Neurobiological linkage between stress and sleep

Larry D. Sanford, Laurie L. Wellman
Sleep Research Laboratory, Department of Pathology and Anatomy,
Eastern Virginia Medical School, P.O. Box 1980, Norfolk, VA USA 23507.

SanforLD@evms.edu; Phone 1-757-446-7081; FAX 1-757-446-5719

ABSTRACT

Stress can have a significant negative impact on health and stress-induced alterations in sleep are implicated in both human sleep disorders and in psychiatric disorders in which sleep is affected. We have demonstrated that the amygdala, a region critical for regulating emotion, is a key modulator of sleep. Our current research is focused on understanding how the amygdala and stressful emotion affect sleep and on the role sleep plays in recovery from stress. We have implemented animal models to examine the how stress and stress-related memories impact sleep. Experiencing uncontrollable stress and reminders of uncontrollable stress can produce significant reductions in sleep, in particular rapid eye movement sleep. We are using these models to explore the neurobiology linking stress-related emotion and sleep. This research is relevant for sleep disorders such as insomnia and into mental disorders in which sleep is affected such as post-traumatic stress disorder (PTSD), which is typically characterized by a prominent sleep disturbance in the aftermath of exposure to a psychologically traumatic event.

Keywords: amygdala, arousal, sleep, stress

1. INTRODUCTION

Interactions among stress, sleep, and arousal systems are recognized factors in the etiology of a variety of medical disorders. By definition, stress produces arousal [1] and can have the potential to alter subsequent sleep. Highly stressful traumatic life events virtually always produce at least temporary sleep disturbances that may include insomnia or subjective sleep problems [2] and the persistence of these disturbances may be predictive of the future development of emotional and physical disorders [3, 4]. Sleep disturbances also are commonly associated with stress-related disorders and difficulties with can be the primary complaint of post-traumatic stress disorder (PTSD) patients [5].

There are significant overlaps of the neural circuitry and neurochemistry underlying the stress response and the neural systems regulating arousal and sleep. Thus, it is not surprising that the interaction between stress and sleep is implicated in a variety of disease processes and psychiatric disorders. However, it also is important to note that even significant stress can be experienced without producing permanent or pathological changes. The stress response engages the physiological and behavioral resources needed to cope with a life challenge and it is usually is followed by a return to normalcy when the situation is resolved. Indeed, the purpose of the stress response is to restore homeostasis [1], which may include alterations in sleep.

In this review, we will discuss the complex relationship between stress, sleep and arousal by examining the effects of stress on sleep, stress parameters that appear to be important in determining post-stress sleep and the role of the

Nanosystems in Engineering and Medicine, edited by Sang H. Choi, Jin-Ho Choy, Uhn Lee, Vijay K. Varadan,
Proc. of SPIE Vol. 8548, 85482V · © 2012 SPIE · CCC code: 1605-742/12/$18 · doi: 10.1117/12.981788

amygdala in regulating the relationship between stress and sleep. Lastly, we will discuss current concepts linking stress and sleep in stress-related disorders.

2. STRESS

Stress is broadly defined as a nonspecific physiological response to a situation or event that is psychologically or physiologically demanding [1]. In response to stressors, neurochemical mediators are released that act acutely to promote adaptive physiological and behavioral responses to the existing challenge [1]. This includes activation of the hypothalamo-pituitary-adrenal (HPA) axis as well as the sympathetic nervous system and the adrenal medulla, (the sympathoadrenal system) [1, 6] to initiate and regulate behavioral and physiological adaptations to the challenge as well as the restoration of homeostasis when the threat is removed [1].

Problems can arise when the stress response is inadequate to meet the challenge or the stress system is overcome by intense or prolonged stressful events. In this case, stress can have a significant, long-lasting negative impact on health [7-9] and severe stress has been linked to the genesis of mood and anxiety disorders. However, stressors are commonly encountered in daily life without producing permanent or pathological changes. Even the traumatic life events that can give rise to PTSD do so in only a percentage of the population [10-12] whereas the majority of individuals may cope with similar situations while exhibiting only transitory detrimental effects arising from the experience. The difference between successful and unsuccessful coping with stress and whether it has transitory or lasting effects can vary with characteristics of the stressful event including its duration, intensity [13, 14], predictability [15, 16] and controllability [17, 18]. Differences in resilience and vulnerability are also significant factors in the ability of an individual to cope with stress [19].

3. SLEEP AND AROUSAL STATES

Mammals (and birds) exhibit three basic arousal states: wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM and REM sleep are also known as slow wave sleep and paradoxical sleep, respectively. NREM sleep is characterized by high-amplitude, low-frequency (e.g., 0.5 – 4.5 Hz) waves recordings in the encephalogram (EEG). REM sleep is characterized by an EEG with low amplitude, higher frequency activity more typical of a waking animal at the same time that there is a nearly complete loss of voluntary muscle tone and the maintenance of behavioral quiescence. REM sleep can be distinguished behaviorally by involuntary twitching and jerking that occurs on a background of muscle atonia. Sleep in mammals also can be identified behaviorally by (i) a typical posture, (ii) behavioral quiescence (iii) increased stimulus threshold for arousal to an alert state, and (iv) rapid reversibility to wakefulness once aroused [20].

A full discussion of neural regulation of sleep is beyond the scope of this paper; however, various brain regions located from the forebrain to brain stem have been implicated in the generation and expression of sleep-related neural activity. Rostral regions include the basal forebrain-preoptic area which contains sleep-active neurons that begin to fire during drowsiness and then fire maximally during NREM [21]. Electrophysiological studies of these neurons [21] as well as lesion [22, 23] and stimulation [24, 25] studies in this region suggest that they may have a role in triggering NREM. The ventrolateral preoptic (VLPO) region of the hypothalamus also has demonstrated roles in regulating both NREM and REM sleep [26, 27].

Caudally in the brain, the pons contains three cell groups that are central to prevailing conceptions of how REM sleep is generated: cholinergic neurons in the laterodorsal tegmentum and peduculopontine tegmentum (LDT/PPT), noradrenergic (NA) neurons in the locus coeruleus (LC) and serotonergic (5-HT) neurons in the dorsal raphe nucleus (DRN). Putatively cholinergic REM-on cells in LDT/PPT progressively increase their discharge from W to NREM to REM sleep and may be possible generators of REM (reviewed in [28]). Both NA neurons in LC and 5-HT neurons in DRN are most active in W and reduce their discharge rates during sleep until they fall silent in REM, giving rise to the idea that their silence may play a permissive role in REM generation (reviewed in [28]). The forebrain also has an, as yet, poorly understood role in the control of REM sleep, though it appears likely that any forebrain influence on REM sleep would be exerted on REM sleep generator regions in the pons.

Studies of sleep control have concentrated on three basic regulatory processes. Sleep is homeostatically regulated such that sleep deficits are followed by compensatory increases in sleep [29-31]. Homeostatic processes are responsible for the increase in "sleep pressure" during wakefulness and its subsequent dissipation during sleep (Reviewed in [29-31]). Homeostatic processes also account for compensatory increases in sleep that follow sleep deficits [29]. Circadian processes regulate "sleep propensity" in a clock-like fashion within the 24 hour day (Reviewed in [29]) and ultradian processes are reflected in alternating periods of NREM and REM states within sleep ([32]). These processes can account for the internal "drive" for sleep and for the influence of periodic geophysical zeitgebers such as light on the normal distribution of sleep and wakefulness throughout the day. However, organisms must contend with both periodically- and randomly occurring stressful environmental and social events that can have significance for health and even survival. The ways in which these factors affect the relative occurrence of sleep and wakefulness and the neural linkage between the stress system and sleep are poorly understood.

4. STRESS-INDUCED SLEEP DISTURBANCES

Stress can be a significant factor in insomnia [33] which has been hypothesized to be a disorder of hyperarousal in the central nervous system and not actual sleep loss [33, 34]. This hypothesis is based on data that the HPA axis is more active in insomniacs, who show higher levels of ACTH and cortisol, than do individuals without insomnia [33, 34]. Based on elevated HPA axis activity and the fact that elevated levels of nocturnal cortisol found in insomnia are markers of elevated corticotropin releasing hormone (CRH), it has been suggested that treating the underlying disturbance in CRH could be a potential treatment for insomnia [35]. CRH also acts in the brain to regulate arousal and sleep [36, 37].

Stress-related disturbances in sleep are also factors in stress-related disorders. For example, sleep problems and insomnia are core features of PTSD [5] and alterations in both REM and NREM sleep have been reported. Alterations in REM sleep have not been fully explained. REM sleep in PTSD patients has been variously reported to be increased [38], decreased [39, 40], or to show differences in architecture, but not amounts [41, 42]. There also are significant changes in NREM sleep in PTSD [40] including reductions in both visually scored delta sleep and EEG delta amplitude (reviewed in [43]). Neylan et al. [43] suggest that the changes in NREM sleep and delta may involve persistent increases in CRH activity coupled with either enhanced negative feedback or downregulated CRH receptors.

Interestingly, the decreased REM sleep [44-46] and increased light NREM sleep [44] reported in rats and mice after extensive training with inescapable footshock are consistent with many of the findings of PTSD. However, while significant sleep disturbances occur in PTSD, delineating the role that stress-induced alterations in sleep might play in the genesis of the disorder is difficult. There are few studies of sleep in the immediate aftermath of traumatic stress and Mellman et al. [47, 48] made the important point that studies conducted months, years or even decades after the traumatic event may be influenced by factors not related to the development of PTSD. Only a few studies have examined sleep in the initial stages of PTSD. Polysomnographic studies conducted within a month of a traumatic experience found a more fragmented pattern of REM sleep characterized by shorter average duration REM sleep episodes before shifting stage or awakening in PTSD patients compared to patients without PTSD and a non-traumatized comparison group [47, 48]. There were also a greater number of REM sleep episodes in the PTSD patients than in patients that experienced trauma without developing PTSD. These data collected earlier in the progression of PTSD suggest that disturbances in REM sleep may be important for stress-related pathology. Mellman et al. [47, 48] suggested that intact REM sleep may in aid in the processing of the memory for trauma and we, based on our work with animals, have suggested that REM sleep may play an adaptive function in recovery from stress [49].

5. EXPERIMENTAL STRESS AND SLEEP

There has long been an interest in determining the effects of stress on sleep using animal models and sleep has been recorded after a great number of experimental stressors including avoidable footshock [50, 51], restraint [52-60], water maze [50], exposure to novel objects [61-64], open field [62, 64], ether exposure [65, 66], cage change [62, 64] and social stress [67, 68] (for a comprehensive review see [69]). This has produced a significant body of work describing the effects of a variety of stressors on sleep. However, for the most part, these studies have provided little real insight into the mechanisms by which stress alters sleep.

One promising line of work has begun to examine the role of stressor control and stress-related memories on sleep using variations of fear conditioning and learned helplessness paradigms. Fear conditioning is typically utilized as a learning paradigm in which an association is made between previously neutral auditory cues or situational context information and the presentation of an uncontrollable stressor (usually footshock). Afterwards, presenting the fearful cues or contexts alone elicit physiological and behavioral responses similar to those produced by the footshock stressor. By comparison, most variants of learned helplessness train animals with controllable and uncontrollable stress (usually escapable and inescapable footshock) using a yoked design such that both animals receive identical amounts of shock. Subsequently, many of the animals trained with inescapable footshock will show deficits in performance in situations where escape is possible [70]. The advantage of paradigms like conditioned fear and learned helplessness is that they allow the examination of both the actual stressor and of memories of previously experienced stress on behavior and sleep. This has tremendous value for modeling processes related to the long-term effects of stressful events. Indeed, stress-related fear conditioning is thought to play a significant role in the development of anxiety disorders [71, 72] and PTSD [9, 73] and learned helplessness has been used to model depression [74].

Studies of fear conditioning typically have focused on memory mechanisms and have measured immediate responses to fearful cues or contexts, or to their effects on modifying responses to other stimuli. Thus, behavioral responses such as freezing (e.g., [75-77]), and fear-potentiated startle amplitude are well established [78, 79] and have been used to assess fear memory and fear extinction, a type of new learning that inhibits subsequent fear behavior without erasing the original memory for fear conditioning [80].

Fear conditioned alterations in sleep are also now well-established though the specific changes produced in sleep can vary with amount of training, animal strain and training conditions. Brief training as generally used in studies of fear memory have been reported to increase NREM sleep [81] whereas extensive training has been associated with alterations in both NREM and REM sleep. These alterations are generally greater and of longer duration in stress vulnerable strains, consistent with the role of resilience and vulnerability in stress responses [19]. With extensive training with inescapable footshock, the primary and most consistent effect is a marked reduction in REM sleep (Figure 1) that occurs both after the shock training and after presentation of shock-associated fearful cues and contexts [45, 46, 49]. Reduced REM sleep has been reported across species and across strains [45, 46, 82] and can occur without rebound or recovery REM sleep [83]. By comparison, enhanced REM sleep has been reported to occur after virtually all other experimental stressors.

We have found reductions in NREM sleep after shock training and fearful contexts in some strains and not in others [45]. Increased light slow wave sleep and decreased REM sleep have been reported in rats after extensive, inescapable shock training [44]. There also may be relatively less EEG delta (slow wave activity) during NREM sleep in animals that show greater fear-conditioned changes in sleep [84]. Thus, both increases and decreases in NREM sleep and variations in NREM EEG spectra can occur after shock training, though the reason for these differences are not known.

While much emphasis has been put on the role fear conditioning in the long-term negative consequences of stressful events, it also can underlie adaptive behavior that occurs only so long as the fear-inducing stimulus is predictive of, or associated with, an aversive event [72, 85]. For example, after shock training, repeated presentation of a fearful cue or context without a shock contingency typically results in fear "extinction." It is the failure of extinction that has been linked to stress-related psychopathology (e.g., PTSD [86]) though the processes that make behaviors resistant to extinction remain mostly unknown.

There appears to be a relationship between extinction and sleep. Both NREM and REM sleep normalize following extinction of contextual fear whereas rats that continued to show fear exhibited reductions in REM sleep [87]. Additionally, post-training REM sleep deprivation has been reported to impair extinction (as indicated by freezing) for light cues [88], but not for auditory cues [89] previously paired with shock. REM sleep-deprived rats did show greater spontaneous recovery of freezing on a second day with presentation of the fearful auditory cue alone. In contrast, post-training REM sleep deprivation did not significantly alter contextual fear extinction learning or spontaneous recovery of freezing on a second day of testing [88, 89].

In summary, stress, stress-related memories and fear extinction can have a significant impact on sleep that likely plays roles in determining whether or not stressful events produce persisting or even permanent effects. Thus, delineating the

linkage between stress and sleep will be important for fuller understanding the processes by which stress can negatively influence health and behavior.

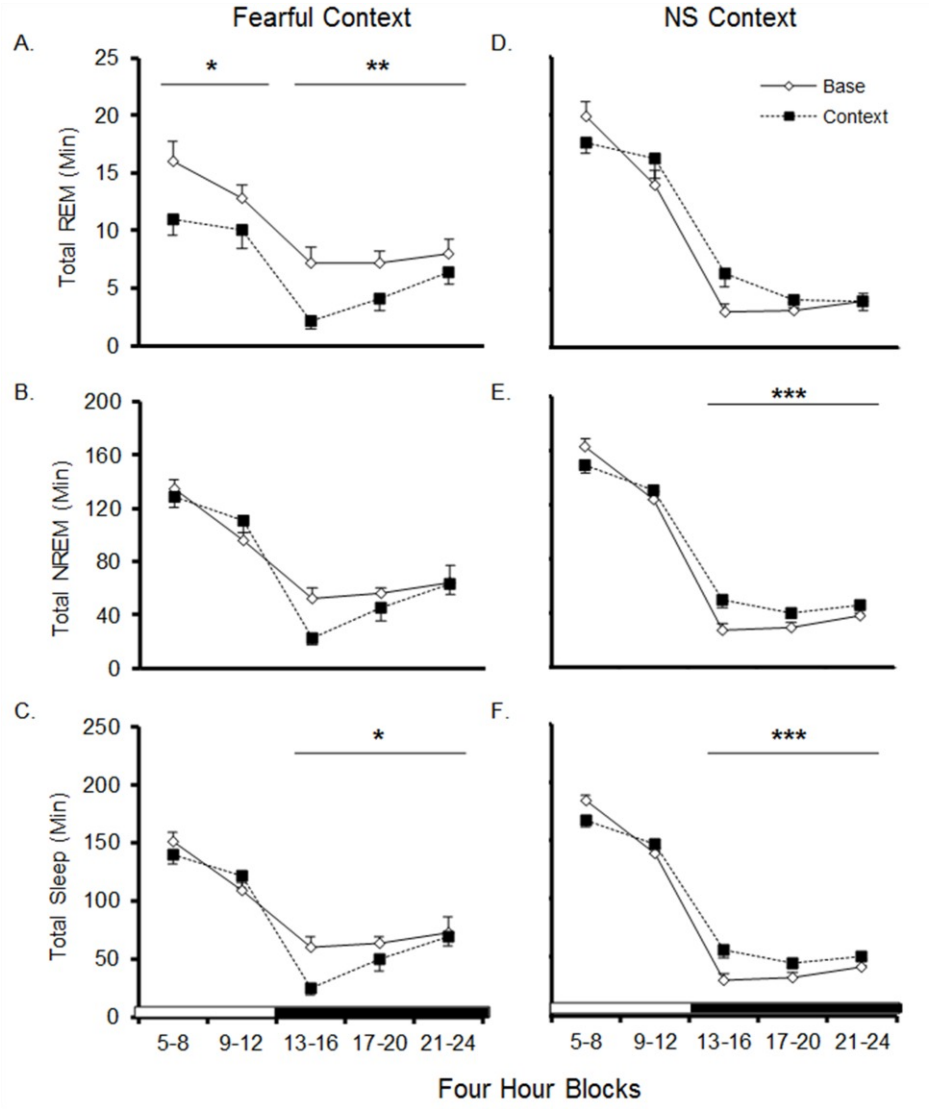

Figure 1. Total rapid eye movement (REM) sleep (A), total non-rapid eye movement (NREM) sleep (B) and total sleep (C; REM + NREM) plotted in four hour blocks after exposure to a context made fearful by shock training and for time matched baseline recordings in DBA/2J mice. For comparison, total REM (D), total NREM (E) and total sleep (F) after exposure to a context not made fearful by shock training (NS Context). In each instance, the mice had experienced either four days of shock training (n=11; 20 shocks, 0.2 mA at 0.5 sec duration, 1 min interstimulus interval) or four days of exposure to the same context without receiving shock (n=11) prior to testing. Exposure to the fearful context resulted in significant reductions in REM sleep and a reduction in total sleep in the dark period. In contrast, exposure to the NS Context resulted in significant increases in NREM and total sleep during the dark period. *, p <.05; **, p <.01; ***, p<.001. Dark bar on the horizontal axis indicates the dark period.

6. Amygdala and Stress-Induced Alterations in Sleep and Arousal

Several lines of evidence suggest that the amygdala plays an important role in regulating the linkage between stress and sleep. The amygdala has generally become regarded as the center of emotion in the limbic system [77]. It has a well-

established role in conditioned fear, and probably anxiety [79] and it is important in the forebrain regulation of the stress response. The central nucleus of the amygdala (CNA) plays a role in the modulation of autonomic phenomena including heart rate, blood pressure and respiratory activity patterning [90-93], particularly as related to stress [93]. Further, the amygdala is the recipient of sensory information of all modalities from cortical and subcortical structures; and, in turn, it projects to diverse neural structures including thalamic, hypothalamic and brainstem target regions important for the regulation of fear, arousal and sleep (see Figure 2, adapted from various sources, e.g., [94-97]). Also, the amygdala appears to be necessary for both explicit, cue-specific fear conditioning and contextual fear conditioning [77, 98].

The amygdala plays a role in regulating the stress response. The bed nucleus of the stria terminalis (BNST) is an important relay for the influence of the amygdala on the hypothalamic paraventricular nucleus (PVN) [99], the final common pathway for information influencing the HPA axis [1, 100, 101]. GABAergic neurons in BNST can directly inhibit PVN and reduce ACTH secretion [100]. By comparison, the CNA has minimal direct projections to PVN [102] and lesions of CNA do not directly influence PVN activation [103]. However, CNA can influence PVN via trans-synaptic pathways through the dorsomedial hypothalamic and BNST [102].

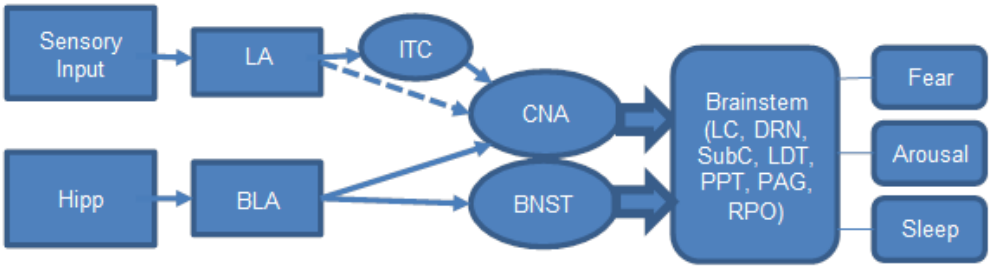

Figure 2. Simplified diagram of amygdala circuitry regulating fear-conditioned behavior and fear-conditioned changes in sleep. The lateral nucleus (LA) of the amygdala receives afferent sensory input during fear conditioning. The LA projects, via the intercalated cell masses (ITC), to the central nucleus (CNA), which has outputs to brainstem regions that control the expression of the fear, arousal and REM sleep. Projections from the hippocampus (Hipp) to the basolateral nucleus of the amygdala (BLA) process contextual information during conditioning and BLA regulates fear expression and the influence of contextual fear memory on sleep via projections to CNA and bed nucleus of the stria terminalis (BNST) which has similar descending outputs to those of CNA. LC: locus coeruleus; DRN: dorsal raphe nucleus; SubC: n. subcoeruleus; LDT: laterodorsal tegmental nucleus; PPT: pedunculopontine tegmental nucleus; PAG: periaqueductal grey; RPO: reticularis pontis oralis. Dashed line indicates a direct connection of LA to CNA in some models of fear. The ventromedial prefrontal cortex supplies inhibitory input to the amygdala during extinction (not shown).

The first suggestion that the amygdala might be involved in the actual regulation of sleep occurred in the early sixties [104]. Throughout the years since, studies by sleep researchers have reported on the effects of electrically stimulating the amygdala on EEG [105], ponto-geniculo-occipital (PGO) waves [105], and REM sleep [106] and several studies have examined the influence of the amygdala on autonomic variables during wakefulness and sleep (e.g., [91, 107-109]). Studies in narcoleptic dogs have also implicated the amygdala in cataplexy [110, 111]. In addition, a finding of increased cerebral blood flow in the amygdala during REM in humans [112] was interpreted as a possible link between emotionality controlled by the limbic system and dream content.

Research over the last several years has demonstrated that indeed the amygdala is a significant modulator of sleep. The majority of studies on the role of the amygdala in regulating sleep has focused on its influence on REM sleep (e.g., [113-117]) and REM sleep related phenomena such as PGO waves, which are one of the key signs of REM sleep [105, 114, 118]. However, a number of studies also indicate that the amygdala can influence NREM sleep [114, 116, 117, 119] as well as arousal [114, 120, 121]. The influence of the amygdala on sleep and arousal most likely involves projections to thalamic, hypothalamic and brainstem target regions [94]. These include direct projections via the CNA (e.g., [122-126]) and the lateral division of the BNST (reviewed in [94, 95]), the sources of the major descending outputs of the amygdala,

to brainstem regions that regulate REM sleep. A role for CNA in regulating sleep has been well established whereas the BNST has been minimally investigated.

Inhibition of CNA suppresses REM sleep whereas its activation (e.g., with electrical stimulation [106]) can promote REM sleep in some situations. For example, functional inactivation of CNA with microinjections of the $GABA_A$ agonist, muscimol, produces a relatively selective decrease in REM sleep whereas blocking GABAergic inhibition with the $GABA_A$ antagonist, bicuculline, enhances REM sleep [113]. Functional lesions of the CNA by TTX, which inactivates both cell bodies and fibers of passage also decrease REM sleep and reduce arousal [121]. The decrease in REM sleep can occur without recovery [121], a finding seen with training with inescapable shock and fearful cues and contexts.

Stress-induced inactivation of CNA appears to regulate decreases in REM sleep produced by training with inescapable shock and by presentation of shock associated cues and contexts. This is suggested by the lack of Fos activation, a marker of neural activation, in CNA after conditioned fear [127] and by findings that bicuculline microinjected into CNA attenuate footshock-induced reductions in REM sleep whereas inactivation of CNA with muscimol do not [128]. That activation of CNA promotes and that inactivation of CNA reduces REM sleep appear at odds with the prevailing conventional view that CNA activation is responsible for regulating fear responses via projections to the periaqueductal gray and other brainstem and (Reviewed in [129]). In fact, CNA neurons do fire in response to footshock stress [130] and in response to conditioned stimuli [129]. However, CNA is inhibited by stimulation of the basolateral (BLA) and lateral nuclei of the amygdala [130] both of which show high Fos expression after footshock [127]. Thus, it is possible that CNA activation during fearful/stressful events does regulate fear behavior in wakefulness, but subsequently, with certain stressors, can be inhibited to decrease REM sleep in the post-stress period.

Other than the CNA, the BLA has received the most attention with respect to a potential role in regulating sleep. In rats, bilateral electrolytic and chemical lesions of BLA have been reported to increase NREM sleep and total sleep time in rats [117] whereas electrical and chemical stimulation of BLA increase low voltage, high frequency activity in the cortical EEG and decrease NREM sleep and total sleep time [117, 131]. Bilateral chemical lesions of the amygdala in Rhesus monkeys produce more consolidated sleep during chair restraint [132], a finding consistent with activation of BLA by stress and a role for BLA in the regulation of sleep and arousal. BLA may also selectively influence REM sleep. Microinjections into BLA of the Group II metabotropic glutamate (mGlu) receptor agonist, LY379268, selectively reduced REM sleep without significantly altering wakefulness or NREM sleep [133].

The central CRH system plays a major role in mediating responses to stressors [134, 135]. Administration of CRH in animals produces many of the signs associated with anxiety in humans, including increased wakefulness [136-138], altered locomotor activity, and an exaggerated startle response [139, 140]. By comparison, CRH antagonists attenuate behavioral responses to stress (e.g., [141-143]). CRH also plays an important, but poorly understood, role in regulating spontaneous and stress-induced alterations in sleep (e.g., [36, 137, 144-147]).

The amygdala (including extended amygdala) is a critical region for the central effects of CRH, and it appears to mediate a number of the anxiogenic effects of CRH as evidenced by intra-amygdala microinjections of CRH agonists and antagonists (Reviewed in [95]). For example, local application of CRH or urocortin [148] into the BLA in rats produces dose-dependent increases in anxiety behaviors. CRH in the amygdala also plays a significant role in regulating stress-induced alterations in sleep. In rats, bilateral microinjections of the CRH receptor 1 antagonist, antalarmin, into CNA block reductions in REM sleep normally produced by contextual fear and attenuate Fos expression in regions important in stress and REM sleep regulation including the PVN, LC, and DRN [149]. Similarly, bilateral microinjections of antalarmin into BLA in rats do not alter spontaneous sleep, but do block the reduction in REM sleep produced by inescapable footshock [150]. Further, microinjecting antalarmin into BLA prior to shock training also blocked the subsequent effects of contextual fear on REM, but did not block fear memory or behavior as indicated by freezing. Thus, CRH can act within CNA and BLA to affect stress- and fear-induced alterations in REM sleep. CRH may also act within BLA to modulate the formation of memories that can subsequently influence sleep.

7. CONCLUSION

Stress and stress-related memories can have a significant impact on sleep. Fear conditioning has significant promise for modeling the effects of stressful memories on sleep. The amygdala has demonstrated roles in regulating physiological

responses to stressors, adaptive behaviors, and arousal and sleep. There is evidence that it influences pontine regions involved with regulating and generating REM sleep. It also plays significant roles in mediating the effects of stress and stressful memories on sleep and arousal and altered amygdalar functioning is implicated in pathological states. These factors indicate that the amygdala is a critical neurobiological link between stress, fear conditioning and sleep.

Acknowledgments: This work was supported by NIH research grant MH64827.

References

[1] Chrousos, G.P., "Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture," Ann N Y Acad Sci 851, 311-35 (1998).
[2] Lavie, P., "Sleep disturbances in the wake of traumatic events," N Engl J Med 345, 1825-1832 (2001).
[3] Koren, D., I. Arnon, P. Lavie, and E. Klein, "Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents," Am J Psychiatry 159, 855-857. (2002).
[4] Klein, E., D. Koren, I. Arnon, and P. Lavie, "Sleep complaints are not corroborated by objective sleep measures in post-traumatic stress disorder: a 1-year prospective study in survivors of motor vehicle crashes," J Sleep Res 12(1), 35-41 (2003).
[5] Harvey, A.G., C. Jones, and D.A. Schmidt, "Sleep and posttraumatic stress disorder: a review," Clin Psychol Rev 23(3), 377-407 (2003).
[6] Klimes, I., et al., "Mapping of genetic determinants of the sympathoneural response to stress," Physiol Genomics 20(2), 183-7 (2005).
[7] Van Dijken, H., J. Mos, J. van der Heyden, and F. Tilders, "Characterization of stress-induced long-term behavioural changes in rats: evidence in favor of anxiety," Physiol Behav 52, 945-951 (1992).
[8] Adamac, R. and T. Shallow, "Lasting effects on rodent anxiety of a single exposure to a cat," Physiol Behav 54, 101-109. (1993).
[9] Pynoos, R., R. Ritzmann, A. Steinberg, A. Goenjian, and I. Prisecaru, "A behavioral animal model of posttraumatic stress disorder featuring repeated exposure to situational reminders " Biol Psychiatry 39 129-134 (1996).
[10] Yehuda, R. and J. LeDoux, "Response variation following trauma: a translational neuroscience approach to understanding PTSD," Neuron 56(1), 19-32 (2007).
[11] Cohen, H., J. Zohar, and M. Matar, "The relevance of differential response to trauma in an animal model of posttraumatic stress disorder," Biol Psychiatry 53(6), 463-73 (2003).
[12] Kerns, J.G., et al., "Anterior cingulate conflict monitoring and adjustments in control," Science 303(5660), 1023-6 (2004).
[13] Buydens-Branchey, L., D. Noumair, and M. Branchey, "Duration and intensity of combat exposure and posttraumatic stress disorder in Vietnam veterans," J Nerv Ment Dis 178(9), 582-7 (1990).
[14] Natelson, B.H., "Stress, hormones and disease," Physiol Behav 82(1), 139-43 (2004).
[15] Adell, A., R. Trullas, and E. Gelpi, "Time course of changes in serotonin and noradrenaline in rat brain after predictable or unpredictable shock," Brain Res 459(1), 54-9 (1988).
[16] Abbott, B.B., L.S. Schoen, and P. Badia, "Predictable and unpredictable shock: behavioral measures of aversion and physiological measures of stress," Psychol Bull 96(1), 45-71 (1984).
[17] Bolstad, B.R. and R.E. Zinbarg, "Sexual victimization, generalized perception of control, and posttraumatic stress disorder symptom severity," J Anxiety Disord 11(5), 523-40 (1997).
[18] Foa, E.B., R. Zinbarg, and B.O. Rothbaum, "Uncontrollability and unpredictability in post-traumatic stress disorder: an animal model," Psychol Bull 112(2), 218-38 (1992).
[19] Yehuda, R., J.D. Flory, S. Southwick, and D.S. Charney, "Developing an Agenda for Translational Studies of Resilience and Vulnerability Following Trauma Exposure," Annals of the New York Academy of Sciences 1071(1), 379-396 (2006).
[20] Zepelin, H., J.M. Siegel, and I. Tobler, [Mammalian sleep.], in *Principes and Practice of Sleep Medicine*, M.H. Kryger, T. Roth, and W.C. Dement, Editors., Elsevier Saunders: Philadephia. p. 91-100. (2005).
[21] Szymusiak, R. and D. McGinty, "Sleep-related neuronal discharge in the basal forebrain of cats," Brain research 370(1), 82-92 (1986).

[22] Alam, M.N. and B.N. Mallick, "Differential acute influence of medial and lateral preoptic areas on sleep-wakefulness in freely moving rats," Brain research 525(2), 242-8 (1990).
[23] Szymusiak, R. and D. McGinty, "Sleep suppression following kainic acid-induced lesions of the basal forebrain," Experimental neurology 94(3), 598-614 (1986).
[24] Sterman, M.B. and C.D. Clemente, "Forebrain inhibitory mechanisms: sleep patterns induced by basal forebrain stimulation in the behaving cat," Experimental neurology 6, 103-17 (1962).
[25] Sterman, M.B. and C.D. Clemente, "Forebrain inhibitory mechanisms: cortical synchronization induced by basal forebrain stimulation," Experimental neurology 6, 91-102 (1962).
[26] Lu, J., et al., "Selective activation of the extended ventrolateral preoptic nucleus during rapid eye movement sleep," Jrn Neurosci 22(11), 4568-76 (2002).
[27] Lu, J., M.A. Greco, P. Shiromani, and C.B. Saper, "Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep," Jrn Neurosci 20(10), 3830-42 (2000).
[28] Steriade, M. and R. McCarley, [Brainstem Control of Wakefulness and Sleep]New York: Plenum Press (1990).
[29] Borbely, A. and P. Achermann, [Sleep homeostasis and models of sleep regulation], in *Principes and Practice of Sleep Medicine*, M.H. Kryger, T. Roth, and W.C. Dement, Editors., Elsevier Saunders: Philadephia. p. 405-417. (2005).
[30] Borbely, A.A., P. Achermann, L. Trachsel, and I. Tobler, "Sleep initiation and initial sleep intensity: interactions of homeostatic and circadian mechanisms," Journal of biological rhythms 4(2), 149-60 (1989).
[31] Strogatz, S.H., R.E. Kronauer, and C.A. Czeisler, "Circadian regulation dominates homeostatic control of sleep length and prior wake length in humans," Sleep 9(2), 353-64 (1986).
[32] McCarley, R.W. and J.A. Hobson, "Neuronal excitability modulation over the sleep cycle: a structural and mathematical model," Science 189(4196), 58-60 (1975).
[33] Basta, M., G.P. Chrousos, A. Vela-Bueno, and A.N. Vgontzas, "Chronic Insomnia and Stress System," Sleep Med Clin 2(2), 279-291 (2007).
[34] Vgontzas, A.N., et al., "Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications," J Clin Endocrinol Metab 86(8), 3787-94 (2001).
[35] Roth, T., M. Franklin, and T.J. Bramley, "The state of insomnia and emerging trends," Am J Manag Care 13(5 Suppl), S117-20 (2007).
[36] Opp, M.R., "Corticotropin-releasing hormone involvement in stressor-induced alterations in sleep and in the regulation of waking," Adv Neuroimmunol 5(2), 127-43 (1995).
[37] Opp, M.R., "Rat strain differences suggest a role for corticotropin-releasing hormone in modulating sleep," Physiology & behavior. 63(1), 67-74 (1997).
[38] van der Kolk, B., R. Blitz, W. Burr, S. Sherry, and E. Hartmann, "Nightmares and trauma: a comparison of nightmares after combat with lifelong nightmares in veterans," Am J Psychiatry 141(2), 187-90 (1984).
[39] Lavie, P., A. Hefez, G. Halperin, and D. Enoch, "Long-term effects of traumatic war-related events on sleep," Am J Psychiatry 136(2), 175-8 (1979).
[40] Schlosberg, A. and M. Benjamin, "Sleep patterns in three acute combat fatigue cases," J Clin Psychiatry 39(6), 546-9 (1978).
[41] Ross, R.J., et al., "Motor dysfunction during sleep in posttraumatic stress disorder," Sleep (Abstract Supplement) 17(8), 723-32 (1994).
[42] Ross, R.J., et al., "Rapid eye movement sleep changes during the adaptation night in combat veterans with posttraumatic stress disorder," Biol Psychiatry 45(7), 938-41 (1999).
[43] Neylan, T.C., C. Otte, R. Yehuda, and C.R. Marmar, "Neuroendocrine regulation of sleep disturbances in PTSD," Ann N Y Acad Sci 1071, 203-15 (2006).
[44] Adrien, J., C. Dugovic, and P. Martin, "Sleep-wakefulness patterns in the helpless rat " Physiol Behav 49, 257-262 (1991).
[45] Sanford, L., L. Yang, and X. Tang, "Influence of contextual fear on sleep architecture in mice: A strain comparison," Sleep (Abstract Supplement) 26, 527-540. (2003).
[46] Sanford, L.D., X. Tang, R.J. Ross, and A.R. Morrison, "Influence of shock training and explicit fear-conditioned cues on sleep architecture in mice: strain comparison," Behav Genet 33(1), 43-58 (2003).
[47] Mellman, T.A., V. Bustamante, A.I. Fins, W.R. Pigeon, and B. Nolan, "REM sleep and the early development of posttraumatic stress disorder," Am J Psychiatry 159(10), 1696-701 (2002).
[48] Mellman, T.A., W.R. Pigeon, P.D. Nowell, and B. Nolan, "Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma," J Trauma Stress 20(5), 893-901 (2007).

[49] Tang, X., L. Yang, and L.D. Sanford, "Rat strain differences in freezing and sleep alterations associated with contextual fear," Sleep (Abstract Supplement) 28(10), 1235-44 (2005).
[50] Smith, C., "Sleep states and memory processes," Behav Brain Res 69(1-2), 137-45 (1995).
[51] Sanford, L.D., J. Xiao, X. Liu, L. Yang, and X. Tang, "Influence of avoidance training (AT) and AT cues on sleep in C57BL/6J (B6) and BALB/cJ (C) mice," Sleep (Abstract Supplement) 28, A6 (2005).
[52] Gonzalez, M.M., G. Debilly, J.L. Valatx, and M. Jouvet, "Sleep increase after immobilization stress: role of the noradrenergic locus coeruleus system in the rat," Neuroscience letters 202(1-2), 5-8 (1995).
[53] Meerlo, P., A. Easton, B.M. Bergmann, and F.W. Turek, "Restraint increases prolactin and REM sleep in C57BL/6J mice but not in BALB/cJ mice," Am J Physiol Regul Integr Comp Physiol 281(3), R846-54 (2001).
[54] Rampin, C., R. Cespuglio, N. Chastrette, and M. Jouvet, "Immobilisation stress induces a paradoxical sleep rebound in rat," Neuroscience letters 126(2), 113-8 (1991).
[55] Gonzalez, M.M. and J.L. Valatx, "Effect of intracerebroventricular administration of alpha-helical CRH (9-41) on the sleep/waking cycle in rats under normal conditions or after subjection to an acute stressful stimulus," Journal of sleep research 6(3), 164-70 (1997).
[56] Bonnet, C., L. Lger, V. Baubet, G. Debilly, and R. Cespuglio, "Influence of a 1 h immobilization stress on sleep states and corticotropin-like intermediate lobe peptide (CLIP or ACTH18-39, Ph-ACTH18-39) brain contents in the rat," Brain research 751(1), 54-63 (1997).
[57] Marinesco, S., C. Bonnet, and R. Cespuglio, "Influence of stress duration on the sleep rebound induced by immobilization in the rat: a possible role for corticosterone," Neuroscience 92(3), 921-33 (1999).
[58] Meerlo, P., E.A. de Bruin, A.M. Strijkstra, and S. Daan, "A social conflict increases EEG slow-wave activity during subsequent sleep," Physiol Behav 73(3), 331-5 (2001).
[59] Cespuglio, R., S. Marinesco, V. Baubet, C. Bonnet, and B. el Kafi, "Evidence for a sleep-promoting influence of stress," Adv Neuroimmunol 5(2), 145-54 (1995).
[60] Palma, B.D., D. Suchecki, and S. Tufik, "Differential effects of acute cold and footshock on the sleep of rats," Brain research 861(1), 97-104 (2000).
[61] Schiffelholz, T. and J.B. Aldenhoff, "Novel object presentation affects sleep-wake behavior in rats," Neuroscience letters 328(1), 41-4 (2002).
[62] Tang, X., X. Liu, L. Yang, and L.D. Sanford, "Rat strain differences in sleep after acute mild stressors and short-term sleep loss," Behav Brain Res 160(1), 60-71 (2005).
[63] Tang, X., J. Xiao, B.S. Parris, J. Fang, and L.D. Sanford, "Differential effects of two types of environmental novelty on activity and sleep in BALB/cJ and C57BL/J mice," Physiol Behav 85, 419-429 (2005).
[64] Tang, X., J. Xiao, X. Liu, and L.D. Sanford, "Strain differences in the influence of open field exposure on sleep in mice," Behav Brain Res 154(1), 137-47 (2004).
[65] Bodosi, B., et al., "An ether stressor increases REM sleep in rats: possible role of prolactin," Am J Physiol Regul Integr Comp Physiol 279(5), R1590-8 (2000).
[66] Roky, R., et al., "Prolactin and rapid eye movement sleep regulation," Sleep. 18(7), 536-42 (1995).
[67] Koolhaas, J.M., P. Meerlo, S.F. De Boer, J.H. Strubbe, and B. Bohus, "The temporal dynamics of the stress response," Neurosci Biobehav Rev 21(6), 775-82 (1997).
[68] Meerlo, P. and F.W. Turek, "Effects of social stimuli on sleep in mice: non-rapid-eye-movement (NREM) sleep is promoted by aggressive interaction but not by sexual interaction," Brain research 907(1-2), 84-92 (2001).
[69] Pawlyk, A.C., A.R. Morrison, R.J. Ross, and F.X. Brennan, "Stress-induced changes in sleep in rodents: Models and mechanisms," Neurosci Biobehav Rev 32(1), 99-117 (2008).
[70] Anisman, H. and Z. Merali, [Learned helplessness induced in mice], in *Mood and anxiety related phenotypes in mice*, T.D. Gould, Editor Humana Press: New York. p. 177-196. (2009).
[71] Charney, D. and A. Deutch, "A functional neuroanatomy of anxiety and fear: implications for the pathophysiology and treatment of anxiety disorders," Critical Rev Neurobiol 10, 419-446 (1996).
[72] Pitman, R.K., L.M. Shin, and S.L. Rauch, "Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging," J Clin Psychiatry 62 Suppl 17, 47-54 (2001).
[73] Jha, S.K., F.X. Brennan, A.C. Pawlyk, R.J. Ross, and A.R. Morrison, "REM sleep: a sensitive index of fear conditioning in rats," Eur J Neurosci 21(4), 1077-80 (2005).
[74] Shaffery, J., R. Hoffmann, and R. Armitage, "The neurobiology of depression: perspectives from animal and human sleep studies," Neuroscientist 9(1), 82-98 (2003).
[75] Blanchard, R.J. and D.C. Blanchard, "Crouching as an index of fear," J Comp Physiol Psychol 67(3), 370-5 (1969).

[76] Paylor, R., R. Tracy, J. Wehner, and J. Rudy, "DBA/2 and C57BL/6 mice differ in contextual fear but not auditory fear conditioning " Behav Neurosci 108, 810-817 (1994).
[77] Phillips, R.G. and J.E. LeDoux, "Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning," Behav Neurosci 106(2), 274-85 (1992).
[78] Davis, M., "Animal models of anxiety based on classical conditioning: the conditioned emotional response (CER) and the fear-potentiated startle effect," Pharmaco Therapeut 47, 147-165 (1990).
[79] Davis, M., "The role of the amygdala in fear and anxiety," Ann Rev Neurosci 15, 353-375 (1992).
[80] Bouton, M.E., "Context and behavioral processes in extinction," Learn Mem 11(5), 485-94 (2004).
[81] Hellman, K. and T. Abel, "Fear conditioning increases NREM sleep," Behav Neurosci 121(2), 310-23 (2007).
[82] Sanford, L.D., A.J. Silvestri, R.J. Ross, and A.R. Morrison, "Influence of fear conditioning on elicited ponto-geniculo-occipital waves and rapid eye movement sleep," Arch Ital Biol 139(3), 169-83 (2001).
[83] Sanford, L.D., J. Fang, X. Tang, D.o.P. Sleep Research Laboratory, and E.V.M.S.N.V.A.U.S.A.S.e.e. Anatomy, "Sleep after differing amounts of conditioned fear training in BALB/cJ mice," Behavioural brain research. 147(1-2), 193-202 (2003).
[84] Tang, X., L. Yang, and L.D. Sanford, "Spectral EEG Power after Uncontrollable Shock (US) and Fearful Context (FC): Variability amongst Mouse Strains.," Sleep (Abstract Supplement) 29, A11 (2006).
[85] Kishimoto, T., et al., "Deletion of crhr2 reveals an anxiolytic role for corticotropin-releasing hormone receptor-2," Nat Genet 24(4), 415-9 (2000).
[86] Myers, K.M. and M. Davis, "Mechanisms of fear extinction," Mol Psychiatry 12(2), 120-50 (2007).
[87] Wellman, L.L., B.D. Holbrook, L. Yang, X. Tang, and L.D. Sanford, "Contextual fear extinction eliminates sleep disturbances found following fear conditioning in rats. Sleep, 31: 1035-1042. ," Sleep (Abstract Supplement) 31, 1035-1042 (2008).
[88] Silvestri, A.J., "REM sleep deprivation affects extinction of cued but not contextual fear conditioning," Physiol Behav 84(3), 343-9 (2005).
[89] Fu, J., et al., "Rapid eye movement sleep deprivation selectively impairs recall of fear extinction in hippocampus-independent tasks in rats," Neuroscience 144(4), 1186-92 (2007).
[90] Frysinger, R., J. Zhang, and R. Harper, "Cardiovascular and respiratory relationships with neuronal discharge in the central nucleus of the amygdala during sleep-waking states," Sleep 11, 317-332 (1988).
[91] Frysinger, R., J. Zhang, and R. Harper, "Cardiac and respiratory correlations with unit discharge in human amygdala and hippocampus," Electroencephal clin Neurophysiol 72, 463-470 (1989).
[92] Roozendaal, B., J. Koolhaus, and B. Bohus, "Central amygdala lesions affect behavioral and autonomic balance during stress in rats " Phys Behav 50, 777-781 (1991).
[93] Roozendaal, B., J. Koolhaus, and B. Bohus, "Attenuated cardiovascular, neuroendocrine, and behavioral responses after a single footshock in central amygdaloid lesioned male rats " Phys Behav 50, 771-775 (1991).
[94] Amaral, D., J. Price, A. Pitkanen, and S. Carmichael, [Anatomical organization of the primate amydaloid complex], in *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*, J. Aggleton, Editor Wiley-Liss, Inc: New York. p. 1-66. (1992).
[95] Davis, M. and P.J. Whalen, "The amygdala: vigilance and emotion," Molecular psychiatry 6(1), 13-34 (2001).
[96] LeDoux, J.E., "Emotion circuits in the brain," Annual review of neuroscience 23, 155-84 (2000).
[97] Pare, D., G.J. Quirk, and J.E. Ledoux, "New vistas on amygdala networks in conditioned fear," Journal of neurophysiology 92(1), 1-9 (2004).
[98] Muller, J., K. Corodimas, Z. Fridel, and J. LeDoux, "Functional inactivation of the lateral and basal nuclei of the amygdala by muscimol infusion prevents fear conditioning to an explicit conditioned and to contextual stimuli " Behav Neurosci 111, 683-691 (1997).
[99] Forray, M.I. and K. Gysling, "Role of noradrenergic projections to the bed nucleus of the stria terminalis in the regulation of the hypothalamic-pituitary-adrenal axis," Brain Res Brain Res Rev 47(1-3), 145-60 (2004).
[100] Herman, J.P., N.K. Mueller, and H. Figueiredo, "Role of GABA and Glutamate Circuitry in Hypothalamo-Pituitary-Adrenocortical Stress Integration," Ann N Y Acad Sci 1018, 35-45 (2004).
[101] Pacak, K. and M. Palkovits, "Stressor specificity of central neuroendocrine responses: implications for stress-related disorders," Endocr Rev 22(4), 502-48 (2001).
[102] Prewitt, C.M. and J.P. Herman, "Anatomical interactions between the central amygdaloid nucleus and the hypothalamic paraventricular nucleus of the rat: a dual tract-tracing analysis," J Chem Neuroanat 15(3), 173-85 (1998).

[103] Prewitt, C.M. and J.P. Herman, "Hypothalamo-Pituitary-Adrenocortical Regulation Following Lesions of the Central Nucleus of the Amygdala," Stress 1(4), 263-280 (1997).
[104] Adey, W.R., R.T. Kado, and J.M. Rhodes, "Sleep: Cortical and Subcortical Recordings in the Chimpanzee," Science 141(3584), 932-3 (1963).
[105] Calvo, J.M., S. Badillo, M. Morales-Ramirez, and P. Palacios-Salas, "The role of the temporal lobe amygdala in ponto-geniculo-occipital activity and sleep organization in cats," Brain Res 403(1), 22-30 (1987).
[106] Smith, C.T. and D.E. Miskiman, "Increases in paradoxical sleep as a result of amygdaloid stimulation," Physiol Behav 15(1), 17-9 (1975).
[107] Frysinger, R., J. Zhang, and R. Harper, "Cardiovascular and respiratory relationships with neuronal discharge in the central nucleus of the amygdala during sleep-waking states," Sleep 11, 317-332 (1988).
[108] Harper, R.M., R.C. Frysinger, R.B. Trelease, and J.D. Marks, "State-dependent alteration of respiratory cycle timing by stimulation of the central nucleus of the amygdala," Brain Res 306(1-2), 1-8 (1984).
[109] Zhang, J.X., R.M. Harper, and R.C. Frysinger, "Respiratory modulation of neuronal discharge in the central nucleus of the amygdala during sleep and waking states," Exp Neurol 91(1), 193-207 (1986).
[110] Mignot, E., et al., "Central alpha 1 adrenoceptor subtypes in narcolepsy-cataplexy: a disorder of REM sleep," Brain research 490(1), 186-91 (1989).
[111] Mignot, E., C. Guilleminault, S. Bowersox, A. Rappaport, and W.C. Dement, "Effect of alpha 1-adrenoceptors blockade with prazosin in canine narcolepsy," Brain research 444(1), 184-8 (1988).
[112] Maquet, P., et al., "Functional neuroanatomy of human rapid-eye-movement sleep and dreaming," Nature 383(6596), 163-6 (1996).
[113] Sanford, L.D., B. Parris, and X. Tang, "GABAergic regulation of the central nucleus of the amygdala: implications for sleep control," Brain Res 956(2), 276-84 (2002).
[114] Sanford, L.D., S.M. Tejani-Butt, R.J. Ross, and A.R. Morrison, "Amygdaloid control of alerting and behavioral arousal in rats: involvement of serotonergic mechanisms," Arch Ital Biol 134(1), 81-99 (1995).
[115] Calvo, J., K. Simón-Arceo, and R. Fernández-Mas, "Prolonged enhancement of REM sleep produced by carbachol microinjection into the amygdala," NeuroRep 7, 577-580 (1996).
[116] Sanford, L.D., P. Nassar, R.J. Ross, J. Schulkin, and A.R. Morrison, "Prolactin microinjections into the amygdalar central nucleus lead to decreased NREM sleep," Sleep Res Online 1(3), 109-13 (1998).
[117] Zhu, G.Q., et al., "[Role of basolateral amygdaloid nuclei in sleep and wakeful state regulation]," Sheng Li Xue Bao 50(6), 688-92 (1998).
[118] Deboer, T., R.J. Ross, A.R. Morrison, and L.D. Sanford, "Electrical stimulation of the amygdala increases the amplitude of elicited ponto-geniculo-occipital waves," Physiol Behav 66(1), 119-24 (1999).
[119] Sanford, L.D., L. Yang, X. Liu, and X. Tang, "Effects of tetrodotoxin (TTX) inactivation of the central nucleus of the amygdala (CNA) on dark period sleep and activity," Brain Res 1084(1), 80-8 (2006).
[120] Cain, M.E., B.S. Kapp, and C.B. Puryear, "The contribution of the amygdala to conditioned thalamic arousal," The Journal of neuroscience : the official journal of the Society for Neuroscience 22(24), 11026-34 (2002).
[121] Tang, X., L. Yang, X. Liu, and L.D. Sanford, "Influence of tetrodotoxin inactivation of the central nucleus of the amygdala on sleep and arousal," Sleep (Abstract Supplement) 28(8), 923-30 (2005).
[122] Krettek, J.E. and J.L. Price, "Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat," J Comp Neurol 178(2), 225-54 (1978).
[123] Peyron, C., J.M. Petit, C. Rampon, M. Jouvet, and P.H. Luppi, "Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods," Neuroscience 82(2), 443-68 (1998).
[124] Price, J., F. Russchen, and D. Amaral, [The limbic region. II: The amygdaloid complex], in *Handbook of chemical neuroanatomy. Integrated systems of the CNA, Part I*, L. Swanson, Editor Elsevier: New York. p. 279-375. (1987).
[125] Semba, K. and H.C. Fibiger, "Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study," J Comp Neurol 323(3), 387-410 (1992).
[126] Inagaki, S., Y. Kawai, T. Matsuzaki, S. Shiosaka, and M. Tohyama, "Precise terminal fields of the descending somatostatinergic neuron system from the amygdaloid complex of the rat," J Hirnforsch 24(3), 345-56 (1983).
[127] Liu, X., X. Tang, and L.D. Sanford, "Fear-conditioned suppression of REM sleep: relationship to Fos expression patterns in limbic and brainstem regions in BALB/cJ mice," Brain Res 991(1-2), 1-17 (2003).

[128] Liu, X., L. Yang, L.L. Wellman, X. Tang, and L.D. Sanford, "GABAergic antagonism of the central nucleus of the amygdala attenuates reductions in rapid eye movement sleep after inescapable footshock stress," Sleep (Abstract Supplement) 32(7), 888-96 (2009).
[129] Duvarci, S., D. Popa, and D. Pare, "Central amygdala activity during fear conditioning," Jrn Neurosci 31(1), 289-94 (2011).
[130] Rosenkranz, J.A., D.M. Buffalari, and A.A. Grace, "Opposing influence of basolateral amygdala and footshock stimulation on neurons of the central amygdala," Biological psychiatry 59(9), 801-11 (2006).
[131] Dringenberg, H.C. and C.H. Vanderwolf, "Cholinergic activation of the electrocorticogram: an amygdaloid activating system," Exp Brain Res 108(2), 285-96 (1996).
[132] Benca, R.M., W.H. Obermeyer, S.E. Shelton, J. Droster, and N.H. Kalin, "Effects of amygdala lesions on sleep in rhesus monkeys," Brain Res 879(1-2), 130-8 (2000).
[133] Dong, E., L.L. Wellman, L. Yang, and L.D. Sanford, "Group II Metabotropic Glutamate (mGlu) Receptors in the Basal Amygdala (BA) Regulate Rapid Eye Movement Sleep (REM)," Sleep (Abstract Supplement) 32, A8 (2009).
[134] Koob, G.F. and S.C. Heinrichs, "A role for corticotropin releasing factor and urocortin in behavioral responses to stressors," Brain Res 848(1-2), 141-52 (1999).
[135] Koob, G.F., "Corticotropin-releasing factor, norepinephrine, and stress," Biol Psychiatry 46(9), 1167-80 (1999).
[136] Ehlers, C.L., T.K. Reed, and S.J. Henriksen, "Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats," Neuroendocrinology 42(6), 467-74 (1986).
[137] Chang, F.C. and M.R. Opp, "Role of corticotropin-releasing hormone in stressor-induced alterations of sleep in rat," Am J Physiol Regul Integr Comp Physiol 283(2), R400-7 (2002).
[138] Chang, F.C. and M.R. Opp, "Corticotropin-releasing hormone (CRH) as a regulator of waking," Neurosci Biobehav Rev 25(5), 445-53 (2001).
[139] Swerdlow, N., M. Geyer, W. Vale, and G. Koob, "Corticotropin-releasing factor potentiates acoustic startle in rats: Blockade by chlordiazepoxide " Psychopharmacology 88, 147-152 (1986).
[140] Heilig, M., G. Koob, R. Ekman, and K. Britton, "Corticotropin-releasing factor and neuropeptide Y: role in emotional integration," TINS 17, 80-85 (1994).
[141] Spina, M.G., et al., "Behavioral effects of central administration of the novel CRF antagonist astressin in rats," Neuropsychopharmacology 22(3), 230-9 (2000).
[142] Basso, A.M., M. Spina, J. Rivier, W. Vale, and G.F. Koob, "Corticotropin-releasing factor antagonist attenuates the "anxiogenic-like" effect in the defensive burying paradigm but not in the elevated plus-maze following chronic cocaine in rats," Psychopharmacology (Berl) 145(1), 21-30 (1999).
[143] Aloisi, A.M., M. Zimmermann, and T. Herdegen, "Sex-dependent effects of formalin and restraint on c-Fos expression in the septum and hippocampus of the rat," Neuroscience 81(4), 951-8 (1997).
[144] Kimura, M., et al., "Conditional corticotropin-releasing hormone overexpression in the mouse forebrain enhances rapid eye movement sleep," Molecular psychiatry 15(2), 154-65 (2010).
[145] Machado, R.B., S. Tufik, and D. Suchecki, "Modulation of Sleep Homeostasis by Corticotropin Releasing Hormone in REM Sleep-Deprived Rats," International journal of endocrinology 2010, 326151 (2010).
[146] Yang, L., X. Tang, L.L. Wellman, X. Liu, and L.D. Sanford, "Corticotropin releasing factor (CRF) modulates fear-induced alterations in sleep in mice," Brain research 1276, 112-22 (2009).
[147] Yang, L., L.L. Wellman, X. Tang, and L.D. Sanford, "Effects of corticotropin releasing factor (CRF) on sleep and body temperature following controllable footshock stress in mice," Physiology & behavior 104(5), 886-92 (2011).
[148] Sajdyk, T.J., D.A. Schober, D.R. Gehlert, and A. Shekhar, "Role of corticotropin-releasing factor and urocortin within the basolateral amygdala of rats in anxiety and panic responses," Behav Brain Res 100(1-2), 207-15 (1999).
[149] Liu, X., et al., "Antagonizing corticotropin-releasing factor in the central nucleus of the amygdala attenuates fear-induced reductions in sleep but not freezing," Sleep (Abstract Supplement) 34(11), 1539-49 (2011).
[150] Wellman, L.L., M.A. Ambrozewicz, L. Yang, and L.D. Sanford, "Antagonizing corticotropin releasing factor 1 receptors (CRF1R) in the Basolateral Amygdala (BLA) Attenuates the Effect of Footshock Training on Sleep in Rats. ," Sleep (Abstract Supplement) 33, A44 (2010).