



Neurochemistry of Sleep Deprivation

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Abstract

Sleep, a process that repeats itself each night and adheres to the circadian rhythm, is an essential component in maintaining various functions throughout the human body. However, the significance of obtaining enough of this homeostatic process often goes underemphasized in many, such as adolescents and adults, possibly due to necessary further research to adequately understand specific mechanisms and pathways behind sleep's role in the body. With a lack or deprivation of sleep, a multitude of adverse consequences deteriorate physiological and cognitive performance, such as memory consolidation, working memory, learning, awareness, attentiveness, and neural development. This review focuses on the results and methods of previous research examining the effects of sleep deprivation on the expression and abundance of molecules as well as components that influence neural signaling and development in various regions of the brain. This review aims to provide a thorough review on neurotransmitters, with functions including memory and learning, attentiveness and arousal, modulation of neurons, as well as inflammatory signaling in the brain resulting from sleep deprivation and causing deficits in cognitive performance.

Methods

Sources were obtained from Google Scholar based on relevancy and accessibility.

Dopamine

Dopamine is a vital neurotransmitter in learning, motivation and focus, and coordinating locomotor activity. In normal conditions, dopaminergic activity increases early in the day, spiking and returning to baseline levels in response to events, and during sleep, the neurotransmitter regulates sleep stages as various regions of the brain increase or decrease dopaminergic signaling (Kesner and Lovinger). With sleep deprivation (SD), however, dopaminergic activity deviates significantly from typical levels, deteriorating behavior and cognitive functions.

Researchers investigated the effects of sleep deprivation on the binding of dopamine receptors D2 and D3 (Volkow, Wang, et al.). The study included 15 healthy male volunteers, with each participant serving as their own control as they all underwent both a non-SD and a SD session, in a randomized order (Volkow, Wang, et al.). Subjects were kept awake for the entirety of the night during the SD session, while being allowed to sleep during the non-SD session before being woken at 7:00am (Volkow, Wang, et al.). After 3-4 hours from being woken from the non-SD session, participants took a PET scan with [11C]cocaine to examine changes in DAT activity, then took PET scan with [11C]raclopride 1-2 hours after the initial scan to examine changes in endogenous dopamine levels and dopamine receptor availability (Volkow, Wang, et al.). The [11C]cocaine and [11C]raclopride PET scans were performed 27-31 hours after SD session at similar times of the day as the non-SD scans (Volkow, Wang, et al.). To examine behavioral measures, participants were asked to self-report their tiredness, sleepiness, and

restedness on scales from 1-10, with 1 being low experience of the feeling and 10 being strong experience for the feeling, before radiotracers were injected for each scan (Volkow, Wang, et al.). Cognitive performance was measured via a visual attention (VA) test; subjects were asked to keep track of select objects on a screen as they moved around amongst other objects while staring at the screen's center, then were asked to identify the select objects once the screen had stopped moving (Volkow, Wang, et al.). An "n-back" test was also used to evaluate working memory (WM), where subjects were presented with different letters one at a time and were asked to identify if the given letter was the same as the current letter, the one before, or the two before (Volkow, Wang, et al.).

Following SD sessions, subjects reported significantly higher levels of tiredness and desire to sleep and reported significantly lower scores of restedness compared to non-SD reports, while scores for mood did not differ between the two sessions (Volkow, Wang, et al.). SD significantly impaired cognitive performance in the visual attention task and the working memory task, but reaction time did not differ between the two groups (Volkow, Wang, et al.). Analyzing the PET scans revealed that SD did not significantly change DAT levels nor [11C]cocaine binding in the caudate nor putamen, while [11C]raclopride binding significantly decreased in these two regions as well as the thalamus (Volkow, Wang, et al.). Lower levels of [11C]raclopride binding, interpreted as higher levels of extracellular dopamine, were associated with higher scores of sleepiness and tiredness, poorer performance in VA tasks, and deteriorated WM (Volkow, Wang, et al.).

To determine if the decrease in [11C]raclopride binding was due to increased competition with dopamine or if it was due to lower abundance of D2/D3 receptors, several researchers from the previous study continued the investigation in another study (Volkow, Tomasi, et al.). Researchers focused on a pool of 20 volunteer participants using similar exclusion criteria as the initial study, and subjects also participated in a SD and non-SD session in a randomized order to serve as their own control (Volkow, Tomasi, et al.). Subjects self-reported their levels of tiredness, desire to sleep, and restedness on a scale of 1-10 before undergoing PET scans (Volkow, Tomasi, et al.). This time, subjects underwent two scans with [11C]raclopride scheduled similarly to the initial study (around 3-4 hours after waking from non-SD then another scan around 1-2 hours after, while scans were taken 27-28 hours after waking from SD session), but the first scan was performed after a placebo with the second scan being performed with methylphenidate administration (Volkow, Tomasi, et al.).

ROI analysis showed that methylphenidate injection resulted in a decrease of D2/D3 receptor availability in the caudate and putamen between non-SD and SD scans (Volkow, Tomasi, et al.). Researchers theorized that if increased extracellular dopamine were the cause behind the observed decrease in receptor availability, then [11C]raclopride and D2/D3 receptor availability would significantly change with methylphenidate administration inhibiting reuptake of extracellular dopamine; alternatively, if the decreased receptor availability was due to the downregulation of D2/D3 receptors, then administering methylphenidate would not produce a significant change in [11C]raclopride binding nor receptor availability (Volkow, Tomasi, et al.). As

observed, methylphenidate indeed did not produce significant changes in [11C]raclopride nor D2/D3R availability, suggesting the decreased D2/D3 receptor availability caused by SD was caused by downregulation of these receptors (Volkow, Tomasi, et al.).

Results from a microdialysis experiment on 12 male Sprague Dawley rats conducted by researchers corroborated these findings, as SD did not cause significant changes in dopamine levels from control levels, while methylphenidate administration caused a similar increase of dopamine levels in both SD and non-SD mice (Volkow, Tomasi, et al.).

Researchers investigated the effect of sleep deprivation on D2/D3 receptors during visual attention tasks by conducting a study observing fourteen healthy male participants (Tomasi et al.). Each subject participated in a well rested (RW) and sleep deprivation (SD) session set two weeks apart from one another; during SD sessions, participants were kept awake for the duration of the night from midnight to 7:00am, which RW subjects would be woken at the same time (Tomasi et al.). Following each session, participants underwent PET scans, where they were injected with [11C]raclopride beforehand (Tomasi et al.). Afterwards subjects performed a visual attention task while taking an fMRI: the visual attention task involved a ball tracking task that asked participants to track 2-4 balls in a set of ten as they randomly moved around, then were asked to identify if a set of highlighted balls were the same as the ones they were required to track (Tomasi et al.).

SD participants reported significantly higher sleepiness following the sleep deprivation session (Tomasi et al.). Accuracy on the visual attention task decreased in the SD group compared to the RW group, but reaction time was not significantly influenced by sleep deprivation (Tomasi et al.). PET scanning with [11C]raclopride showed that sleep deprivation caused a significant decrease in D2/D3 receptor availability in the ventral striatum, dorsal caudate, and putamen (Tomasi et al.). Association of the D2/D3 receptors with visual-attention activation in the thalamus for the RW group weakened in the SD group and were no longer significant (Tomasi et al.). Researchers found associations between regions of the dorsal striatum and receptor availability during visual attentions tasks, which did not significantly differ between the RW and SD groups; higher caudate to ventral striatum receptor availability ratios were associated with greater activation in the superior parietal cortex and greater deactivation in the ventral anterior precuneus, while higher putamen to ventral striatum receptor availability ratios were associated with greater activation in the anterior cingulate cortex (Tomasi et al.). Larger inaccuracies caused by sleep deprivation in the visual attention tasks were associated with lower activation in the prefrontal cortex (Tomasi et al.).

A preclinical study by researchers was conducted to examine the effects of sleep deprivation on anti-apoptotic response in the brain involving preexisting dopamine shortages (Ahmadian et al.). Researchers utilized Parkisonian male Wistar rats and organized them into four groups: a non-Parkisonian control group that underwent sham surgery, an OH group that received 6-hydroxydopamine to create Parkisonian models, an OH+SD group that received 6-OHDA and were sleep deprived via the modified-multiple platform method (rats were placed on platforms above water which allowed them to freely move between platforms but caused

them to come into contact with water and awaken when entering REM sleep), and a OH+GC group that received 6-OHDA and served as a control for the OH+SD environment with a grid floor above the water allowing them to rest (Ahmadian et al.). After each procedure, rats underwent an open field test in a black, opaque arena for 5 minutes where researchers observed distance travelled to determine motor activity (Ahmadian et al.). The subjects were then euthanized and brain samples were extracted to measure Bcl-2 mRNA and protein expression, Bax mRNA and protein expression, and BDNF levels (Ahmadian et al.).

Distance travelled in OH and OH+GC groups significantly decreased by similar amounts compared to the sham group, while distance travelled in the OH+SD group remained similar to that of the sham group (Ahmadian et al.). Researchers found that striatal BDNF levels were similar between the OH and OH+GC groups and were both significantly higher than the sham group, while BDNF levels in the OH+SD group decreased to below levels in the sham group (Ahmadian et al.). Bcl-2 mRNA and protein expression was significantly higher in OH and OH+GC groups compared to the sham group, while the OH+SD group experienced significantly lower levels of expression compared to the sham group, with expression decreasing beneath the sham group (Ahmadian et al.). Bax mRNA and protein expression in the OH and OH+GC groups did not change significantly from the administration of 6-OHDA, as levels of expression did not significantly differ from the sham group (Ahmadian et al.). In the OH+SD group, though, Bax mRNA and protein expression significantly increased (Ahmadian et al.). Researchers calculated the Bcl-2/Bax expression ratios of OH and OH+GC mice to be significantly higher than sham mice, while OH+SD mice had significantly lower Bcl-2/Bax ratios compared to the sham group, suggesting higher apoptotic signaling (Ahmadian et al.).

Researchers analyzed the effects of sleep deprivation on memory and neuroinflammation in a study involving a sample of CD1 mice (Ugalde-Muñiz et al.). These mice were divided into four groups: a control group, a RSD group that underwent REM sleep deprivation using the multiple-platform method, a QUIN group that received a dose of quinolic acid, and a RSD+QUIN group that underwent REM sleep deprivation while receiving quinolic acid (Ugalde-Muñiz et al.). The mice were examined in several behavioral tests (Ugalde-Muñiz et al.). Swimming speed, distance swam, and latency to reach an escape platform were measured in a Morris Water Maze test where mice were placed into a tank of water with a platform on the surface to evaluate spatial learning and memory; the novel object recognition test observes investigative behaviors and time around new novel objects or familiar objects introduced to the mice, then calculated the percentage in which mice explored the novel object compared to total exploration time; anhedonia was tested for in a sucrose preference test with a 2% sucrose solution and a tap water dish, then calculated the preference for sucrose (indicating the ability to experience pleasure) by measuring the amount of sucrose solution drank versus total volume of fluid consumed (Ugalde-Muñiz et al.). Body mass was also measured before and after RSD and QUIN application (Ugalde-Muñiz et al.). Afterwards, the mice were euthanized and hippocampus, cerebral cortex, and striatum samples were taken to examine TNF- α , IL-1 β , IL-6, and IL-10 levels (Ugalde-Muñiz et al.).

In the cerebral cortex and striatum, cytokine levels were not significantly affected by REM sleep deprivation alone, as levels in RSD mice did not significantly differ from those in the control, but the administration of QUIN decreased the levels of IL-1 β in the cerebral cortex and striatum and decreased IL-10 levels in the striatum, while IL-6 striatal levels increased in RSD+QUIN mice compared to the control (Ugalde-Muñiz et al.). In the hippocampus, REM sleep deprivation increased TNF- α , IL-1 β , and IL-6 levels, while QUIN reduced the levels of these cytokines when administered to RSD mice (IL-10 levels did not significantly change from REM sleep deprivation) (Ugalde-Muñiz et al.). In the Morris Water Maze test and novel object recognition test, REM sleep deprivation was found to significantly impair spatial memory and recognition (Ugalde-Muñiz et al.). Compared to the control group, RSD mice had higher latencies reaching the target platform in the Morris water maze test, spent more time in the water, and swam longer distances while spending less time near the target platform's proximity (Ugalde-Muñiz et al.). Moreover, RSD mice were unable to recognize novel objects, reflected by a reduced preference in novel objects compared to control mice (Ugalde-Muñiz et al.). Administering QUIN to RSD mice significantly reversed the effects of RSD on memory and learning impairment observed in both of these tests (Ugalde-Muñiz et al.). In the sucrose preference test, behavioral signs of anhedonia were observed by the reduced preference for sucrose water in RSD mice and increased weight loss compared to the control group (Ugalde-Muñiz et al.). QUIN attenuated weight loss and the decreased preference for sucrose in RSD mice, while weight loss in non-RSD mice administered with QUIN was significantly lower than RSD mice but still higher than control mice (Ugalde-Muñiz et al.). Moreover, total sucrose solution and water consumption in RSD, QUIN, and RSD+QUIN mice were similar to one another and all significantly lower than total consumption in control mice (Ugalde-Muñiz et al.).

GABA

GABA and GABAergic signaling in the brain acts as an inhibitor, reducing neural activity. In healthy individuals, GABAergic signaling increases before and throughout sleep to slow brain activity in preparation for sleep, while decreasing signaling activity and increasing neural activity in particular regions of the brains that become active during NREM and REM sleep (Ono et al.). In healthy humans, this cycle of GABAergic signaling decreases helps maintain the body's circadian rhythm. Disruptions to this sleep cycle through sleep deprivation, though, significantly alters the GABAergic signaling cycle.

Investigating homeostatic changes in GABA and glutamate receptors, researchers conducted a study on twenty eight adult C57BL/C mice separated into four groups: a control group (SC), a sleep deprived group that was kept awake for 2 hours (SD2), a sleep deprived group that was kept awake for 4 hours (SD4), and a sleep deprived group that was allowed to sleep for 2 hours following a 4 hour period of being kept awake (SR) (del Cid-Pellitero et al.). Sleep deprivation was maintained by brushing the rat's whiskers each time they exhibited signs of entering sleep (del Cid-Pellitero et al.). Behavioral analysis scored each rat on 18 principle behaviors as well as sleep behaviors (del Cid-Pellitero et al.). EEG readings were also obtained

via electrodes cemented underneath the skin (del Cid-Pellitero et al.). Afterwards, the mice were euthanized and brain samples were obtained to conduct immunohistochemistry analyses (del Cid-Pellitero et al.).

In the SD4 group, whisker stimulation was required more often than in the SD2 group in order to keep the mice awake, while the behavior of remaining low increased significantly in SD mice compared to control (del Cid-Pellitero et al.). Researchers associated different brain activities with different stages of sleep: wakefulness, gamma waves; non-REM sleep, delta waves; and REM sleep, theta waves (del Cid-Pellitero et al.). Total gamma activity was found to be the highest in the SD2 group, but this total increase was attributed to the longer duration SD2 mice spent awake, as the average gamma activity between each group did not differ significantly (del Cid-Pellitero et al.). Total gamma activity levels were highest in the SD2 group, attributable to their longer duration awake, while average gamma activity during wakefulness between each group did not differ significantly (del Cid-Pellitero et al.). In SR mice, average delta wave activity during NREM sleep was found to be similar to control mice, which was attributed to increased duration spent in NREM following sleep deprivation to allow for more rest in the delta wave state of sleep (del Cid-Pellitero et al.).

Using immunofluorescent staining for CaMII α to mark pyramidal and similar excitatory neurons, researchers were able to visualize IEG proteins in the barrel cortex of the mice (del Cid-Pellitero et al.). CaMII α + neuron abundance was found to have an insignificant difference between the different groups (del Cid-Pellitero et al.). Staining and looking at c-Fos proteins within these CaMII α + neurons, researchers were able to find a significant abundance in marked cells from SD2 and SD4 mice (staining was slightly lower in the SD4 group compared to SD2, but still remained significantly higher than SC), while the control group had little to no visible c-Fos staining, and the SR group had c-Fos staining mostly in the cytoplasm outside the nucleus as it returned to baseline levels (del Cid-Pellitero et al.). Staining with immunofluorescence to examine Arc displayed a similar trend, with SC cells displaying light staining in the cytoplasm and primary dendrites, which spread to the nucleus and increased to be more evident in SD2 cells and even more evident in SD4 cells, while SR cell staining returned to baseline levels, displaying light Arc staining in the cytoplasm (del Cid-Pellitero et al.). Immunofluorescent staining examining GABA-A receptors on CaMII α + neurons displayed more prominent staining and greater amounts of cells with staining in SD2 and SD4 cells (slightly less than SD2) while SR cells displayed staining on portions of the membrane for some cells, similar to that of the SC group (del Cid-Pellitero et al.). Immunofluorescent staining examining GluA1R displayed increased amounts of GluA1R internalization deeper into the cytoplasm in SD2 and SD4 groups compared to the SC group, with SR staining displaying GluA1R receptors migrating back towards the cell membrane (del Cid-Pellitero et al.).

Investigating associations between GABAergic signaling during REM sleep deprivations and its influence on memory deficits, researchers conducted a study focusing on samples of B6129SF1/J wild-type mice and 3xTg-AD mice to model Alzheimer's disease; researchers separated both groups of mice into a sleep deprivation group, resulting in a sleep control

wild-type group (WT), a sleep deprived wild-type group (WT+SD), a sleep control 3xTg-AD group (3xTg), and a sleep deprived 3xTg-AD group (3xTg+SD) (Varinthra et al.). REM sleep deprivation was induced using the modified-multiple platform method for 4 hours per day for 5 consecutive days (Varinthra et al.). After the 5 days, each mouse underwent a series of behavioral tests, including an open field test, a T-maze test, and a novel object recognition test (Varinthra et al.). In the T-maze test, mice were placed in the stem of the T and only the right branch was initially opened (Varinthra et al.). Afterward, both branches of the T-maze were opened for mice to explore both branches, and preference between the novel and familiar branches were recorded (Varinthra et al.). After the behavioral tests, mice were euthanized and brain samples were collected to observe levels of GABA, GABRA1, GABBR1, and GAD67 in the prefrontal cortex, hippocampus, and dentate gyrus using immunofluorescent staining (Varinthra et al.).

In the T-maze behavioral tests, mice in the WT group showed no preference of a particular branch over the other, while WT+SD mice spent significantly more time in the familiar arm and made significantly less entrances into the novel arm, suggesting a deficit in spatial working memory (Varinthra et al.). The 3xTg and 3xTg+SD groups displayed a similar trend in the reduction in spatial working memory as the WT+SD group, and both made significantly fewer entries into the novel arm and spent significantly more time in the familiar arm (Varinthra et al.). REM sleep deprivation did not induce a significant change in spatial working memory in the 3xTg-AD mice, as the behaviors between the 3xTg and 3xTg+SD mice were not significantly different from one another (Varinthra et al.). In the open field test, locomotor activity and behavior between WT and WT+SD mice did not significantly differ (Varinthra et al.). REM sleep deprivation was found to significantly decrease anxiety-like behaviors in 3xTg-AD mice, as 3xTg+SD mice spent significantly less time near the walls of the field than 3xTg mice (Varinthra et al.). Moreover, REM sleep deprivation increased locomotor activity (distance travelled and speed) in 3xTg+SD mice compared to 3xTg mice, but locomotor activity among 3xTg-AD mice was still significantly lower than both WT groups (Varinthra et al.). In the novel object recognition test, no significant difference was found between the behaviors of WT and WT+SD mice (Varinthra et al.). Overall exploration time for all four groups also did not significantly differ (Varinthra et al.). 3xTg mice had a significantly lower discrimination index compared to WT and WT+SD mice, while the increase in the discrimination index of 3xTg+SD mice to 3xTg mice was found to be statistically insignificant (Varinthra et al.). However, time spent exploring the novel object was significantly lower in 3xTg mice compared to WT and WT+SD mice, and 3xTg+SD mice spent significantly more time exploring novel objects than 3xTg mice (Varinthra et al.).

In the prefrontal cortex, GABA staining in WT and 3xTg mice were similar, while REM sleep deprivation significantly increased the amount of GABA staining in 3xTg mice compared to WT and 3xTg mice and significantly decreased GABA staining in WT+SD mice compared to the baseline (Varinthra et al.). A significant decrease was found among WT+SD, 3xTg, and 3xTg+SD mice compared to WT mice in GAD67 staining (Varinthra et al.). No significant difference was found between GABRA1 staining among the four groups, but GABBR1 staining

was found to be significantly higher in WT+SD mice compared to the other three groups (Varinthra et al.).

In the hippocampal CA1 region, significantly higher amounts of GABA staining were observed between the two sleep deprived groups WT+SD and 3xTg+SD compared to the WT group (Varinthra et al.). WT and 3xTg GABA staining remained statistically similar (Varinthra et al.). GAD67 staining was found to be significantly lower in WT+SD and 3xTg mice compared to WT levels (Varinthra et al.). Like the prefrontal cortex, no significant difference in GABRA1 staining was observed between the four groups, while GABBR1 staining was found to be significantly higher in WT+SD mice compared to 3xTg and 3xTg+SD mice (statistical significance between WT and WT+SD GABBR1 staining was almost reached, but remained statistically insignificant) (Varinthra et al.).

In the hippocampal CA3 region, GABA staining in 3xTg and 3xTg+SD was found to be significantly higher than WT mice with 3xTg+SD GABA staining also being significantly higher than 3xTg levels (an increase in WT+SD staining compared to WT was observed but was found to be statistically insignificant) (Varinthra et al.). GAD67 staining significantly decreased from WT levels in WT+SD, 3xTg, and 3xTg+SD mice (Varinthra et al.). Like the other regions, no significant difference in GABRA1 staining was found between the four groups (Varinthra et al.). GABBR1 staining in WT+SD mice significantly increased compared to WT, 3xTg, and 3xTg+SD mice, with WT and 3xTg mice displaying similar staining levels (Varinthra et al.). 3xTg+SD mice exhibited significantly lower GABBR1 staining than WT mice, but were not significantly different from 3xTg mice (Varinthra et al.).

In the dentate gyrus, GABA staining in 3xTg and 3xTg+SD mice was significantly increased compared to WT, with 3xTg+SD staining levels being significantly higher than 3xTg mice (WT+SD had a statistically insignificant increase from WT) (Varinthra et al.). GAD67 staining levels in 3xTg and 3xTg+SD mice were significantly lower than mice in the WT group, while the reduced levels of staining in the WT+SD group compared to the WT group was found to be statistically insignificant (Varinthra et al.). Uniquely, changes in GABRA1 were observed: GABRA1 staining in WT+SD, 3xTg, and 3xTg+SD mice were significantly higher than WT mice (Varinthra et al.). GABBR1 staining in WT+SD, like the other observed regions, was found to be significantly higher than the other three groups (Varinthra et al.).

Spatial working memory in wild-type mice was directly associated with GABA in the PFC, GAD67 in the CA1 and CA3 regions of the hippocampus, and was negatively associated with GABA in the two hippocampal regions and in the dentate gyrus, and GABBR1 in the PFC and CA3 region (Varinthra et al.). In the 3xTg mice, different associations between GABAergic signaling and spatial working memory were found; spatial working memory in these mice were directly associated with GAD67 in the CA1 as well as GABRA1 in the PFC as well as the CA1 and CA3 hippocampal regions, and negative associations were made with GABBR1 in the PFC and GAD67 in the dentate gyrus (Varinthra et al.).

Researchers studied the effects of sleep deprivation on GABA and cancer growth (Bao et al.). A group of male C57BL/6 mice and BALB/C mice were utilized for the study, with the

C57BL/6 mice being used in a sleep deprivation model; the C57BL/6 mice were separated into a control and sleep deprivation group kept awake by a sliding rod at the bottom of their enclosure (Bao et al.). Mice from the control and sleep deprivation group were then utilized in the AOM/DSS-induced mouse colon cancer model, while the BALB/C mice were separated into the xenograft subcutaneous implantation mode or the pulmonary metastasis model (Bao et al.). In the AOM/DSS model, mice were injected with AOM followed by a DSS feeding pattern for 10 weeks with half of them also receiving administrations of GABA, after which they were euthanized and colon samples were obtained (Bao et al.). With the samples, researchers examined peripheral blood GABA levels, colon polyp growth, lung metastasis, macrophage recruitment, as well as epinephrine, norepinephrine, and serotonin levels (Bao et al.). In the xenograft model, the mice were separated into a sleep deprivation model or a group with various treatments; in the sleep deprivation model, colon cancer cells were injected subcutaneously while tumor growth was monitored every 5 days for 20 days before subjects were euthanized; the other group of mice were injected with colon cancer cells subcutaneously as well, with some of them receiving cells transfected with mimic siRNA overexpression plasmids, after which tumor growth was monitored weekly before the mice were euthanized after 4 weeks (Bao et al.). The samples were then analyzed to observe tumor growth and miR-233-3p, CBLB, cMYB pathway markers (Bao et al.). BALB/C mice in the pulmonary metastasis model were separated in a similar manner as the xenograft model with a sleep deprivation model and a group involving similar transfected cells (Bao et al.). This injection this time, however, occurred in the tail vein of the mice, after which the mice were euthanized after 2 months in order to examine cancer development using HE staining and immunohistochemistry (Bao et al.).

In each of the models, cancer cell development was found to be significantly higher and tumors to be significantly larger in sleep deprivation groups than in control groups (Bao et al.). In the AOM/DSS sleep deprivation model, researchers found that VGAT and GAD1 expression significantly increased with sleep deprivation while GAT1 expression decreased, suggesting increased GABA synthesis and transport with decreased reuptake, explaining increased peripheral blood GABA levels (Bao et al.). Immunohistochemical staining, moreover, revealed that colon cancer spread and growth increased with higher peripheral blood GABA levels induced by sleep deprivation (Bao et al.). In the xenograft and pulmonary model, researchers also found increased cancer development in the form of increased abundance and size of pulmonary nodules in sleep deprived mice compared to control groups (Bao et al.). Additionally, mice treated with GABA in these models also had a significant increase in tumor size and weight as well as an increased amount of pulmonary nodules compared to the non-GABA PBS treated groups, suggesting promoted the growth and spread of these tumors (Bao et al.). In the pulmonary model, immunofluorescence also revealed that macrophage recruitment significantly increased in the GABA treated mice compared to the PBS treated mice (Bao et al.).

Aiming to track the effects of sleep deprivation on GABA and mGluR expression, researchers conducted a study around a set of male Wistar rats separated into a control and

sleep deprived group that was kept awake by gentle tapping or prodding whenever the rats assumed sleeping posture (Tadavarty et al.). After 12 hours of sleep deprivation, the rats were euthanized and brain samples were collected and transverse sections of the hippocampus were obtained (Tadavarty et al.). Through various assays, researchers were able to determine measurements of various characteristics and levels: pEPSP amplitude, LTD magnitude, GABA-B-R1 and GABA-B-R2 co-localization, mGlu5R, mGlu1 α R, heterodimerization, intracellular Ca²⁺, and serum corticosterone (Tadavarty et al.).

Researchers found that LTD in sleep deprived rats significantly strengthened when pEPSPs was measured, suggesting weakening synaptic strength in the SD group (Tadavarty et al.). Moreover, when determining the requirement for mGluRs in LTD, LTD response was found to be significantly reduced when mGluRs were blocked (Tadavarty et al.). Additionally, although LTD became partially blocked when GABA-B receptor agonists were introduced in the control group, LTD was entirely blocked in the SD group with the introduction of GABA-B receptor agonists (Tadavarty et al.). Similarly, when blocking the release of Ca²⁺ from intracellular stores, reduced LTD induction, indicating a requirement for Ca²⁺ in LTD (Tadavarty et al.). In the CA1 region of the hippocampus, GABA-B-R1 and mGlu1 α expression were found to be significantly increased in the SD group compared to the control, with mGlu α also associating with GABA-B-R1 and GABA-B-R2 more strongly in SD rats (Tadavarty et al.). These two receptors, GABA-B-R1 and GABA-B-R2, were also found to display stronger co-localization in the SD group than the control (Tadavarty et al.).

TNF

Tumor Necrosis Factor (TNF) is a crucial pro-inflammatory cytokine responsible for immune response, cell differentiation, and cell death. Typically, TNF will accumulate over the day as one remains awake before gradually declining during sleep before returning to baseline levels in the morning (Zielinski and Gibbons). However, without the opportunity to allow TNF levels in the brain to naturally return to baseline levels at night, TNF and its pro-inflammatory effects can remain in the brain after sleep deprivation, causing neuroinflammation and possible harm to nearby cells.

Investigating the effects of sleep deprivation on morning markers of inflammation, researchers conducted a study focusing on 30 healthy adult volunteers, comprising 17 men and 13 women (Irwin). Subjects underwent 3 days of baseline sleep where they were able to sleep from 11pm to 7am (Irwin). Subjects then underwent partial sleep deprivation and were kept awake 11pm to 3am before being allowed to rest until 7am (Irwin). After each baseline and partial sleep deprivation session, blood samples were collected at 8am, 12pm, 4pm, 8pm, and 11pm (Irwin). Several assays were conducted on the samples: an assessment of intracellular production of IL-6 and TNF- α by monocytes using flow cytometry; RT-PCR to quantify IL-6 and TNF- α gene expression; and DNA microarray tracking genome-wide mRNA expression (Irwin).

Following partial sleep deprivation sessions at 8am, the percentage of monocytes producing IL-6 and TNF- α significantly increased compared to baseline levels, which eventually

returned to baseline levels in subsequent samples (Irwin). The RT-PCR assay showed a significant increase of IL-6 and TNF- α mRNA expression compared to baseline levels, with IL-6 increasing by a factor of 3.5 and TNF- α by a factor of 2 (Irwin). Moreover, researchers were able to identify twenty-two genes significantly upregulated after partial sleep deprivation from the DNA microarray and one gene (GOLGIN-67) that was significantly downregulated after partial sleep deprivation (Irwin)). Many of the twenty two genes that were upregulated were associated with an increase in inflammatory signaling and cellular stress response. No significant difference between the sexes were observed in the results (Irwin)).

Researchers studying the influence of TNF- α ligands and TNF- α receptors on sleep conducted a study involving a sample of mice possessing four genotypes: wild-type mice (WT), ligand knockout mice (KO), TNF- α receptor 1 knockout mice (R1KO), and TNF- α receptor 2 knockout mice (R2KO) (Deboer et al.). EEG electrodes over the right occipital cortex and EMG electrodes over neck muscles were implanted in each mouse to monitor wakeful and sleep activity (Deboer et al.). Afterwards, each mouse underwent a 24 hour baseline session, then a 6 hour sleep deprivation session, and lastly a 18 hours of sleep recovery (Deboer et al.). Sleep deprivation was induced by cage tapping when signs of sleepiness were displayed, and cages were swapped halfway through the sleep deprivation period to provide stimulation and exploratory behavior (Deboer et al.).

During baseline sleep, KO and R2KO mice displayed a statistically significant decrease in the amount of REM sleep compared to WT mice, while the decrease in R1KO REM sleep was found to be statistically insignificant; this difference in REM sleep was attributed to a decrease in REM sleep episodes rather than decreased duration of each episode (Deboer et al.). No significant difference was found in responses to sleep deprivation between each group, and during sleep recovery, all four groups displayed a similar pattern of an increase then gradual decrease in slow-wave NREM activity before declining over time (Deboer et al.). EEG recordings of slow-wave activity were split into slow (0.75-2.5Hz) and fast (2.75-4.0Hz) slow-wave activity, and during baseline sleep, a significantly higher amount of EEG power in portions of the slow-wave range in KO mice was shown compared to the other three groups (Deboer et al.). After sleep deprivation each group experienced changes in slow and fast SWA (Deboer et al.). Both slow and fast SWA significantly increased from baseline sleep in the WT group before declining during the dark period; KO slow SWA did not significantly change, but fast SWA significantly increased, exceeding WT levels and remaining elevated for a longer duration; slow SWA in R1KO mice followed a similar pattern to WT mice after sleep deprivation, increasing significantly before eventually declining, while fast SWA in R1KO mice did not significantly change; both slow and fast SWA in R2KO mice significantly increased, fast SWA exceeding WT levels, before declining similarly to WT (Deboer et al.).

Researchers investigated the impact of TNF- α on memory loss and anxiety compounded with sleep deprivation and focused on a sample of C57BL/6 mice (Zhang et al.). The mice were organized into two groups: a control group and a sleep deprivation group that was sleep deprived for 72 hours (Zhang et al.). Prior to the sleep deprivation session, mice in the SD group

were given various experimental treatments: a saline injection, PGRN injection (PGRN was injected 3 days before sleep deprivation), TNF- α injection, a PGRN or TNF- α injection along with thalidomide, or both PGRN and TNF- α (Zhang et al.). Sleep deprivation was induced by using the water platform method, which researchers reported reduced slow wave sleep and a majority of REM sleep (Zhang et al.). 24 hours after sleep deprivation or rest, the mice underwent a set of behavioral evaluations, including a novel object recognition test, an object-location recognition test encountering a familiar object in a different location, a Morris Water Maze test, an open field test, and an elevated plus maze test evaluating duration and instances mice spent in enclosed or exposed sections of a platform (Zhang et al.). Following behavioral tests, mice from each experimental group were euthanized either immediately after or after 6 hours, 12 hours, or 24 hours of sleep recovery after behavioral tests (Zhang et al.). Several analyses were conducted on the brain samples, including western blot measuring protein levels, Golgi-Cox staining measuring dendritic spine density, and EdU staining measuring neurogenesis (Zhang et al.).

Sleep deprivation significantly influenced the behaviors of mice in each behavioral test (Zhang et al.). Mice in the SD group spent significantly less time exploring novel objects in the novel object recognition test compared to the control group, while overall movement between the groups were not significantly different, indicating impaired recognition memory in SD mice (Zhang et al.). In the novel object-location test, SD mice displayed significantly lower preference to displaced objects compared to control mice, while overall movement did not significantly differ, indicating impaired spatial memory in SD mice (Zhang et al.). In the Morris Water Maze test, SD mice displayed a longer latency in locating and reaching the target platform as well and spent less time in the target quadrant compared to control mice, while swimming velocities between the two groups did not significantly differ (Zhang et al.). In the open field test, SD mice travelled significantly shorter distances and significantly shorter time spent in the center than control mice, displaying anxiety in their behavior (Zhang et al.). In the elevated plus maze test, overall entries into the closed and open arms were similar, but SD mice made significantly fewer entries and spent less time in the open arms than the control group, indicating anxious behavior (Zhang et al.).

Western blot analysis showed that sleep deprivation significantly increased TNF- α and p-IkB α levels as well as increased p-IkB α /IkB α ratios, while PGRN and p-CREB in the hippocampus significantly decreased after sleep deprivation (Zhang et al.). TNF- α and PGRN levels returned back to baseline levels after 24 hours of sleep recovery (Zhang et al.). In SD mice, PGRN administration significantly increased p-CREB levels while significantly reversing the increased TNF- α levels and the increased p-IkB α signaling levels caused by sleep deprivation (Zhang et al.). Thalidomide administration significantly decreased TNF- α levels (Zhang et al.). The Golgi-Cox analysis showed that sleep deprivation significantly reduced spine density in the CA1 region (Zhang et al.). TNF- α administration did not significantly attenuate reduced dendritic spine density, but PGRN administration was able to significantly increase dendritic spine density (Zhang et al.). EdU staining showed that sleep deprivation significantly

decreased the abundance of EdU-positive cells in the dentate gyrus (Zhang et al.). PGRN treatment significantly reduced the decrease in EdU-positive cells caused by sleep deprivation, while the administration of TNF- α did not cause any further reduction of EdU-positive cells (Zhang et al.).

Investigating the TNF- α pathway's role in sleep deprivation's impact on cognitive dysfunction, researchers focused on a sample of male C57BL/6 mice and mice with a TNF- α receptor double knockout genome (Ramesh et al.). EEG and EMG electrodes were implanted in the mice (Ramesh et al.). A portion of mice from each group underwent sleep fragmentation using a sleep fragmentation cage with a motorized sweeper (Ramesh et al.). Mice experienced sleep fragmentation during their typical sleep period from 7am to 7pm for 15 days (Ramesh et al.). Moreover, a portion of sleep-fragmented mice from both groups were injected with TNF- α neutralizing antibodies throughout the sleep fragmentation session (Ramesh et al.). Afterwards, mice underwent a series of behavioral tests, including a Morris Water Maze test, a forced swim test, and an elevated plus maze test (Ramesh et al.). Following the behavioral tests, the mice were euthanized and brain samples were collected for various assays: qRT-PCR measuring mRNA expression of various inflammatory and inflammatory-signaling molecules, ATP bioluminescence, TNF- α ELISA, western blot, CREB DNA-binding, and immunohistochemistry assays (Ramesh et al.).

Compared to control groups, sleep-fragmented groups displayed significantly more wake episodes and wake episodes during the light periods as well as increased theta activity during wakefulness, while slow-wave sleep latency significantly decreased (Ramesh et al.). However, total time spent awake, in slow-wave sleep SWS, and in REM sleep did not significantly change after sleep fragmentation nor delta power during SWS (Ramesh et al.). In the Morris Water Maze test, sleep fragmentation significantly hindered the mice's performance, as they displayed high latencies to reach the target platform as well as longer paths taken to reach the platform compared to mice that had not undergone sleep fragmentation (Ramesh et al.). Swim speed, though, was not affected by sleep fragmentation (Ramesh et al.). In the forced swim test, sleep-fragmented mice spent significantly more time immobile during the last 4 minutes of the test as well as overall (Ramesh et al.). In the elevated plus maze test, sleep-fragmented mice spent significantly less time in the open arms and made more entry in the closed arms (Ramesh et al.). However, the effects of sleep fragmentation on sleepiness and spatial memory in these tests among the TNF- α double knockout mice as well as mice injected with TNF- α neutralizing antibodies were significantly reduced (Ramesh et al.).

The qRT-PCR assay showed a significant increase in expression of TNF- α mRNA and TNFR1 mRNA after sleep fragmentation as well as increased expression of PDE4, while IL-6 mRNA and IL-1 β mRNA expression did not significantly change after sleep fragmentation (Ramesh et al.). Moreover, cortical TNF- α levels significantly increased after sleep fragmentation (Ramesh et al.). The immunofluorescence assay showed a significant increase in TNF α staining following sleep fragmentation and was associated with cells marked with NeuN (Ramesh et al.). Sleep fragmentation was associated with significantly reduced CREB activity

and p-CREB, but there were no significant changes in either ATP or AMPK- α levels after sleep fragmentation (Ramesh et al.).

Researchers studying the involvement of TNF- α and TNF- α receptors in narcolepsy conducted a study focusing on 30 volunteers with narcolepsy (Himmerich). One hundred twenty healthy control volunteers were age-and-sex-matched with the volunteers with narcolepsy, and another 101 healthy control volunteers were age-and-sex-BMI matched with the volunteers with narcolepsy for a second control group (Himmerich). Researchers collected blood samples from each volunteer following an overnight fast of 6-10 hours (Himmerich). Afterwards, researchers conducted ELISA assays on the blood samples to measure plasma concentrations of sTNF-R p55 and sTNF-R p75 (Himmerich).

The BMIs of subjects with narcolepsy were found to be significantly higher than the sex-and-age matched control group, while the BMIs of the narcolepsy and sex-and-age-and-BMI matched control group had no significant difference (Himmerich). Plasma concentrations of TNF- α were not significantly different between all three groups (Himmerich). Plasma concentrations of sTNF-R p55 were found to be significantly higher in subjects with narcolepsy, particularly female subjects, than sex-and-age matched subjects, but when also matched for BMI, the difference became statistically insignificant (Himmerich). Plasma concentrations of sTNF-R p75, however, were found to be significantly increased in subjects with narcolepsy than both control groups matched for sex-and-age as well as sex-age-and-BMI, with a more pronounced increase of sTNF-R p75 plasma concentrations in female volunteers with narcolepsy (Himmerich).

Orexin

Orexin is a neuropeptide that plays a key role in regulating arousal, wakefulness, and attentiveness while preventing the onset of REM sleep during wakeful periods. In the onset of sleep in a healthy human, orexin production will decrease to allow sleep-promoting regions of the brain to induce rest, but orexin still plays a role during sleep in regulating and inhibiting REM sleep during NREM sleep (Grivel et al.). However, with sleep deprivation, desired cycles and levels of orexin can fluctuate and progress into sleeping disorders, affecting wakefulness and attentiveness throughout one's waking period.

Investigating the influence of orexin-A on the effects of sleep deprivation, researchers conducted a study involving eight adult male rhesus monkeys, each of which underwent six experimental conditions: no SD, no SD with intravenous orexin-A, no SD with intranasal orexin-A, sleep deprivation for 30-36 hours, sleep deprivation for the same duration with intravenous orexin-A, and sleep for the same duration with intranasal orexin-A (Deadwyler et al.). To induce sleep deprivation, researchers kept each monkey in a lighted room with videos, music, occasional treats, cage shaking, and interactions with researchers (Deadwyler et al.). During orexin-A conditions, orexin-A was administered to monkeys before cognitive tests; saline was administered to monkeys during sessions not involving orexin-A (Deadwyler et al.). Under each condition, monkeys performed a delayed match-to-sample test to evaluate visual and

working memory as well as attention (Deadwyler et al.). Moreover, monkeys underwent a low-cognitive load delayed match-to-sample test as well as a high-cognitive load delayed match-to-sample test with more stimuli to memorize and longer delays between each prompt (Deadwyler et al.). FDG was administered before each monkey underwent PET scans to track FDG uptake and CMRglc, particularly in dorsolateral prefrontal cortex, dorsal striatum, thalamus, and medial temporal lobe (Deadwyler et al.).

After 30-36 hours of sleep deprivation, delayed match-to-sample performance significantly deteriorated with more errors compared to rested monkeys; this performance deterioration was amplified in high-cognitive load tests (Deadwyler et al.). Administering orexin via i.v., though, reduced the deteriorated performance caused by sleep deprivation and continued to improve performance with larger doses; orexin-A performance in sleep deprived monkeys was especially improved in high-cognitive load trials (Deadwyler et al.). The reversal effects of orexin-A on sleep deprivation were even greater when administered intranasally, and high-cognitive load performance in sleep deprived monkeys surpassed low-cognitive load performance with intranasally administered orexin-A (Deadwyler et al.). With rested monkeys, though, orexin-A did not produce a significant change in performance when administered (Deadwyler et al.). PET scans showed that sleep deprivation caused a significant decrease in CMRglc in the DLPFC, dorsal striatum, and thalamus, while CMRglc in the medial temporal lobe significantly increased (Deadwyler et al.). When administered with orexin-A via i.v., the effects of sleep deprivation on CMRglc were reversed, with decreased levels of CMRglc significantly increasing in the DLPFC, dorsal striatum, and thalamus and increased levels of CMRglc in the medial temporal lobe decreasing (Deadwyler et al.). The reversal effects of orexin-A on sleep deprivation's impact on CMRglc were greater when administered intranasally (Deadwyler et al.).

Researchers studying the effects of sleep deprivation on GABA receptors on orexin (Orx) and melanin-concentrating hormone (MCH) neurons studied a sample of adult male C57BL/6 mice, which were divided into three groups: a normal rested group (SC), a 2-hour sleep deprivation group (SD), and a sleep deprivation group followed by sleep recovery (SR) (Toossi et al.). Sleep deprivation was induced by whisker stimulation whenever mice displayed behavioral signs of falling asleep (Toossi et al.). Researchers implanted EEG and EMG electrodes in each mouse before each sleep session (Toossi et al.). Afterwards, the mice were euthanized and brain samples were collected (Toossi et al.). Researchers used immunohistochemical analysis to measure c-Fos, Arc, GABA-AR, GABA-BR, and GluA as well as immunofluorescence to detect Orx and MCH neurons (Toossi et al.).

After SD the percentage of Orx neurons present with GABA-AR staining and staining intensity significantly increased from the SC group (Toossi et al.). The decrease in percentage of MCH neurons present with GABA-AR was found to be statistically insignificant, but the intensity of GABA-AR staining on these neurons significantly decreased (Toossi et al.). After 2 hours of sleep recovery in the SR group, the percentage of GABA-AR stained neurons and staining intensity returned back to baseline levels (Toossi et al.). The percentage of Orx and MCH neurons containing GABA-BR staining did not significantly change after SD compared to mice in

the SC group, but GABA-BR intensity followed a similar pattern to that of GABA-AR following SD, as GABA-BR staining intensity increased on Orx neurons, while it decreased on MCH neurons (Toossi et al.).

Researchers investigating the effects of sleep deprivation on orexin-A conducted a study focusing on fourteen adult male Sprague Dawley rats separated into either an acute sleep deprivation group or a chronic sleep deprivation group, and were implanted with EEG and EMG electrodes as well as a cannula to administer orexin-A into the ventrolateral preoptic area (VLPO) (DePorter et al.). Before conducting sleep deprivation, each rat underwent a sleep control session without deprivation (DePorter et al.). Prior to the sleep deprivation sessions, orexin-A was administered into the VLPO via the cannula then once more after the experimental session, and infrared sensors were utilized to monitor each rat's movement, including distance travelled and physical movement, while researchers calculated the rats' energy expenditure and energy expenditure on physical activity as well as their respiratory quotients (DePorter et al.). Sleep deprivation was induced by exposing rats to prerecorded noises; acute SD rats were sleep deprived for 12 hours and chronic SD rats were sleep deprived for 8 hours a day for 9 days (DePorter et al.). Afterwards, orexin-A was administered through the cannula again, and movements and metabolic measurements were reassessed (DePorter et al.).

Prior to sleep deprivation, administration of orexin-A reduced NREM and REM sleep in the mice, increasing wakefulness (DePorter et al.). Movement and physical activity also increased, as distance travelled was measured to be significantly greater; total energy expenditure and energy expended on physical activity also increased following orexin-A administration, and the calculated respiratory quotient decreased (suggesting increased fat oxidation) (DePorter et al.). Following acute sleep deprivation, the effects of orexin-A increasing each measurement were attenuated by sleep deprivation, as the increases in several factors (distance travelled and energy expenditure) were no longer statistically significant, while orexin-A's effect on energy expenditure during physical activity was significantly reduced by deprivation (respiratory quotient, though, was not significantly affected by SD) (DePorter et al.). The effect of chronic sleep deprivation on orexin-A's effects attenuated each of these factors even further; orexin-A's effect on increasing distance travelled, total energy expenditure, and energy expenditure on physical activity were significantly reduced by chronic sleep deprivation, and orexin-A's reduction of the respiratory quotient, which was shown to be unaffected by acute SD, was now significantly reduced by chronic sleep deprivation, indicating a significant reduction of fat oxidation (DePorter et al.).

Researchers studied the effects of sleep deprivation on orexin neurons and their response to noradrenaline by focusing on a sample of Sprague-Dawley rats (Grivel et al.). The rats underwent a sleep control session without sleep deprivation or a sleep deprivation session (Grivel et al.). Afterwards, the rats were euthanized and hypothalamic brain slices containing orexin (Orx) neurons were collected (Grivel et al.). Electrophysiological experiments were conducted before and after the application of noradrenaline alone or paired with tetrodotoxin or paired with a high-magnesium/low-calcium solution onto the brain samples (Grivel et al.).

In Orx neurons, noradrenaline caused an excitatory response in most neurons observed, while sleep deprivation caused a statistically significant change in Orx neuron response to noradrenaline, as a noradrenaline instead caused an inhibitory response in Orx neurons when applied (Grivel et al.). Electrophysiological results showed a lack of significant difference in resting membrane potential and firing frequency between Orx neurons in the sleep control and the sleep deprivation studies (Grivel et al.). However, after applying noradrenaline, the membrane potential and firing frequency significantly increased in Orx neurons from the sleep control group, while the membrane potential and firing frequency of the sleep deprivation Orx neurons significantly decreased (Grivel et al.). The persisted inhibition response to noradrenaline from Orx neurons from the sleep deprived group and the excitatory response to noradrenaline from Orx neurons from the sleep control groups after the application of tetrodotoxin and high-magnesium/low-calcium solutions verified that noradrenaline's impact on these neurons were postsynaptic (Grivel et al.).

Discussion

As shown by previous clinical and preclinical research, sleep consistently plays a vital role in preserving cognitive function and processes. These studies have associated deprivation of REM sleep with significant deterioration of spatial and working memory as well as learning, displayed by poorer accuracies in memory and recognition. Moreover, these studies found sleep deprivation to have a significant impact in inhibiting and reducing neural activity via increased sensitivity and response to GABAergic signaling through various pathways. Observations have also found different levels of glucose uptake in regions of the brain and neurons associated with sleep or typically increasing activity during sleep, such as MCH neurons and areas within the medial temporal lobe (Toossi et al.). A consistent result of increased inflammatory markers and cytokines has also been linked to sleep deprivation in these studies, particularly by increases in these signaling molecules and respective receptors, which were associated with deficits in cognitive function.

Notably, several of these studies have found specific molecular procedures that reduced or blocked the pathways of these harmful consequences caused from sleep deprivation, such as the administration of orexin-A reversing the deterioration of working memory (Deadwyler et al.), PGRN attenuating inflammatory signaling molecule levels (Zhang et al.), or the disruption of inflammatory signaling altogether (Deboer et al.). These treatments suggest that there may be solutions to combat the reduction of cognitive efficiency caused by sleep deprivation, possibly being able to allow one to function near normal levels. Alternatively, these treatments could be used to directly combat chemical accumulation or deficiencies in the brain caused by sleep deprivation and associated with said cognitive deterioration.

Several pharmaceutical drugs have already been approved that have been proven to be effective in combating various sleep disorders. Already widely available to consumers, melatonin has been found to be effective in improving sleep quality by realigning sleep-wake cycles that have been disrupted by conflicts with an individual's day-night schedule or sleep

disorder (Xie et al.). More recently, orexin-2 agonist oreporexton has been more recently approved by the FDA as a treatment against narcolepsy type 1 in adults; in a clinical study, adults with narcolepsy treated with oreporexton showed significant reduction in attention lapses, improvements in working memory, and improved executive function such as recognition speed, attenuating effects of narcolepsy (Lammers et al.). American Ginseng has been found to significantly reduce various cognitive deterioration caused by sleep deprivation in rats, and when paired with Muscimol, Ginseng was able to reverse the effects of sleep deprivation back to or nearly back to baseline levels (Chanana and Kumar).

However, the consequences of REM sleep deprivation must not be understated, as even with these observed treatments that have seemingly negated the impact of sleep deprivation in cognitive function, the physiological impact, from degenerative disease to proliferation of cancer and tumor growth, likely still remains with chronic poor sleep hygiene (Bao et al.). Inhibition of neurogenesis, increased expression of genes and proteins associated with the promotion of neural apoptosis, and conversely the decreased expression of regulatory genes preventing this cell death have been linked to sleep deprivation (Ahmadian et al.); these consequences are largely irreversible if accumulated to a great magnitude over time, as regeneration of new neurons to compensate is a lengthy process that may not be sufficient enough to completely restore damage.

Yet, many of the specific pathways linking sleep deprivation to these health and molecular changes are still not fully understood and have not been solidified. Additional research is necessary to effectively address key components or processes of pathways through which sleep deprivation promotes these widespread consequences. A portion of this hurdle may be attributed to the conventional, invasive procedures required to administer effective, but invasive, experimental procedures to accurately simulate desirable conditions and precise measurements of observed molecules; procedures such as neural toxins or acids destroying target components of the brain as well as Alzheimer's and Parkinson's models required to isolate the effects of signaling pathways, then need to euthanize subjects to extract brain and measure samples are too invasive to perform in clinical research, restricting many of these studies to preclinical studies on mice or rat subjects. While these preclinical studies have provided substantial insight into the nature of sleep deprivation and cognitive function, it simply cannot completely replicate the effects of sleep deprivation on human subjects, such as emotion, perception, or social interaction.

Further research into the mechanisms of sleep and health consequences resulting from a lack of it, as well as incorporating sleep's role into maintaining the health of the human body similar to other physiological processes may combat widespread deteriorations in cognitive and physiological symptoms caused by unsuspected lack of proper sleep.

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