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The Molecular Relationship between Stress and Insomnia

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The bi-directional relationship between sleep and stress has been actively researched as sleep disturbances and stress have become increasingly common in society. Interestingly, the brain and underlying neural circuits important for sleep regulation may respond uniquely to stress that leads to post-traumatic stress disorder (PTSD) and stress that does not. In stress that does not lead to PTSD, the hypothalamic-pituitary-adrenal axis (HPA) pathway is activated normally that results in sympathetic nervous system activation that allows the brain and body to return to baseline functioning. However, exposure to stress that leads to PTSD, causes enhanced negative feedback of this same pathway and results in long-term physiological and psychological changes. In this review, how stress regulates glucocorticoid signaling pathways in brain glial cells called astrocytes, and then mediates stress-induced insomnia are examined. Astrocytes are critical sleep regulatory cells and their connections to sleep and stress due to disturbed glucocorticoid signaling provide a novel mechanism to explain how stress leads to insomnia. This review will examine the interactions of stress neurobiology, astrocytes, sleep, and glucocorticoid signaling pathways and will examine the how stress that leads to PTSD and stress that does not impacts sleep-regulatory processes.

1. Introduction

Stress comes in many forms and can vary in severity across a spectrum from relatively innocuous everyday stressors like paying bills or getting stuck in traffic, to major traumas that can lead to the development of trauma- and stressor-related disorders, including post-traumatic stress disorder (PTSD).[1] The physiological response to stress is dependent on the type of stress, the individual, their neuroendocrine system, and the combination of these factors dictate how the brain and body respond to a specific stressor. Interestingly, not all people develop PTSD when they experience the same stressor. An example of this can be found in a study that examined the prevalence and incidence of PTSD following the 9/11 attacks in New York City. These data revealed that while many people witnessed the attack and subsequent aftermath, some individuals developed PTSD, while others only experienced a mild stress response.[2] As this study suggests, there are many considerations when determining whether stress will lead to PTSD or not, including differences in stressor duration, the intensity of the stressor, sex differences, and varying genetic or environmental factors, and health conditions that mediate susceptibility to PTSD.[3–7]

There are unique features of stressors that lead to PTSD compared to stressors that do not. Short-term feelings of panic or dread typically subside over time is usually from stress that does not lead to PTSD, while stress that does result in PTSD causes persistent negative experiences, significantly decreased quality of life, and long-term changes in underlying neurophysiology. Interestingly, a common side effect of exposure to stress, regardless of the intensity, is the development of disordered sleep, specifically, insomnia. Indeed, most everyone has had an acute bout of insomnia related to daily life stressors, and sleep disturbances are considered a hallmark symptom of PTSD. Sleep is critical for maintaining physical and mental health, therefore, the physiological interactions of sleep with stress are likely critical regulators in the development of stress-induced pathophysiology. The goal of this review is to examine the molecular regulation of the interactions between stress and the development of insomnia. We will additionally examine molecular and cellular mechanisms that may be responsible for the development of stress-induced insomnia by differentiating the difference between stress that leads to PTSD and stress that does not. As a society with increasing levels of both stress and sleep disturbance, a primary goal of future research will be to improve our understanding of the interactions between stress and sleep in order to develop more personalized medicine and identify sleep-specific therapeutics that can stave off the development of stress-induced pathophysiology including insomnia and PTSD.

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Stress, in all its forms activates the hypothalamic-pituitary-adrenal (HPA) axis and can lead to the development of sleep disturbances, including insomnia. However, low-intensity stressors such as getting stuck in traffic, being late for a meeting, or paying bills are typically unlikely to develop into PTSD due to them being a low-intensity event that was not life-threatening. On the other hand, high-intensity stressors that are physically life threatening or psychologically traumatic result in continuous physiological and psychological distress that persists over time. Examples of this type of trauma may include car accidents, witnessing a murder, or experiencing acts of violence during combat. These phytological or physical stressors are more likely to lead to PTSD and often result in life-long deficits of functioning. Additionally, an increase of risk in development of PTSD is also seen in an increasing frequency of a stressful event.[8,9] Chronic stress exposure may build up over time and result in cumulative effects on patient wellbeing.

Unique individual characteristics of people may also impact how someone responds to stress. For example, people who have mental disorders such as major depressive disorder, alcohol use disorder, and anxiety disorders[8–10] are more at risk of developing PTSD. Recent studies have also shown borderline personality disorder and antisocial personality disorder to increase the risk as well.[11] Personality traits can also affect the risk such as neuroticism[12] and avoidance coping.[13] Peritraumatic emotional responses such as intense fear, helplessness, panic, and dissociation also increase the risk of developing PTSD.[13,14]

Additionally, female and male experiencing the same stressor can have a different risk of developing PTSD. Females are two to three times more like to develop PTSD than men.[10,15] Females tend to not report traumatic events even though they experience more sexual trauma than males which can both lead to a greater risk of development.[16] The comorbidities, personality traits, and peritraumatic emotional responses mentioned previously have been shown to be more common in females, still supporting the complications of sex difference in PTSD development.[16–22] In addition, sex differences in PTSD development risk can be traced to physiological functioning differences in animal models.[23] The pituitary adenylate cyclase activating polypeptide pathway is a regulator of the HPA axis, which is a key mechanism behind PTSD which will be discussed later in this paper. This pathway has been shown to be positively correlated to PTSD development in females due to its interactions with estrogen.[24,25] Gene modifications;[26,27] and methylations[28,29] have also been shown to increase the risk of development in females. There have been transcriptional changes in females that adject the stress response which could affect the risk as well.[28–31] Heritability of PTSD in varied descent women is higher than nonvaried, which would increase the risk of developing PTSD again.[32]

For this review, we will focus on examining the molecular and anatomical mechanisms that regulate how stress exposure results in insomnia, a hallmark feature of PTSD. We will examine how an animal model can be used to identify unique neurobiological molecular and anatomical pathways responsible for stress induced sleep disturbances that will help guide prevention and treatment of this debilitating condition into the future.

1.1. Neuroendocrine Regulation of Stress

The HPA axis responds to stress via hormone secretion.[33] The paraventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing hormone (CRH) which then activates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) which then stimulates glucocorticoid secretion from the adrenal glands. Cortisol, the main secreted glucocorticoid from the adrenal glands, is elevated during times of stress which then modifies cardiovascular, metabolic, and behavioral responses. Cortisol then acts via glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) to self-regulate the HPA axis by downregulating CRH and ACTH signaling in the hypothalamus and pituitary gland.[34]

While the HPA pathway contributes to adaptation in response to stress that does not lead to PTSD, stress that results in PTSD can lead to dysfunction in this pathway and structural damage to the brain that has deleterious effects on cognition, learning, and sleep.[33–35] The PVN is a key neural circuit in the regulation of the HPA pathway feedback inhibition of glucocorticoid signaling due to its high concentration of GR.[33–36] In addition to the secretion of CRH, arginine vasopressin (AVP) is also stored in and released from the PVN neurons.[39] While not important in low-intensity acute stress events, chronic stressors that can lead PTSD show AVP and CRH amplification of ACTH release suggesting more dysregulated biochemical interactions after exposure to these specific events indicate that there is a distinct biochemical and physiological difference in how the brain responds to stress that leads to PTSD compared to stress that does not

The HPA works in cooperation with the sympathetic adrenomedullary system (SAM) to cause a short-lasting and rapid response to an acute stressor, also known as the "fight or flight" response. The fight or flight response causes physiological changes that allow our bodies to face or flee the stress via activation of sympathetic preganglionic neurons that form cholinergic synapses with chromaffin cells in the adrenal gland.[34] These chromaffin cells secrete mostly epinephrine and some norepinephrine which stimulate the sympathetic response to stress and increase blood flow to the brain and increase glucose availability. While the SAM and HPA pathways are activated at the same time by the stressor, SAM is quick to stimulate physiologic changes, while the HPA takes longer to produce a response and is more critical for regulating the response to long-term or severe stressors. Working together in concert these stress-sensing pathways allow us to respond to stress in an adaptive way, however increasing the severity of stress exposure may have long-lasting cumulative negative impacts on sleep and brain function.

1.2. Stress and the Brain

Based on translational work in rodents and humans, we know that stress significantly alters the function of discrete neural circuits that include the prefrontal cortex (PFC), hypothalamus, hippocampus, amygdala, and locus coeruleus (LC).[41] These brain areas are involved in processing learning, memory, fear, and sleep/wake cycling.[42–47] The PFC is involved in inhibiting

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stress-induced amygdala-based fear responses,[48] and contributes to emotion regulation, decision-making, and executive functions such as working memory, learning, extinction of associative learning, and attention.[49] Following traumatic stress exposure that leads to PTSD, there is reduced signaling from the PFC to the amygdala, the fear processing center of the brain which, in turn, can result in aberrant fear responses.[47,48,50,51] Further, communication between the PFC and amygdala plays an important role in stress regulation by mediating glucocorticoid signaling in the HPA.[40,52] Catecholamines are released from the medial prefrontal cortex during times of nontraumatic or traumatic stress which then acts to inhibit the HPA pathway.[53] The hypothalamus coordinates with the endocrine system and has many functions including hormone secretion and signaling, temperature regulation, appetite regulation, autonomic nervous system regulation, and sleep homeostasis.[54–56] The dorsomedial hypothalamic nucleus and preoptic areas of the hypothalamus project to the PVN and this pathway is activated in rats when experiencing stress. GABAergic neurons in these areas of the hypothalamus project to the PVN, specifically the medial area, which have been shown to be activated following stress exposure in rat models.[57] The hippocampus is the center of learning and memory,[58–60] and contributes to the monitoring of the HPA axis, and inhibits the hypothalamus via negative feedback from glucocorticoid signaling pathways.[37] The amygdala is critical for emotional processing, which is important for fear learning and extinction.[61] Stress activates neurons specifically in the medial and central nuclei of the amygdala[62] and, as opposed to the prefrontal cortex, the amygdala is an activator of the HPA axis via glucocorticoid synthesis.[63] Finally, the LC innervates the forebrain with wake-promoting noradrenaline to regulate long-term potentiation of downstream circuits[64–66] and increases attention to the stimulus contributing to the experienced stress via stimulation of the HPA axis.[67] Further, dysregulated noradrenergic signaling in the LC causes rampant long-term potentiation and reduces hippocampal depotentiation required for learning.[50] Although we know that trauma exposure results in dysfunction in these brain circuits, the contribution of these neural circuits in the development of stress-induced sleep disturbances is understudied. Interestingly, the neural circuits regulating sleep and stress may contain significant overlap in both biochemical and neural circuit components because a well-established bi-directional relationship exists between stress and sleep.[2–4,10,38–40,65–68] Stress leads to sleep disturbances and insomnia, while poor sleep quality can lead to a decreased ability to manage and respond to stress.[68] For example, in one study, 78% of insomnia patients reported a previous acute psychological, social, or medical stress,[69] while another study reported that during low stress, sleep was increased, and during high stress, sleep was decreased.[70]

1.3. Sleep Physiology

Sleep is a behavior displayed by all animals and can be characterized by behavioral or physiological means. From a behavioral perspective, sleep is defined by the presence of extended periods of quiescence that are rapidly reversible, enhanced arousal thresholds, and by the presence of a homeostatic response to sleep deprivation. This behavioral definition can be applied in organisms as simple as the fruit fly, *Drosophila melanogaster*,[71,72] worm, *Caenorhabditis elegans*,[73] or jellyfish, *Cassiopea*.[74] The presence of sleep phenomena across many species provides investigators with robust models for studying the interrelationship between stress and sleep. However physiological polysomnogram recordings are used as the gold standard to determine sleep state in species such as rodents and primates. Polysomnograms consist of electroencephalogram (EEG) and electromyogram (EMG) recordings of brain activity, electrooculogram (EOG) eye movements, and electrocardiogram (EKG).[75] These physiological measures more reliably determine sleep states such as REM or nonrapid eye movement (NREM) sleep than the behavioral measures of sleep. Indeed, 4 different sleep stages have been identified that all produce unique physiological activity signatures and are considered the gold standard for determining sleep state.[76] Stage 1 is a relatively short period in which EEG activity shows slightly increased slow-wave power, decreased heart rate, and breathing with decreased frequency of brain waves compared to waking. In stage 2, sleep is classified as NREM and is characterized by a decreased body temperature and slowed brain waves with some electrical bursts. Stage 3 NREM sleep is considered a deep sleep where brain waves become slower with increased amplitude and the heart rate and breathing reach their lowest levels. The last stage is stage 4, in which REM sleep predominates. REM sleep is characterized by a lack of EMG activity with robust EOG activity and heart rate, breathing patterns, and EEG activity look similar to those seen when someone is physiologically awake.[76,77] Brain wave activity is a way to indicate which sleep stage someone is in and is measured via EEG. Sleep has been found in all organisms tested to date and has been, and continues to be, studied in many animals.[78–80]

Sleep is gated by circadian mechanisms that allow for sleep to occur when it is permissive.[81] The body's circadian clock is maintained by the suprachiasmatic nuclei (SCN) of the anterior hypothalamus via activation of rod and cone photoreceptors in the eye by light/dark cycles which signal daily synchronization of the SCN.[82] This brain area is critical for regulating hormone secretion, mood stability, body temperatures, and many other bodily functions.[83–87] Photostimuli induces arousal by the release of norepinephrine from the pineal gland which allows for melatonin synthesis.[88] Melatonin synthesis can be altered by artificial lighting which can suppress circadian rhythms.[89] Appetite, body temperature, and corticosteroid secretion are also influenced by the circadian process, specifically through the dorsomedial hypothalamus.[90]

Wakefulness is supported by cortical activation of excitatory neurons throughout the subcortical structures. Norepinephrine, serotonin, histamine, dopamine, and acetylcholine secretion within the LC, raphe nuclei, tuberomammillary nucleus, ventral periaqueductal gray matter, and the pons, respectively, are all important to this activation.[91] Waking occurs when the cortex is activated through the brainstem and its dorsal pathways via the thalamus and the forebrain.[92] The main excitatory neurotransmitter in the brain is glutamate which stimulates the sensory-motor, autonomic neural, and cerebral cortex.[93] The LC contains noradrenergic neurons while the dorsal raphe nuclei contain dopaminergic neurons critical for sleep-to-wake changeover.[94,95] It is clear, many dynamic networks are

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interacting to regulate sleep wake cycles and there are many of these networks that may impact how stress can modify sleep/wake needs.

1.4. Trauma-Associated Dysregulation of Glucocorticoid Signaling

PTSD is a psychiatric disorder caused by exposure to a traumatic event that leads to a wide variety of psychological and physical symptoms such as intrusive re-experiencing, avoidance of related thoughts or experiences, alterations in cognition, mood, arousal, and reactivity.[1] Hyper-arousal, insomnia, nightmares, and other sleep abnormalities are additional hallmark diagnostic criteria for PTSD.[96,97] People commonly exposed to traumatic events such as individuals in combat, firefighters, EMT, and the like, have been shown to develop PTSD symptoms and sleep problems following traumatic experiences at work.[98–100] In patients with PTSD, there is an increased GR expression and sensitivity, and this alteration in expression is additionally associated with an inflammatory response,[101] both of which have been linked to altered sleep. Further, the HPA axis becomes dysregulated in PTSD suggesting that there is a relationship between the GR signaling, sleep, HPA function, and the development of PTSD.[102–104]

Neural circuits important for sleep, learning, and memory are negatively impacted by trauma exposure that may be mediated in part by dysregulated glucocorticoid signaling.[105] In individuals with PTSD, hippocampal volume is decreased, suggesting its importance in memory-related problems in PTSD.[106] Interestingly, hippocampal volume increases in response to cognitive behavioral therapy, suggesting that this impairment in brain function is reversible. Additionally, Levy–Gigi found that the FK506-binding protein 51 (FKBP5) in the hippocampus recovers following cognitive behavior therapy for individuals with PTSD who, at baseline, show a lower expression of this gene. FKBP5, is a chaperon that modulates GR activity when responding to stressors and has recently become known as a biomarker for PTSD.[107,108]

Stress is capable of modifying activity in multiple systems including the SAM, HPA, and the circadian clock which influences sleep via cortisol secretion. Stress exposure and sleep deprivation similarly cause excessive cortisol secretion and glucocorticoid release is regulated by the circadian clock which is critical in HPA axis regulation.[109,110] These data further link glucocorticoid signaling mechanisms to the interactions of the stress and sleep systems and dysfunction in the regulation of this system may be the reason for memory and sleep defects following stress exposure.[111]

1.5. Single Prolonged Stress Model of PTSD to Examine Sleep/Stress Interactions

Examining the neurobiological consequences of trauma exposure and the interactions between trauma and sleep is typically prohibitively difficult in human populations because the timing and intensity of trauma exposure are unpredictable, and it is difficult to obtain brain tissue from trauma-exposed humans. Therefore, to examine the underlying neurobiology that regulates the interactions of sleep and trauma exposure, a preclinical rodent model must be employed. The single prolonged stress (SPS) model is an animal model that has been used to induce PTSD to better understand and research the neurobiological mechanisms of this psychiatric condition. SPS was developed by Liberzon and Young and includes exposure to a 20 min group swim, 2 h of physical restraint, exposure to ether vapors (<5 min) until loss of consciousness, and 7 days of social isolation.[112,113] PTSD is a human condition, and this multimodal protocol was designed to mimic biobehavioral features of it by conserving neurobiology processes in rodents. This model mimics the enhanced negative feedback of the HPA axis seen in human populations with PTSD and causes molecular, anatomical, and behavioral changes that resemble some critical features of PTSD in humans.[112–116] This pattern of time-dependent response and the neuroendocrine response is relatable to the course and the neurobiology of PTSD.[112,117] In addition, SPS results in trauma-induced alterations in acute and long-term sleep duration that mirror those seen in trauma-exposed humans.[116,118–120] Additionally, SPS induces fear-associated memory impairments that include enhanced fear-renewal and deficits in extinction-retention for both contextual and cued fear[119–121] and enhanced fear conditioning through medial prefrontal cortex inhibition of the basolateral amygdala via GABA-ergic neurons, which is suggested as a novel model of intrusive memories in PTSD.[122] SPS exposed rats show the hallmark feature of enhanced negative feedback of the HPA axis and modulation of this pathway leads to hyperexcitability of the PVN due to no negative feedback being processed. This hyperexcitability leads to overloading of the stress systems, while also negatively affecting the reward system.[123,124] This SPS-induced dysregulation of the HPA axis leads to decreased cortisol levels and a unique alteration in GR and MR levels across the brain, including within the hippocampus.[125]

1.6. Astrocytes – Cells of Stress and Sleep Regulation

Astrocytes are brain glial cells that express GR and MR and have been shown to mediate aversive learning and fear-conditioning. Importantly, these cells have also recently been identified as sleep regulatory cells.[80,118,126–133] Astrocytes, an abundant cell type in the CNS, have been studied due to their contribution to the pathology of stress and the overproduction of glucocorticoids[129,134] and are critical for neurogenesis support, neuronal migration, ion regulation, synaptogenesis, recycling of neurotransmitters, and neuroendocrine functions.[135] Glial fibrillary acidic protein (GFAP) is an intermediate filament protein that is involved in mediating how astrocytes respond to stress. GFAP can increase in the hippocampus but decreases in other limbic structures when exposed to different stressful situations. This suggests that the relationship between GFAP expression and stress is variable.[132]

In addition to being stress-responsive, astrocytes have been shown to have many critical roles in sleep and its homeostatic regulation.[130,136] Adenosine is a known sleep regulatory substance that is released from astrocytes and regulates sleep homeostasis by its accumulation.[137] Astrocytes have been shown to cause presynaptic inhibition via adenosine 1 receptors (A1R), further supporting their involvement in sleep and

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neuromodulation.[138] Further, a mouse model that blocks gliotransmission by over-expression of a dominant-negative astrocytic soluble *N*-ethylmaleimide–sensitive factor attachment protein receptor (dnSNARE) showed that astrocytic gliotransmission is responsible for the building of sleep pressure through the A1R.[139] Further, A1R coupled with the Gi protein leads to cyclic adenosine monophosphate (cAMP) expression, and sleep deprivation slows and diminishes the rise of cAMP required for memory consolidation,[140] linking sleep, stress, and astrocyte function. Additional work showed that optogenetic stimulation of astrocytes in the posterior hypothalamus increased both REM and NREM sleep.[131] A fruit fly model showed that sleep pressure, the unconscious biological response that makes humans want to go to sleep, decreased interactions between astrocytes, and mushroom body neurons, clusters of neurons in the insect brain thought to be responsible for learning and memory, suggesting that those neural/glial interactions are sensitive to sleep regulation,[80] and neuron-to-astrocyte communication via cytokine/sleep regulatory substance signaling pathways have been shown to regulate sleep dynamics.[133] Cumulatively, these studies suggest that astrocytes are a cell type that is uniquely situated to regulate the interactions of stress and sleep and that these cells might be a novel target for the development of therapeutics to stave off the development of stress-induced sleep disturbances and PTSD.

Indeed, here we present a model in **Figure 1** of how stress can lead to insomnia. This model is based on the interactions of the stress-sensing physiological systems in addition to their effects on downstream neural circuits that regulate sleep. The model shows that stress that does not lead to PTSD can cause a cascade of the HPA axis that results in normal fast feedback activation of downstream GR/MR expression on astrocytes which results in short term insomnia (Figure 1A). Our model also predicts that exposure to stress that leads to PTSD will result in enhanced negative feedback on the HPA axis in the presence of cortisol that causes a significant alteration in the GR/MR ratio that takes significantly longer to regulate itself.

1.7. Future Directions

A systematic examination of the contribution of astrocytes, and specifically glucocorticoid signaling pathways in astrocytes, in mediating trauma-induced sleep pathophysiology, and how sleep and trauma interact is currently understudied. Future work is required to examine the contribution of this signaling mechanism in the context of the impact of stress that lead to or not lead to PTSD on sleep regulatory brain circuits and mechanisms of astrocyte-specific sleep regulation. Exploring astrocyte-specific sleep-regulatory pathways may identify novel molecular pathways to target for pharmaceutical therapeutic interventions to stave off the development of stress-induced pathophysiology, sleep disturbances, and PTSD. Currently, treatments for stress-related pathophysiology do little to improve trauma-induced sleep disturbances. However, based on the bi-directional relationship between sleep and stress, sleep improvements might be first required to improve stress-induced pathology. Indeed, optogenetic enhancement of sleep in SPS trauma-exposed animals is sufficient to ameliorate trauma-induced fear-associated memory impairments,[141] however, the contribution of astrocyte signaling mechanisms have yet to be elucidated in this model. Given the ability of sleep to restore function in trauma-exposed animals, sleep enhancement may also be sufficient to restore trauma-induced GR/MR imbalance, although it is still yet to be experimentally determined.

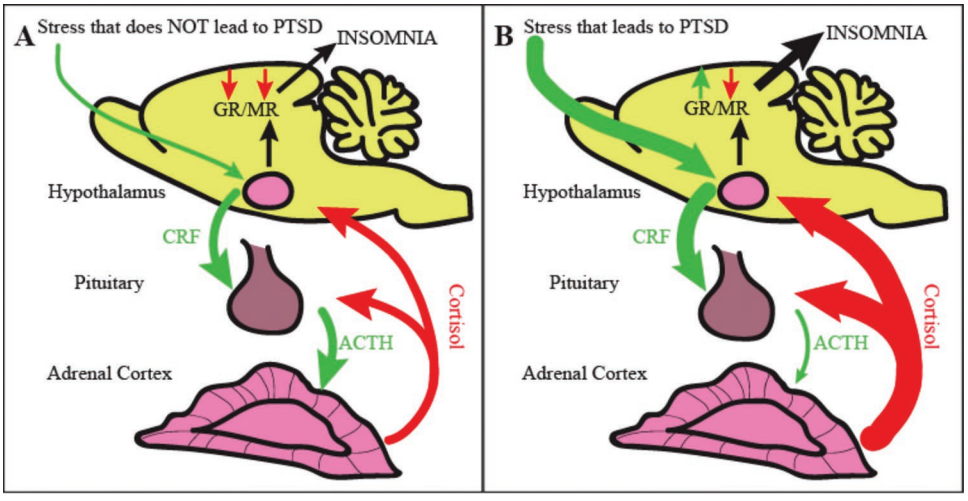

Figure 1. Schematic depicting how stress that does not lead to PTSD (A) and stress that does lead to PTSD (B) similarly result in insomnia. A) Low-intensity stress activates the hypothalamus/pituitary/adrenal (HPA) axis and results in CRF, ACTH, Cortisol feedback that maintains signaling within a normal range for the stress system. The hypothalamus subsequently responds to cortisol feedback by altering expression levels of brain glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) on brain astrocyte cells which results in a brain state that is more susceptible to sleep disruptions by the dysregulated function of arousal systems including the noradrenergic locus coeruleus and dysregulated adenosine receptor function on astrocytes. B) Stress that does result in PTSD shows dysregulated HPA function and enhanced negative feedback in the presence of reduced cortisol signaling. This results in increased GR/MR ratio in the brain and results in significantly prolonged bouts of insomnia and more severe sleep disturbances as those seen in patients with PTSD.

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Additionally, previously identified astrocyte-specific sleep-regulatory molecules such as fatty-acid binding protein 7 (Fabp7), adenosine, and sleep regulatory cytokines will also need to be examined in the context of trauma induced sleep disturbances, and trauma- and stressor-related disorders including PTSD. Fabp7 is a type of fatty-acid binding protein that has been shown to be elevated during sleep in multiple brain regions and is indirectly regulated by BMAL1, a core clock gene.[99,114] A recent study suggests that Fabp7 transcription is controlled by the BMAL1 target, Rev-erbα, in various brain areas such as the cerebral cortex, hippocampus, hypothalamus, striatum, and ventral tegmental area[128] and suggests that Fabp7 may be a critical signaling molecule involved in integrating information about sleep need and circadian clock function. Although Fabp7 is uniquely situated among sleep and circadian regulatory processes, its role in the context of stress and trauma induced sleep disturbances remains to be elucidated.

As previously discussed, adenosine release from astrocytes has been shown to be critical for sleep regulation and homeostasis which suggests it too could be an important molecule to examine following stress and trauma exposure.[131,138,142]

Finally, cytokine signaling pathways of the immune system are sleep regulatory and respond to stress, and therefore may play an important role in the relationship between sleep and stress. Cytokines reinforce and suppress sleep and are additionally important for sleep homeostasis.[143] An increase in the inflammatory cytokine interleukin-1 beta (IL-1b) and tumor necrosis factor alpha (TNF) have been shown to increase NREM sleep, while knockout animals show a disruption of sleep.[143–145] This process occurs through AMPA receptor expression promotion and an increase in cytosolic Ca++.[145] These data additionally suggest that cytokines are sufficient to regulate the HPA axis.[146] Further developing our understanding of how these sleep regulatory cytokines may shift following stress and trauma exposures could lead us to potential medical interventions.

Although the precise mechanisms of stress-induced insomnia are unknown, there is sufficient evidence to suggest that altered glucocorticoid signaling on astrocytes may represent a viable cellular/molecular mechanism to explain a subset of stress induced neurobiological effects and an ability to differentiate exposures leading to stress that lead to PTSD and stress that does not. Further examination of this relationship within sleep-regulatory brain centers with a focus on astrocyte specific mechanisms could lead to a deeper understanding of how these different extremes of stress differ on a biological level. Determining if the GM or RM ratio goes back to normal following PTSD and how sleep if effected in relation to these ratios could advance our ability to target these receptors for future treatments. This knowledge could lead to sleep-specific therapies and specialized interventions to help lessen the incredible financial and emotional burdens that stress and trauma exposure bring to patients, their families, and society.

Conflict of Interest

The authors declare no conflict of interest

Keywords

astrocytes, glucocorticoids, insomnia, post-traumatic stress disorder, sleep, stress, trauma

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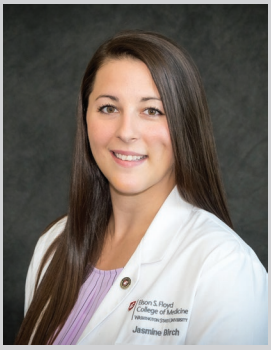

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