Chapter 2
Sleep Deprivation, Cognitive Functions, and Countermeasures

Usha Panjwani, Meetu Wadhwa, Koushik Ray, and Krishna Kishore

Abstract Sleep is necessary for the execution of cognitive functions. Sleep disturbance causes cognitive impairment in humans as well as rodents. Sleep is essential for neurogenesis, synaptic plasticity, and hippocampus-based memory consolidation. This process is impaired by sleep deprivation and may involve multiple pathways. Hippocampus is an essential player in the brain, which is involved in the execution of various cognitive functions and maintains neurogenesis and synaptic processes. At the same time, it is also more vulnerable to stress. Caffeine and modafinil are recognized psychostimulants, known to improve sleep deprivation-induced cognitive function decline in humans as well as animals. Caffeine and modafinil are well-evaluated countermeasures against sleep deprivation-induced alterations in the neuronal cell proliferation and synaptic plasticity mechanism. The article describes the sleep deprivation-induced deficit in cognitive function, its molecular mechanism, and the effect of psychostimulant drugs, caffeine, and modafinil.

Keywords Sleep deprivation · Cognition · Caffeine · Modafinil · Neurogenesis · Synaptic plasticity

Abbreviations

ABP	Arterial blood pressure
ACTH	Adrenocorticotropic hormone
BDNF	Brain-derived neurotrophic factor
BL	Baseline
BP	Blood pressure
CA	Cornu Ammonis
Caf	Caffeine

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CNV	Contingent negative variation
CRH	Corticotropin-releasing hormone
DCX	Doublecortin
DG	Dentate gyrus
EC	Entorhinal cortex
ERP	Event-related potential
HC	Hippocampus
HR	Heart rate
HRV	Heart rate variability
LTD	Long-term depression
LTP	Long-term potentiation
Mod	Modafinil
MWM	Morris water maze
NORT	Novel object recognition test
NREM	Non-rapid eye movement
REM	Rapid eye movement
SD	Sleep deprivation
SGZ	Subgranular zone
SVZ	Subventricular zone
WCST	Wisconsin Card Sorting Test

2.1 Sleep Deprivation: A Phenomenon of Modern Lifestyle

Sleep loss is now recognized as a major problem inherent in modern society. The major factors responsible for sleep disturbance are the competitive lifestyle with professional demands. In humans, the sleep of less than 8 h, and in rodents, any time duration the animal is kept awake forcefully, is termed as sleep deprivation. Sleep deprivation can be either of shorter duration of time (acute) or for long periods (chronic). Acute sleep deprivation leads to poor scores on behavioral tasks involving attention, vigilance, learning, and memory. Reasoning ability, innovative thinking, and decision-making are also impaired. After acute sleep deprivation, the presence of fatigue and need for sleep are persistent. The presence of tremor, discomfort, and increased tonus may also be observed. Task performance may be hampered with a decreased concentration. The sleep-deprived individual becomes irritable and aggressive. Prolonged micro-episodes, perception disorder, illusions, and hallucinations may be experienced. As the duration of sleep deprivation increases, the symptoms become more severe including reasoning disability, disorientation, visual problems, and delusions. Distrust, depersonalization, and attempts to murder-like symptoms are characteristics of chronic sleep loss. Thus, both acute and chronic sleep deprivation have adverse effects on the brain and cognitive functions, but the consequences of chronic sleep loss or disturbance are more severe than acute sleep deprivation. Sometimes sleep loss lasting for several days leads to a compromised day-to-day functioning in common mental tasks (Siegel 2005).

2.1.1 Consequences of Sleep Deprivation

Most of the physiological functions of the body are altered during sleep deprivation, such as autonomic, temperature regulation, hormonal secretion, and immune and cognitive functions. Cardiovascular perturbations are dominant during sleep stages, non-rapid eye movement (NREM) and rapid eye movement (REM). These changes result because of the autonomic both sympathetic and parasympathetic nervous system fluctuations. Various experimental procedures have been adopted to investigate sleep deprivation-mediated consequences in healthy subjects. After acute sleep loss, arterial blood pressure (ABP), heart rate (HR), and blood pressure (BP) tend to rise. Heart rate variability (HRV) analysis shows an enhanced sympathetic activity (increased low frequency component, increased low frequency/high frequency component ratio, reduced vagal control). In a study, during partial sleep deprivation, there was a decrease in vasodilatation without any alteration in autonomic profile, whereas HRV was reduced with significant variations in autonomic parameters after chronic sleep deprivation in healthy subjects (Tobaldini et al. 2016).

Sleep loss affects the immune system with an upregulation in the production and release of pro-inflammatory cytokines. Infections may develop with sleep deprivation due to immunological suppression. During acute sleep deprivation, there is an increase in the concentration of IgG, IgA, and IgM and a reduction in helper T-cell count and natural killer cells. Sleep loss induces an increase in the metabolic rate, food intake, appetite, and hunger and decreases the concentration of leptin with a decrease in body mass. Sleep deprivation influences the hormonal balance, the level of thyroid hormones (thyroxine and triiodothyronine), and corticotropin-releasing hormone (CRH) level in the hypothalamus. Plasma aldosterone and renin concentration decrease, while adrenocorticotropic hormone (ACTH), corticosteroids, and noradrenaline increase, whereas growth hormone level remains unaltered (Orzel-Gryglewska 2010).

Sleep disturbance has been found to be responsible for structural as well as functional changes in the brain. During chronic sleep deprivation, the average rate of brain metabolism is lowered, disrupting the functional capacity of the brain as shown by behavioral changes such as reduced alertness, performance, precision, and cognitive functions. Functional magnetic resonance imaging shows that after sleep deprivation, some brain areas become more active while other brain areas show reduced activity. Studies on humans have shown an impairment in the acquisition and encoding phase of memory following acute sleep loss (Yoo et al. 2007).

Event-related potential (ERP) provides information about the cognitive process including attention, vigilance, concentration, and working memory. Sleep deprivation induces an alteration in ERP morphology. Sleep deprivation reduced the onset and amplitude of P300 (a response as deflection at 300 ms) using the oddball paradigm. Contingent negative variation (CNV) is a measure of readiness to receive a stimulus, also dubbed as “expectancy wave.” During sleep deprivation (24 h) in humans, the sleepiness score, latency of P300 ERP, and reaction time were increased which indicated a reduced information-processing ability. Various parameters such

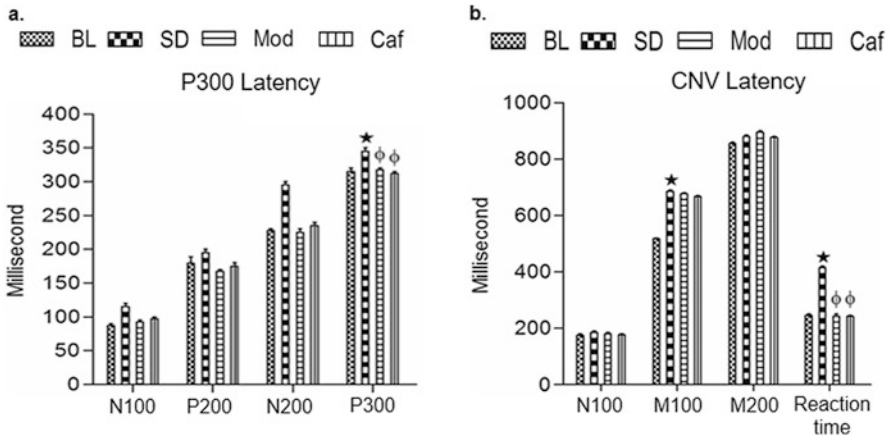

Fig. 2.1 Effect of caffeine and modafinil on event-related potential components during sleep deprivation. Parameters: (**a**) P300, (**b**) CNV Latency. $^{*}p < 0.05$ as compared to baseline, $^{\Phi}p < 0.05$ when compared to sleep deprivation. One-way ANOVA with Bonferroni post hoc test was used for the statistical analysis

as N100 latency (processing of stimulus), P300 latency, CNV latency, and M100 latency were delayed with no significant alteration in N200 latency (stimulus detection) and CNV amplitude (Fig. 2.1) (Ray et al. 2012).

2.1.2 Therapeutic Strategies for Optimization of Cognitive Functions During Sleep Deprivation

Amelioration of cognitive dysfunction following sleep deprivation is an inescapable necessity. There are pharmacological as well as non-pharmacological strategies available against the sleep deprivation-induced dysfunction. The pharmacological treatment includes the readily available stimulants like caffeine, energy drinks, and wake-promoting agent like modafinil. These are beneficial in the improvement of cognitive performance during sleep deprivation (De Valck and Cluydts 2001).

Caffeine acts as a nonselective adenosine receptor antagonist. It is widely used as a stimulant and cognitive enhancer and also consumed in food, beverages, etc. Caffeine has a neuroprotective role against stress-mediated cognitive impairment. It improves the alertness, vigilance, and concentration during sleep deprivation (Bonnet et al. 2005). Modafinil is a wake-promoting drug; its wake-promoting property is due to the competitive binding to dopamine transporter and adrenergic signaling. It is used to treat patients of sleep-related disorders such as narcolepsy, shift work, and sleep apnea; however, the mode of action appears to be multifactorial, and exact mechanism involved in its wake-promoting property is not well understood.

In a study of prolonged sleep deprivation, it was reported that caffeine and modafinil decreased errors and improved scores of Wisconsin Card Sorting Test (WCST) and Stroop test (Wesensten et al. 2004). Modafinil also reduced the latencies of P300 and CNV wave forms during sleep deprivation. Caffeine and modafinil treatment also maintained the cognitive performance as shown by the reduced P300 peak latency, M100 latency, and CNV reaction time following one night of sleep deprivation. However, no major changes in the latency of N100, P100, N200 ERP, and M200 latency during one night sleep deprivation and caffeine/modafinil treatment were found (Fig. 2.1a, b).

The beneficial effect of modafinil may be due to the increased release of histamine, dopamine, and serotonin via inhibiting their transporters (Ray et al. 2012). Alternative non-pharmacologic strategies can also attenuate the negative effects of sleep deprivation. Napping was found to be effective in improving the cognitive functions following 24 h of sleep deprivation as shown by reduced sleepiness score, P300 peak latency, CNV M100 peak latency, and CNV reaction time (Panjwani et al. 2010). Meditation practice for 2 months was also reported to be effective against cognitive dysfunction during sleep deprivation (Chatterjee et al. 2012).

2.2 Sleep Deprivation Studies in Rodents

Rat is the most commonly used animal model for sleep deprivation or restriction studies in order to examine the consequences of sleep deprivation at behavioral, biochemical, molecular, and cellular level. Following chronic sleep deprivation, rats present with sleep deprivation syndrome with changes in food intake, body weight, and thermoregulation, leading to death in case of prolonged sleep deprivation (Rechtschaffen 1998).

2.2.1 Animal Models of Sleep Deprivation

There are several methods that have been used for sleep deprivation in rodents such as flowerpot method (used for selective REM sleep deprivation), forced locomotion, gentle handling, or mild tactile stimulation sometimes including novel material, novel place, etc. Each method has its own advantages and disadvantages. For example, in the forced locomotion method, the effects of sleep deprivation are sometimes reversed or masked because of motor activity, which will give an exercise component, itself a confounding variable. On the other hand, gentle handling technique is laborious needing a constant monitoring as well as a stress for the animal which is suitable for acute but not chronic sleep deprivation studies (Sahu et al. 2013).

2.2.2 *Novel Automated Sleep Deprivation Model*

We developed a novel software-operated method of sleep deprivation that can be used for long-duration sleep deprivation studies (few days) with no need for constant monitoring and 70–90% wakefulness. Using this novel automated method, rats underwent sleep deprivation based on a behavioral scale (Fig. 2.2). Sleep deprivation apparatus includes a tracking software, infrared camera, interface, amplifier, and shaking pads (ANY-maze, Stoelting, USA). The animals are placed in acrylic cages (transparent, open top) individually, and the overhead infrared camera monitors the animal constantly. Data analysis is performed by the ANY-maze software which records freezing and immobility parameters. The interface of ANY-maze is driven by the software, which switches on the amplifier and in turn gives a command to the shaking pads positioned below the cages to give vibration to the immobile animal. Cages are set in side by side with holes on the cage walls to avoid isolation (Sahu et al. 2013; Wadhwa et al. 2015).

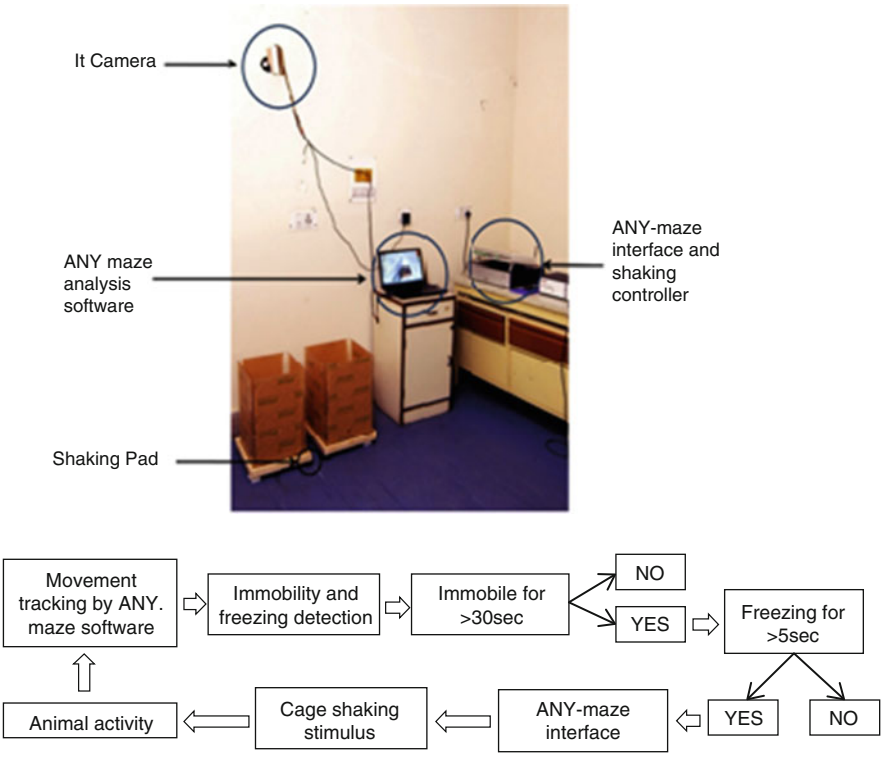

Fig. 2.2 Sleep deprivation setup

2.3 Changes in Learning and Memory During Sleep Deprivation and Therapeutic (Caffeine/Modafinil) Interventions

Sleep loss has been found to impair cognitive performance in humans as well as rodents (Tripathi and Jha 2016). It has been reported that sleep loss produces spatial memory impairment in the Morris water maze (MWM) tasks in rodents (Rauchs et al. 2008). The study in our laboratory revealed that spatial memory performance in MWM test decreased gradually during 48 h sleep deprivation and caffeine/modafinil treatment improved spatial reference memory following sleep deprivation exposure as shown by the track plot (Fig. 2.3a) and test parameters such as path length and path length to reach the target platform (Unpublished Fig. 2.3b, c). There are reports of improved vigilance, psychomotor activities, and fatigue following caffeine and modafinil treatment during sleep deprivation. After sleep deprivation, working memory task is diminished in mice, and modafinil treatment is reported to restore the spatial working memory performance (Killgore et al. 2008; Pierard et al. 2007). Evidence suggests the importance of sleep in the proper encoding, storage, and retrieval of memory during the training phase; besides, sleep also plays an important role in the acquisition of information (Yoo et al. 2007).

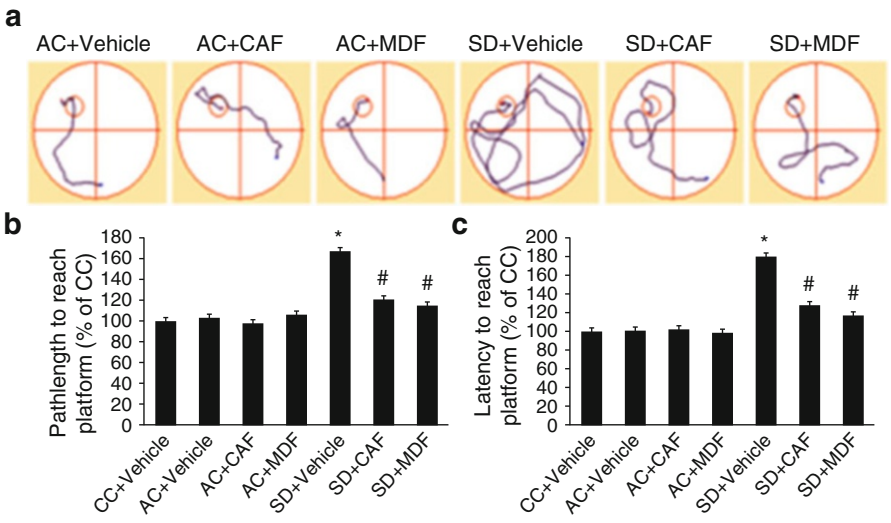

Fig. 2.3 Effect of caffeine and modafinil on sleep deprivation-induced spatial memory impairment. (**a**) Track plot of memory performance of rats. Test parameters: (**b**) path length, (**c**) latency to reach platform. $^{*}p < 0.05$ as compared to control treated with vehicle, $^{\#}p < 0.05$ as compared to sleep deprived treated with vehicle. One-way ANOVA with Bonferroni post hoc test was used for the statistical evaluation

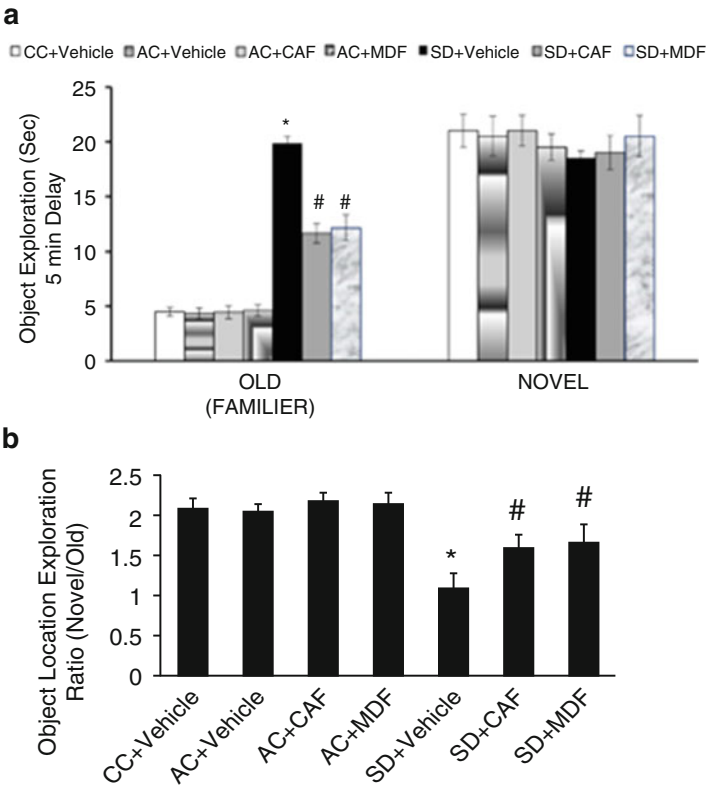

Fig. 2.4 Effect of caffeine and modafinil on sleep deprivation-induced recognition memory impairment. Test parameters: (**a**) object exploration time, (**b**) object location exploration ratio. $^{*}p < 0.05$ as compared to control treated with vehicle, $^{\#}p < 0.05$ as compared to sleep deprived treated with vehicle. One-way ANOVA with Tukey-Kramer multiple comparison test was used for statistical evaluation

Recognition memory is the ability to distinguish novel and familiar stimuli. To study the recognition memory, novel object recognition test (NORT) is widely used. Sleep improves the recognition memory, and any change in sleep impairs the exploration, discrimination, and recognition memory. Improvement in the recognition memory has been reported following acute caffeine/modafinil administration. After 48 h of sleep deprivation, novel object and location recognition memory (5 min delay) in NORT were impaired, and caffeine/modafinil administration improved recognition memory performance during the 48 of h sleep deprivation period (Fig. 2.4a, b) (Wadhwa et al. 2015).

2.4 Mechanisms of Sleep Deprivation-Induced Cognitive Decline

Hippocampus is known as a storage house of memories, which is composed of dentate gyrus (DG), subfields of Cornu Ammonis (CA), and entorhinal cortex (EC). Experimental studies of synaptic plasticity in the hippocampus are designed based on the trisynaptic excitatory pathways between DG, CA1, and EC regions (Scoville and Milner 1957). Several explanations are proposed to explain the impairment of cognitive performance during sleep loss; however, the exact mechanism may involve multiple pathways.

2.4.1 Role of Neuronal Cell Proliferation in Sleep Deprivation-Mediated Changes in the Learning and Memory Performance

Hippocampus is an important site of adult neurogenesis mainly involving sub-ventricular zone (SVZ) and subgranular zone (SGZ) of the DG region. Adult neuronal cells are generated, proliferate, and finally integrate into the neuronal network loop in the hippocampus. Dorsal and ventral hippocampal regions have a role in regulation of neurogenesis and cognition (Deng et al. 2010). Neurogenesis consists of stages such as proliferation, differentiation, survival, and integration, which are known to be modulated by neurotrophins, neurotransmitters, cytokines and drugs, etc. via receptor signaling pathways and epigenetic and transcription factors. There is a strong association between adult neurogenesis and learning/memory process in the hippocampus. Neurogenesis in adult mice correlates positively with learning ability. This is proven by direct evidence: depletion of adult-generated neurons leads to impairment of specific learning tasks like associative learning and fear conditioning. In another study, genetic ablation of rat adult-born neuronal cells decreased the neuronal cell count in DG region, which led to hippocampus-based behavioral abnormalities. On the other hand, hippocampal neurogenesis facilitates synaptic plasticity in the hippocampus (Kitamura et al. 2009).

Growing evidence supports the association between sleep and adult neurogenesis. Recently, sleep and adult neurogenesis have received widespread attention. Sleep favors the neurogenesis process, and any impairment in sleep function produces a decrement in the adult neuronal cell proliferation process in the hippocampus. Acute sleep deprivation did not reduce neurogenesis in sub granular zone of hippocampus; however more than 24 h of total sleep deprivation decreases neurogenesis in the hippocampus (Roman et al. 2005). REM sleep deprivation decreases the cell counts

of proliferating neurons in DG region, whereas immature neuronal cells' number reduces after both REM and NREM sleep deprivation. There are reports of the suppression in the adult neuronal proliferating cell count following sleep disruption of varying durations. A previous study reported the decrement of proliferative neuronal cells as shown by BrdU and doublecortin (DCX; proliferative, intermediate, and postmitotic stage) positive cell counts in the DG region of the hippocampus following 48 h of sleep deprivation. However, no change in the maturational marker of neurogenesis (NeuN) was seen during 48 h of sleep deprivation (Sahu et al. 2013). An association between sleep loss and reduced neurogenesis has also been validated by other studies employing various procedures such as platform method, treadmill, and disk-over-water (Roman et al. 2005).

There are reports about the neuroprotective role of caffeine or modafinil on neuronal cell proliferation process. There is a dose-dependent effect of caffeine on the neurogenesis: low-dose treatment for a shorter period had no effects on adult neuronal cell proliferation, and acute supraphysiological dosage promoted neurogenesis, while very higher dosage repeatedly used decreased neurogenesis and impaired cognition. Treatment of caffeine or modafinil attenuated the reduction of BrdU-positive cell count during 48 h of sleep deprivation (Fig. 2.5a). During 48 h of sleep deprivation, the decrement in the proliferative DCX-positive cell count was found to be attenuated by only caffeine treatment, while the numbers of intermediate-stage DCX-positive cells were improved by only modafinil treatment. On the other hand, postmitotic stage DCX-positive cell count was improved by both caffeine and modafinil during sleep deprivation (Fig. 2.5b) (Sahu et al. 2013). Besides sleep deprivation, caffeine or modafinil treatment also plays a significant role in the improvement of neurogenesis in other stress conditions (Kochman et al. 2009).

Recently, brain-derived neurotrophic factor (BDNF) has emerged as an important regulator of sleep as shown by studies, which report onset of sleep via cortical BDNF expression. BDNF increases spontaneous sleep in rodents (Bachmann et al. 2012). Sleep loss decreases the BDNF expression in the hippocampus, which is improved by caffeine administration. BDNF enhances the hippocampal functions by increasing the adult neuronal cell proliferation and other processes related to the neurogenesis (Alhaider et al. 2011). Gene silencing of hippocampal BDNF by different means produces a negative impact on neurogenesis (Taliaz et al. 2010). The beneficial effects of caffeine in maintaining physiological BDNF level and cognitive functions under stressful conditions such as obesity or aging are reported (Alzoubi et al. 2013). We reported that 48 h sleep deprivation significantly decreased the expression of BDNF in the DG region of the hippocampus, which was found to be improved by caffeine/modafinil treatment (Fig. 2.5c). Caffeine/modafinil administration improved the adult neuronal cell proliferation and differentiation by enhancing the level of BDNF protein in the hippocampus during sleep deprivation. Previous literature also supports the role of BDNF expression in adult newborn

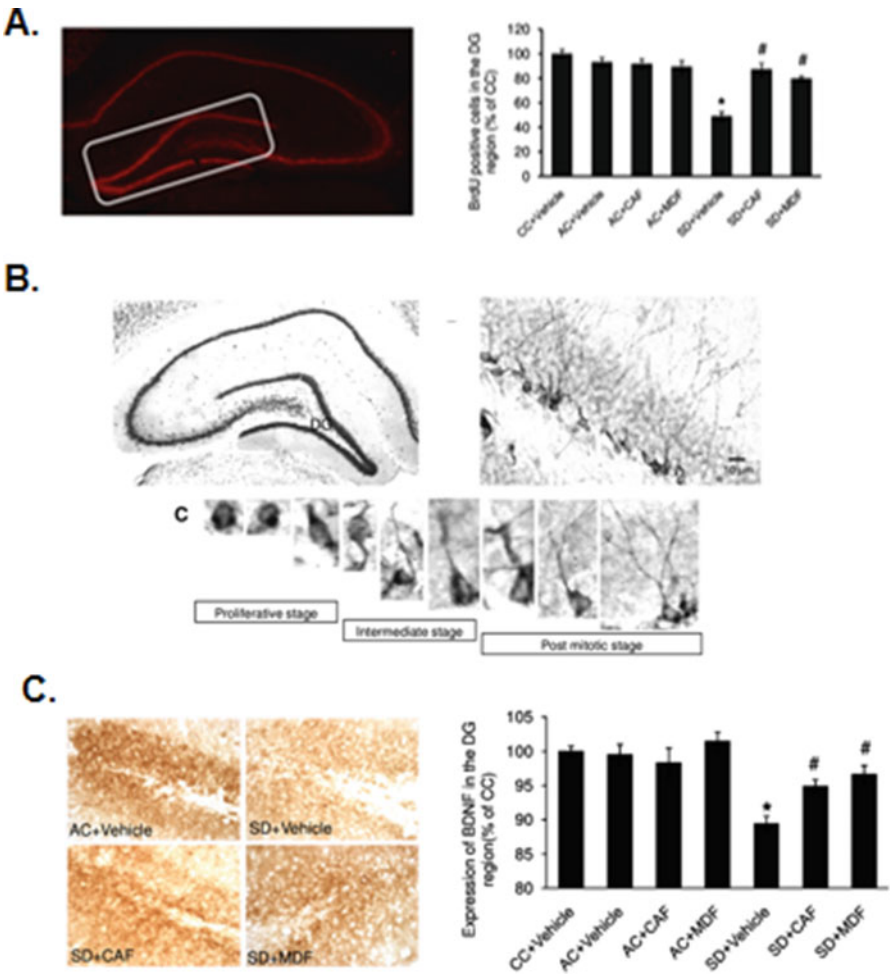

Fig. 2.5 Effect of caffeine and modafinil on changes in proliferation, differentiation, and growth factor proteins during sleep deprivation. Changes in: (**a**) representation of DG region of the hippocampus and BrdU cell count in DG region, (**b**) identification of different stages of DCX-positive cells in DG region of the hippocampus, and (**c**) representative images of BDNF expression in DG region of the hippocampus and changes in the relative mean pixel intensity of BDNF in DG region of the hippocampus. $^{*}p < 0.05$ as compared to control treated with vehicle, $^{\#}p < 0.05$ as compared to sleep deprived treated with vehicle. One-way ANOVA with Tukey-Kramer multiple comparison test was used for statistical evaluation

neurons (Sahu et al. 2013). Hence, caffeine and modafinil treatment during sleep deprivation produce neuroprotective effects by the attenuation of reduced adult neuronal cell proliferation via BDNF expression.

2.4.2 *Role of Synaptic Plasticity in Sleep Deprivation-Induced Learning and Memory Impairment*

In addition to neurogenesis, hippocampus also maintains synaptic plasticity, a dynamic process by which the strength of the connection between neurons continuously changes over time to enable the brain to learn and store memories. The synapse, a highly specialized structure that allows communication between the neurons, is composed of three main elements: the presynaptic terminal, the synaptic cleft, and the postsynaptic membrane. Long-term potentiation (LTP) in the hippocampus is the basis for formation of new learning and memory (Malenka and Bear 2004). BDNF enhances the synaptic transmission and influences synaptic plasticity by the activation of CaMKII protein in the hippocampus. BDNF is essential for the induction and maintenance of LTP in the hippocampus. It also plays a role in synaptic potentiation. There is an increase in the mRNA level of BDNF in the hippocampus during spatial learning (Kesslak et al. 1998). Everyday functions, such as remembering the events of a particular day or learning to navigate around different places, depend on this process of synaptic communication. Morris water maze experiments have shown that rats lose the ability to navigate a known route when synaptic plasticity is blocked (Morris 1989).

Synaptic modulation has a role in the regulation of sleep-wakefulness as documented by molecular studies. Sleep, particularly NREM stage, maintains the restoration process of cells by the transcriptional and translational control in the synthesis and transport mechanisms of macromolecules. NREM sleep loss induces synaptic down-scaling, morphological alteration in synapses (shrinkage), leading to reduce synaptic efficacy. Transcriptional reactivation of immediate early genes (Arc, BDNF, and zif268) happens during REM sleep, while wakefulness is associated with memory consolidation and neuronal activity replay, which have been proposed to be related with sleep (NREM) events such as wave ripples and sleep spindles in the hippocampus. Modulation in the gene expression (REM sleep) and synaptic replay (NREM sleep) favors the synaptic consolidation (Gronli et al. 2013). There are limited studies that examine the effect of sleep deprivation on long-term depression (LTD). It had been found that sleep deprivation for 12 h induced LTD in CA1 region of rat hippocampus (Tadavarty et al. 2009). Sleep loss accelerates the synaptic depression and inhibits synaptic potentiation in the hippocampus. There are some studies which have evaluated the effects of sleep disruption on synaptic plasticity; however, only a limited number of studies investigate the molecular signaling

mechanisms involved in the modulation of synaptic dynamics during sleep deprivation. Sleep loss had been reported to disturb the synaptic homeostasis as shown by the reduction in the immune reactivity and density of synaptic proteins in different regions of the hippocampus (Wadhwa et al. 2015).

Under stressful conditions including sleep loss, administration of caffeine decreases changes in the synaptic plasticity. Long-term treatment of caffeine ameliorated fold changes in phosphorylated CaMKII and altered BDNF expression during early phase of LTP during sleep deprivation (Alhaider et al. 2010). There are limited studies on the effects of modafinil on molecular correlates of synaptic plasticity. Modafinil prevents REM sleep deprivation-induced brain function impairment. Modafinil was reported to upregulate synapsin-1 expression in the dorsal hippocampal CA3 region, along with population spike amplification and augmentation in postsynaptic potentials interrelated to theta rhythm (Tsanov et al. 2010).

The vulnerability of dorsal hippocampus to sleep loss is documented by behavioral changes. Sleep is directly linked to learning, memory, and neural plasticity. During wakefulness, the exposure of surroundings strengthens the synaptic connections in the brain and enhances the learning process. This results in increased demands of the cells for energy and micronutrients, which reduces synaptic strength. During sleep, spontaneous activity stabilizes the synaptic strength and reestablishes homeostasis. The downregulation of synaptic proteins during sleep deprivation supports the beneficial role of sleep in the memory processing (Tononi and Cirelli 2014). The presynaptic regulatory proteins' synaptophysin and synapsin expression in the hippocampus was reduced after sleep deprivation and improved by caffeine/modafinil treatment. Postsynaptic density protein 95 expression in the hippocampus was decreased after sleep deprivation. Modafinil treatment during sleep deprivation increased the expression of PSD 95 in the hippocampus during sleep deprivation. The attenuation of the reduced levels of synaptic plasticity molecules following caffeine/modafinil treatment during sleep deprivation may be involved in the enhancement of cognitive performance (Fig. 2.6a–d) (Wadhwa et al. 2015).

2.5 Concluding Remarks

Sleep deprivation compromises cognitive functions including attention, concentration, learning, and memory in humans as well as animals. Sleep loss diminishes the neuronal cell proliferation and expression of synaptic plasticity molecules in the adult rat hippocampus. The cognitive changes during sleep-deprived conditions may be linked to the changes in the neurogenesis and synaptic plasticity. Psychostimulant drugs, caffeine, and modafinil improve the adult neuronal cell proliferation, preserve synaptic plasticity, and facilitate cognitive performance during sleep deprivation.

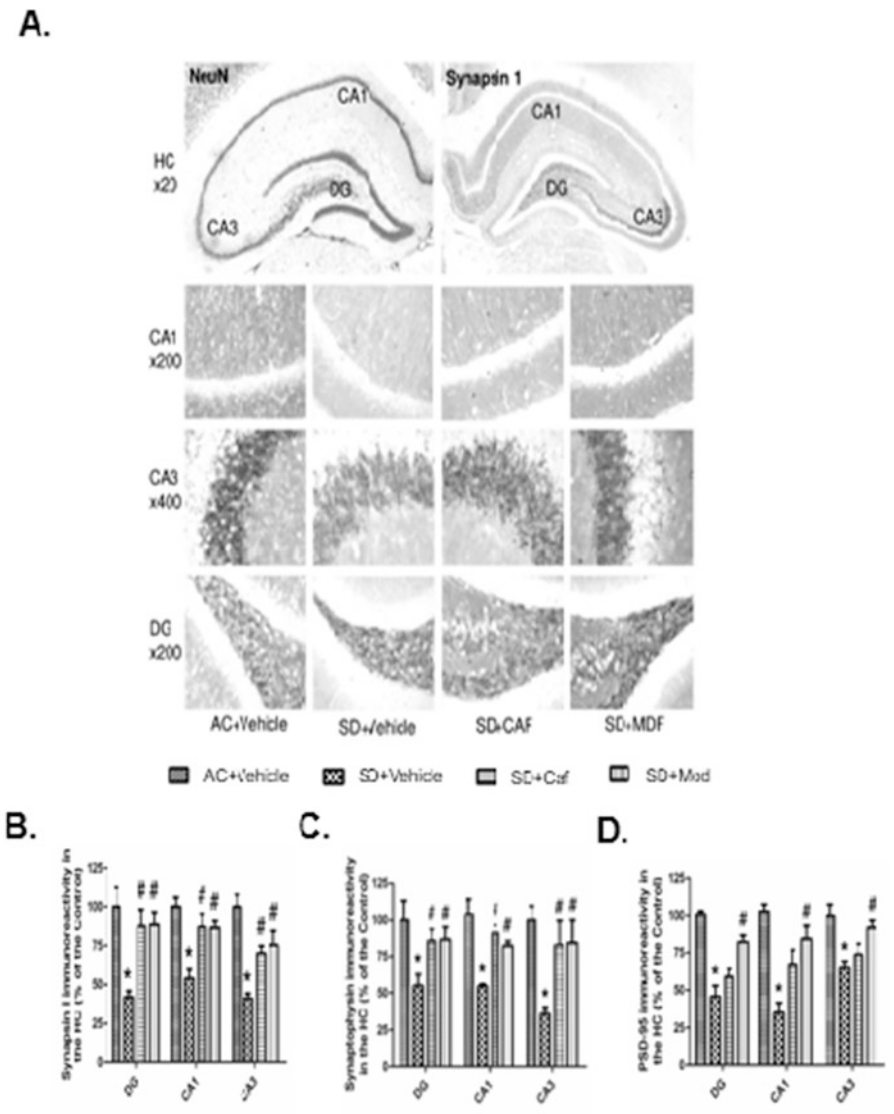

Fig. 2.6 Effect of caffeine and modafinil on sleep deprivation-induced changes in synaptic proteins' expression in the hippocampus. (**a**) Representative image showing synapsin-1 expression in DG, CA1, and CA3 region of the hippocampus. Changes in the relative mean pixel intensity of (**b**) synapsin-1, (**c**) synaptophysin, and (**d**) PSD-95 proteins in DG, CA1, and CA3 region of the hippocampus. $^{*}p < 0.05$ as compared to control treated with vehicle, $^{\#}p < 0.05$ as compared to sleep deprived treated with vehicle. One-way ANOVA with Tukey-Kramer multiple comparison test was used for statistical evaluation

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