending outpatient clinics in the United Kingdom in the early 1980s, an optimal plasma cotinine cut-point of 15 ng ml^{-1} were determined to discriminate smokers from non-smokers (some of whom are exposed to second-hand smoke) [11]. Thus, it is vital to measure the blood cotinine level in the subjects of this study to confirm that the subjects have the standard exposure to the nicotine as the chronic smoker does.

Possible mechanism of nicotine treatment

Nicotine treatment has been suggested to activate pre-synaptic nicotine receptors that lead to the increase of glutamate release from the pre-synaptic terminal and as consequences increase the activity of excitatory neurons [27]. Nicotine treatment could also facilitate the activity of excitatory neurons through desensitization of $\alpha 7$nAch in GABAergic neuron and reduce the release of GABA [35]. In addition to that, chronic nicotine treatment has been demonstrated to reverse stress-induced reductions in protein levels of the Brain-Derived Neutrophic Factor (BDNF) [5], a key protein in hippocampal synaptic plasticity [38]. Thus preventing sleep depression induced impairment in memory using nicotine is an excitingfinding. Having said that, how nicotine treatment ameliorates sleep depression induced learning and memory impairment is still elusive and needs further investigation to elucidate the molecular mechanism.

CONCLUSION AND FUTURE DIRECTION

In brief, there is an increased frequency of nicotine consumption in REM sleep deprivation smokers and the initiation of smoking among non-smokers

during REM sleep deprivation [29, 47]. This scenario might be a form of self-medication as acute nicotine treatment prevented REM sleep deprivation induced impairment of short-term memory and synaptic plasticity of hippocampal CA1 [4]. Although there is a wealth of evidence that proved nicotine treatment attenuates the impairment of learning and memory, the protective effect mechanism of nicotine that improves REM sleep deprivation induced learning and memory impairment remain uncertain. Previous studies have proven that the negative effects of REM sleep deprivation can be reversed by taking low dosage of brain stimulant such as nicotine. Nevertheless, the molecular mechanism of how the 'reversible effect' is still under-explored. While REM sleep deprivation prevents long term potentiates (LTP) of neuron in hippocampus and affected molecular expression of certain receptors and proteins such as NMDA receptors, GABAergic receptors, BDNF, p-CREB and DREAM protein, the relationship of these receptors and proteins when nicotine is administered in REM sleep deprivation model has yet to be discovered. There is also very limited literature on the ultra-structural changes of the hippocampal cell in REM sleep deprivation and none on REM sleep deprivation nicotine treatment. Therefore, this information is vital and it may serve the basic facts in understanding the physiological process of REM sleep deprivation and how nicotine could reverse the learning and memory impairment of REM sleep deprivation.

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