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Experience-dependent plasticity in hypocretin/orexin neurons: re-setting arousal threshold

Xiao-Bing Gao[1] and **Alex Hanxiang Wang**[2]

[1]Department of OB/GYN and Reproductive Science, Yale University School of Medicine, New Haven, CT 06520

[2]Ursinus College, Collegeville, PA 19426-1000

Abstract

The neuropeptide hypocretin is synthesized exclusively in the lateral hypothalamus and participates in many brain functions critical for animal survival, particularly in the promotion and maintenance of arousal in animals - a core process in animal behaviors. Consistent with its arousal-promoting role in animals, the neurons synthesizing hypocretin receive extensive innervations encoding physiological, psychological and environmental cues and send final outputs to key arousal-promoting brain areas. The activity in hypocretin neurons fluctuates and correlates with the behavioral state of animals and intensive activity has been detected in hypocretin neurons during wakefulness, foraging for food and craving for addictive drugs. Therefore, it is likely that hypocretin neurons undergo experience-dependent changes resulting from intensive activations by stimuli encoding changes in the internal and external environments. This review summarizes the most recent evidence supporting experience-dependent plasticity in hypocretin neurons. Current data suggest that nutritional and behavioral factors lead to synaptic plasticity and re-organization of synaptic architecture in hypocretin neurons. This may be the substrate of enhanced levels of arousal resulting from behavioral changes in animals and may help to explain the mechanisms underlying changes in arousal levels induced by physiological, psychological and environmental factors.

Keywords

Lateral hypothalamus; synaptic transmission; sleep regulation; energy homeostasis

1. Introduction

The maintenance of a sufficient level of generalized arousal of the central nervous system is essential to animal behaviors critical to survival (Arrieta-Cruz and Pfaff, 2009). The fluctuation of arousal levels can be detected in various phases of circadian and sleep-wake cycle in animals (Berridge, 2006; Arrieta-Cruz and Pfaff, 2009). Many external and internal environmental cues participate in determining arousal in animals. For instance, sensory stimuli, emotional response and motor activity have influence on arousal levels in animals (Arrieta-Cruz and Pfaff, 2009). It has also been reported that nutritional factors (such as hunger) can modulate arousal state in animals as well (Ribeiro et al., 2007). Although emerging evidence reveals a remarkable array of neural circuits encoding physiological,

Correspondence to: Xiao-Bing Gao, Department of OB/GYN, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06520, Phone 1 203 785-2340, Fax 1 203 737-1883, xiao-bing.gao@yale.edu.

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psychological and environmental cues promoting arousal, mechanisms underlying these processes involving cellular and molecular pathways within arousal-promoting neurons remain to be understood.

The lateral hypothalamus (LH) has long been considered as a sleep-regulating center, in addition to its role in sensorimotor integration, feeding behavior and regulation of the autonomic nervous system. It was originally proposed by von Economo based on his observations on human patients that lesions in the posterior hypothalamus and midbrain junction lead to sleepiness, while anterior hypothalamic inflammation leads to insomnia and chorea (von Economo 1930). Later, the sleep-promoting effect of lesions in the posterior lateral hypothalamus was confirmed in other species including monkeys, rats and cats (Ranson 1939, Nauta 1946, Swett & Hobson 1968). In freely moving cats, microinjection of the GABAergic agonist, muscimol into the middle and anterior parts of the posterior hypothalamus induced along-lasting sleep as determined by behavioral and electroencephalographic (EEG) tests (Lin et al., 1989). However, the research on the role of the LH in sleep regulation was overshadowed by intensive investigations focusing on other brain regions; the discovery of the neuropeptide, hypocretin (also referred to as orexin) put the LH back under the spotlight (de Lecea et al. 1998, Sakurai et al. 1998). It is now clear that the hypocretin system is a key arousal-promoter in the brain. The hypocretin system consists of two peptides, hypocretin-1 (orexin-A) and hypocretin-2 (orexin-B) and two receptor types (hypocretin receptor-1 and hypocretin receptor-2), which have been cloned in human and rodents (Sutcliffe & de Lecea 2002, Sakurai 2007). Neurons synthesizing hypocretin receive innervations from many brain areas, which transmit arousal-promoting cues from external and internal environments to the hypocretin system (Sakurai et al. 2005, Yoshida et al. 2006, Henny and Jones 2006). Therefore, it is conceivable that activity levels in hypocretin neurons closely correlate with stimuli from the environment and that adaptive changes would occur in the function and structure of the hypocretin system. Therefore, it is likely that the arousal levels promoted by the output of the hypocretin system are shaped by environmental cues. In this review, we will summarize the current understanding of adaptive changes in the hypocretin system induced by environmental cues. We will also discuss how arousal levels may be re-set by changes in hypocretin neurons, resulting in significant impacts on animal behaviors and may contribute to health problems (such as sleep disorders) in humans.

2. Arousal state and activity in hypocretin neurons

Since the initial reports of hypocretin, the attention on its role in the central nervous system has switched drastically from orexigenic (promoting food intake) to arousing function. There is a growing body of evidence indicating the participation of the hypocretin system in arousal regulation (see recent reviews by Adamantidis & de Lecea 2009, Szymusiak & McGinty 2008, Jones 2008, Sakurai 2007, Selbach & Haas 2006, Saper et al. 2005). Specifically, it is worthwhile to mention a few findings supporting the strong correlation between the activity in hypocretin neurons and the arousal state of animals. It has been reported that the concentration of hypocretin fluctuates in animals during the day. The arousal level of animals is usually high during the active (waking) phase and is low during the resting (sleeping) phase. In rats, the hypocretin-1 level in cerebrospinal fluid is highest during the dark period when the animals are most active, while it is at its lowest at the end of the inactive period (Fujiki et al. 2001). In freely moving rats, the extracellular concentration of hypocretin-1 in the LH and the medial thalamus slowly elevates during the active phase and decreases during the rest phase (Yoshida et al. 2001). In squirrel monkeys, the hypocretin-1 concentration in cerebrospinal fluid begins to increase after a few hours of wakefulness and reaches a plateau in the active phase; its concentration falls throughout the inactive phase (Zeitzer et al. 2003). These results imply that the activity in hypocretin

neurons (leading to hypocretin release) may change along with the behavioral states of animals, which is directly and indirectly demonstrated by examining c-Fos expression and detecting electrical activity in hypocretin neurons. The expression of c-Fos, an immediate early gene product indicating activation of cells, increases in hypocretin neurons during the dark phase and during sleep deprivation (Estabrooke et al. 2001, Modirrousta et al. 2005). In rats, hypocretin neurons are generally active in the dark phase (awake) and silent in the light phase (sleep) as revealed by directly monitoring action potentials (Lee et al. 2005, Mileykovskiy et al. 2005). It has been shown recently that a direct and selective stimulation of hypocretin neurons increased the probability of transition to wakefulness from either SW sleep or REM sleep (Adamantidis et al. 2007). In Syrian hamsters, some experimental manipulations such as novel wheel running, gentle handling, and physical restraint stimulate behavioral arousal and increase c-fos expression in hypocretin neurons, suggesting the involvement of the hypocretin system in these arousal–promoting processes (Webb et al. 2008). Since hypocretin neurons make projections to major arousal areas such as the locus coeruleus and the basal forebrain through integrating a variety of sensory and homeostatic inputs (Lee et al. 2005, Sakurai et al. 2005, Yoshida et al. 2006), it has been suggested that hypocretin neurons are at a unique position to consolidate wakefulness, probably through setting the threshold for state transitions (Sutcliffe and de Lecea 2002, Saper et al. 2005, Selbach & Haas 2006). An emerging body of evidence indicates that neurotransmitters (e.g. corticotropin releasing factor and thyrotropin-releasing hormone) encoding stress-relevant cues increase activity in hypocretin neurons (Winsky-Sommerer et al. 2004, González et al. 2009, Hara et al. 2009). Therefore, it is likely that the activity in hypocretin neurons changes in response to stimuli from both internal and external environments, contributing to the arousal state of animals required for behaviors critical to the survival of individuals and species, e.g. foraging for food, staying awake in an adverse environment, craving for rewards and memory formation (Yamanaka et al. 2003, Selbach et al. 2004, Winsky-Sommerer et al. 2004, Boutrel et al. 2005, Harris et al. 2005). It is therefore asked whether hypocretin neurons make adaptive changes to accommodate changes in the environment thus leading to an altered arousal state in animals? Evidence from other regions of the brain has provided the first clues that adaptive modifications to neuronal systems do in fact underlie many behavioral changes in animals.

3. Experience-dependent synaptic plasticity underlies behavioral changes in animals

During the past several decades, experience-dependent changes in the brain have been attributed to changes in animal behaviors in response to various inputs for environmental, physiological or behavioral stimuli. These changes have been summarized by the Hebbian theory, which first stated that connections (synapses) between neurons could be strengthened as the result of their coordinated activities (Hebb 1949). The extent to which these changes occur is predominantly due to the level of postsynaptic depolarization resulting from the coordinated activity of pre- and postsynaptic neurons. As summarized, this plasticity serves as the mechanism for a wide range of integrative and higher functioning behaviors, for example, as the basis of learning and memory. From an evolutionary standpoint, the brain may employ this ubiquitous process as a method by which it can make adaptive changes to itself in response to demands to cope with the changing external and internal environments.

Long-term potentiation (LTP) and long-term depression (LTD) of glutamatergic synapses are two mechanisms by which the brain makes adaptive changes to the neuronal circuitry in response to external stimuli to either strengthen or weaken the neural synapses, respectively. These two ubiquitous mechanisms have been intensively investigated in the past decades (see reviews by Malenka & Bear 2004, Kessels & Malinow 2009). Although the exact

mechanisms underlying LTP and LTD remain to be elucidated due to the diverse neurochemical environments of synapses, a general view on specific but widely existing forms of N-methyl-D-aspartate type glutamate receptors (NMDARs)-dependent LTP/LTD has been established (Kessels & Malinow 2009). It is now clear that a significant increase in calcium concentration would lead to activation of a cascade of protein kinases including protein kinase C (PKC), Ca-calmodulin kinase II (CamKII), and others, which leads to up-regulation of postsynaptic AMPARs through enhanced phosphorylation or trafficking from cytoplasm to membrane. Meanwhile, the release of glutamate from presynaptic terminals can be enhanced (Lisman & Raghavachari 2006). LTP is therefore induced. However, if only a modest increase in intracellular Ca^{2+} concentration is induced by activity in postsynaptic neurons, a cascade of protein phosphatases are activated and postsynaptic AMPARs are down-regulated through de-phosphorylation or removal of AMPARs from membrane to cytoplasm. LTD is therefore induced (Kessels & Malinow, 2009). For more comprehensive reviews, see Malenka and Bear 2004, Kopp et al. 2007 and Kessels and Malinow, 2009.

Since the first report of LTP at glutamatergic synapse over 30 years ago, an accumulating body of evidence suggests that behavioral changes in animals are directly linked to LTP/LTD and experience-dependent synaptic plasticity. During the development of the central nervous system, many significant changes occur in the synapses as a result of acquired experience. The formation, discrimination and elimination of synapses during the development of the central nervous system undergo processes resembling the expression of LTP/LTD (See reviews by Waites et al 2005, Flavell & Greenberg, 2008). In mature animals, LTP/LTD has been proposed to be the molecular and cellular substrate for various forms of learning and memory. In the hippocampus, a learning task (one-trial inhibitory avoidance learning) induced experience-dependent synaptic plasticity in the CA1 region, which may share the mechanisms underlying LTP, since learning-induced plasticity occluded the induction of high frequency-induced LTP in the same synapses (Whitlock et al. 2006). This study is consistent with an early report that high frequency stimulation of the perforant pathway in the hippocampus occluded the ability of rats to spatially navigate through a short-term memory-training task, although previously established memories were unaffected (McNaughton et al. 1986). In the motor cortex, learning a new motor skill led to enhanced synaptic strength through an LTP-like mechanism, since the training-induced plasticity impaired induction of LTP and facilitated induction of LTD in rats and humans (Rioult-Pedotti et al. 2000, Ziemann et al. 2004). In addition, behavioral modulations including formation of habits and development of drug addiction are involved in experience-dependent synaptic plasticity in relevant brain areas (See reviews by Yin & Knowlton 2006, Hyman et al. 2006).

It is well established that the experience-dependent synaptic plasticity discussed above serves as a molecular and cellular substrate for learning, memory and addiction to drugs of abuse (an abnormal form of learning and memory). LTP/LTD of synapses in the neural circuitry responsible for cognition and motivated behaviors has long been appreciated. Recent evidence shows that synaptic plasticity may happen not only in the circuitry responsible for higher functions of the brain, but also in neural circuits responsible for homeostatic regulation (Pinto et al. 2004, Horvath& Gao 2005, Rao et al. 2007). Experience-dependent synaptic plasticity may serve as a substrate for adaptive changes in brain areas exerting homeostatic regulation to accommodate environmental changes in animals.

4. Experience-dependent synaptic plasticity in hypocretin neurons

To an extent, learning and memory is an adaptive behavior in animals, in which neural circuitry would make changes to accommodate the development of new behaviors in learning tasks. However, neurons in brain centers regulating homeostatic functions consistently monitor changes in the internal and external environments and are required to make efficient adjustments critical to the survival of animals. Neurons synthesizing hypocretin are among these cells. Recent studies have shown that synapses on hypocretin neurons possess unique characteristics (Horvath & Gao 2005) and adaptive changes in these synapses occur as the result of changes in energy and behavioral states of animals (Horvath & Gao 2005, Rao et al. 2007).

4.1. Unique synaptic architecture in hypocretin neurons

As in other areas of the brain, glutamate is a major excitatory neurotransmitter in the hypothalamus (van den Pol et al. 1990). Modulation of glutamatergic tone onto hypocretin neurons serves as an important mechanism in controlling action potential generation in these neurons (Li et al. 2002). Ionotropic glutamate receptor antagonists CNQX and AP5, which lead to the complete blockade of ionotropic glutamatergic transmission onto hypocretin neurons, significantly attenuate the frequency of spontaneous action potentials in these neurons (Li et al. 2002), while the blockade of GABAergic tone with GABA-A receptor antagonists does not have a significant effect on spontaneous action potential firings in hypocretin neurons (Xie et al. 2006). In addition, the presence of CNQX and AP5 blocks the increase in the frequency of action potentials induced by hypocretin in neurons synthesizing it. These results indicate that the excitability of hypocretin neurons can be regulated by glutamatergic inputs and that these neurons utilize local glutamatergic neurons to form a positive feedback circuit onto themselves (Li et al. 2002). An emerging body of evidence has suggested that glutamatergic innervations onto hypocretin neurons may originate from local glutamatergic neurons and brain areas outside of the LH area (such as basal forebrain) (Li et al. 2002, Henny and Jones 2006). In addition, hypocretin neurons receive intensive afferents from many other brain regions (Yoshida et al 2006), within which glutamatergic fibers may innervate hypocretin neurons.

Later studies revealed mechanisms underlying the dominant role of glutamate in controlling action potential generation in hypocretin neurons. First, whole-cell recordings in hypocretin neurons indicates that the frequency of miniature excitatory postsynaptic currents (mEPSCs) is about 10-fold higher than the frequency of miniature inhibitory postsynaptic currents (mIPSCs) (Horvath & Gao 2005, Xie et al. 2006). Second, ultrastructural analysis has shown that there are more asymmetric (putatively stimulating) synapses than symmetric (putatively inhibitory) synapses on hypocretin neuronal cell bodies (Horvath & Gao 2005). These results demonstrate that cell bodies of hypocretin neurons are mainly innervated by excitatory synapses, which is strikingly different from other long projection neurons such as the pyramidal neurons of the neocortex, in which only inhibitory synapses are found on the somata (Douglas et al. 2004). The unique synaptic organization on hypocretin neurons may make it easier for this system to be excited and helps it undergo adaptive changes when animals are challenged by environmental stimuli as suggested (Horvath & Gao 2005, Rao et al. 2007).

4.2. Energy deficiency induces experience-dependent synaptic plasticity in hypocretin neurons

It has been shown that food deprivation increases wakefulness and decreases sleep in animals (Jacobs and McGinty 1971, Borbély 1977). However, it was not clear how adaptive changes elicited by food deprivation in the brain result in alterations in sleep/wake

regulation. The recent study on the experience-dependent synaptic re-organization in hypocretin neurons induced by food deprivation may shed light on this question (Horvath & Gao 2005), since the findings that food deprivation could not increase arousal in mice lacking hypocretin neurons and that hypocretin neurons were sensitive to glucose strongly suggest the involvement of the hypocretin-mediated signaling in this process (Yamanaka et al. 2003, Burdakov et al. 2006, Guyon et al. 2009). In mice on a C57/B6 gene background, the frequency of mEPSCs recorded in hypocretin neurons in hypothalamic slices significantly increased in a group of mice after they had undergone one episode of overnight fasting (24 hours), as compared with fed mice (Horvath & Gao 2005). The frequency of mIPSCs recorded in hypocretin neurons by the same approach was comparable between fasted and fed mice. Consistent with these electrophysiological findings, the number of asymmetric (putatively excitatory) but not symmetric (inhibitory) synapses on hypocretin-containing somata elevated following one episode of food deprivation in mice (Horvath & Gao 2005) (Figure 1). Next, the effects of leptin on synaptic plasticity in hypocretin neurons induced by fasting was examined, since in fasting animals the levels of leptin is low and leptin replacement during food deprivation may compensate for the effects triggered by fasting. Electrophysiological and ultrastructural results showed that in fasted mice, leptin administration (i.p.) abolished the effects of fasting on glutamatergic synapses on hypocretin neurons. The frequency of mEPSCs recorded in hypocretin neurons from leptin-treated fasted mice was comparable to fed mice. The number of asymmetric synapses on hypocretin perikarya was similar between these two groups as well (Horvath & Gao 2005). In a subsequent set of experiments, electrophysiological and ultrastructural parameters of glutamatergic synapses on hypocretin neurons were examined in mice undergoing fasting and re-feeding. The frequency of mEPSCs and the number of asymmetric synapses on hypocretin neurons were not significantly different between re-feeding and control groups (Horvath & Gao 2005).

Taken together, these data suggest that one episode of food deprivation induces synaptic plasticity in hypocretin neurons, which is reversible with re-feeding and can be abolished by the replenishment of leptin. It has been shown that food deprivation induces a significant increase in c-fos expression in hypocretin neurons, indicating an intensive activation of these cells (Diano et al. 2003). It is possible that fasting-induced synaptic plasticity also originates from this intensive activation and is the consequence of an activity-dependent process. Since leptin can inhibit activity in hypocretin neurons (Yamanaka et al. 2003), the abolishment of synaptic plasticity by leptin replacement during food deprivation further supports the activity-dependent nature of synaptic plasticity in hypocretin neurons. This study may provide an important clue to the mechanisms underlying the original reports that food deprivation increases wakefulness and decreases sleep in animals (Jacobs and McGinty 1971, Borbély 1977). It also indicates for the first time that hypocretin neurons may make adaptive changes in response to environmental changes. However, the mechanisms underlying experience-dependent synaptic plasticity in hypocretin neurons remain to be answered; they are starting to be revealed in the most recent studies.

4.3. Experience-dependent synaptic plasticity in hypocretin neurons may underlie the maintenance of prolonged arousal

As discussed in the previous paragraph, the activity levels of hypocretin neurons correlate with the behavioral state of animals (Estabrooke et al. 2001, Lee et al. 2005, Mileykovskiy et al. 2005). Therefore, it is conceivable that long-term activation of hypocretin neurons underlies the prolonged wakefulness (voluntary or forced) in animals. According to the Hebbian theory, intensive activity in the hypocretin-centered neuronal circuitry may lead to activity-dependent synaptic plasticity of synapses on hypocretin neurons, which convey information encoding environmental cues inducing prolonged wakefulness. Our recent study

has demonstrated that prolonged wakefulness induces experience-dependent synaptic potentiation in hypocretin neurons (Rao et al. 2007). In a murine model for prolonged wakefulness, mice were exposed to either a bout of sleep deprivation by gentle handling or to treatment with the pyschostimulant, modafinil. Modafinil, diphenylmethyl-sulfony-2-acet-amide, is an FDA-approved drug for the treatment of narcolepsy and other conditions (Ballon & Feifel 2006). The administration of modafinil significantly enhances wakefulness in humans and animals through the activation of dopamine-dependent pathways (Wisor et al. 2001, Korotkova et al. 2007).

Hypocretin neurons are among the targets activated by modafinil (Scammell et al. 2000). A single application of modafinil induces a long-lasting (> 2 hr) wakefulness in mice during the light phase. Consistent with these behavioral changes, the efficacy of glutamatergic synapses on hypocretin neurons was significantly potentiated 1 and 2 hr after the administration of modafinil (Figure 2). Synaptic potentiation occurs at both pre- and postsynaptic sites of glutamatergic synapses on hypocretin neurons in modafinil-treated mice as compared to saline-treated controls (Rao et al. 2007). In a parallel experiment, mice were deprived of sleep for 4 hrs through gentle handling, which induces a similar potentiation of glutamatergic synapses on hypocretin neurons at pre- and postsynaptic sites (Rao et al. 2007). Further experiments indicate that after exposure to prolonged wakefulness daily for a week, the number of asymmetric (excitatory) synapses on hypocretin neurons is significantly elevated comparing with control animals, suggesting possible long-term effects of prolonged wakefulness on the hypocretin-centered wake-promoting circuitry (Rao et al. 2007). In mice treated with a single administration of modafinil, synaptic plasticity does not occur in non-hypocretin neurons, demonstrating the specificity of the effects of prolonged wakefulness on hypocretin neurons (Rao et al. 2007).

The mechanisms underlying prolonged wakefulness-induced synaptic plasticity in hypocretin neurons have been explored. The blockade of D1 dopamine receptors abolishes modafinil-induced wake-promoting effects and the potentiation of presynaptic glutamate release in animals, suggesting the involvement of DA-mediated pathways in this process (Rao et al.2007). This piece of evidence is consistent with the effects of modafinil on DA transporters in the brain, which has been suggested as one of the cellular functions of modafinil (Ballon and Feifel 2006). Although the signaling pathways downstream to DA receptor activation in modafinil-induced effects remain to be determined, there is evidence that protein kinase A (PKA)-mediated pathways may be required. It has been shown previously that activation of PKA by forskolin induces LTP in hippocampal neurons and that forskolin-induced LTP occludes the induction of LTP with other stimuli at the same synapses (Frey et al. 1993, Huang and Kandel 1995, Otmakhov et al. 2004). These results suggest that forskolin-induced LTP shares the same pathways with LTP induced by high frequency stimulation in the hippocampus. In hypocretin neurons, forskolin induces LTP at glutamatergic synapses pre- and postsynaptically in control animals, while the induction of forskolin-LTP is significantly occluded in mice acutely or repeatedly exposed to modafinil (Rao et al. 2007). These results indicate that synaptic plasticity induced by modafinil treatment shares common pathways (e.g. PKA-mediated pathways) with forskolin-LTP in hypocretin neurons. It is therefore intriguing to know whether synaptic plasticity induced by other factors (such as sleep deprivation and food deprivation) requires PKA-mediated pathways in hypocretin neurons.

Based on the results discussed in above paragraphs, we propose that environmental and/or behavioral changes may lead to experience-dependent plasticity in hypocretin neurons, which include both early and late changes in hypocretin neurons (Figure 3). In the case of prolonged wakefulness, the early changes comprise of functional potentiation of glutamatergic synapses on hypocretin neurons at pre- and postsynaptic sites, which may

occur within hours after the exposure to an acute episode of prolonged wakefulness (Figure 3B). The presynaptic changes may include the increase in the release of glutamate from presynaptic terminals, which may be achieved by the conversion of glutamate release mode from a kiss-and-run to a full fusion (Lisman and Raghavachari 2006). This process may depend on the synthesis and transportation of new proteins from neuronal soma along neuritis (Blundon and Zakharenko 2008). The postsynaptic changes may include trafficking of AMPA-type glutamate receptors to postsynaptic neuronal membrane (Lisman and Raghavachari 2006,Rao et al 2007) and expansion of dendritic spines as seen in the hippocampus (Blundon and Zakharenko 2008). The late changes resulting from repeated exposure to prolonged wakefulness may involve morphological changes (e.g. addition of new synapses) in glutamatergic synapses on hypocretin neurons (Figure 3C). The latter or late changes should be of particular importance; it may suggest that the projections from certain brain areas to hypocretin neurons have been strengthened and the brain arousal circuitry may be ‘rewired” as the consequence of certain experience. In summary, the consequence of these adaptive changes is the re-shaping of the output of the hypocretin system to accommodate external stimuli.

5. Synaptic plasticity and arousal

The activity in each animal species has evolved to accommodate the transition between day and night. Although there are differences in the regulation of the sleep/wake cycle between diurnal and nocturnal animals, a sufficient level of wake/arousal is required for all animals to conduct tasks essential to their daily lives. One emerging point is that the synaptic efficacy of excitatory synapses at certain wake-promoting neurons changes with the sleep-wake cycle (Tononi and Cirelli 2007, Griffith and Rosbash 2008). Although there has been evidence of cyclic expression of genes encoding proteins involved in synaptic transmission across the sleep-wake cycle and a higher phosphorylation level of GluR1 (a glutamate receptor subunit) after sleep deprivation in the rat cortex (Cirelli et al. 2004, Terao et al. 2006), it is not clear if synaptic efficacy is really potentiated or de-potentiated across the sleep-wake cycle, let alone how synaptic efficacy is modified. The results discussed in the above paragraphs demonstrated for the first time that the synaptic strength of excitatory synapses on wake-promoting neurons (hypocretin neurons in the LH area in this case) is potentiated after exposure of mice to prolonged wakefulness (Rao et al. 2007). These findings are further strengthened by a recent report that in the cortex and hippocampus, synaptic potentiation and depression occur in wake and sleep, respectively (Vyazovskiy et al. 2008). More importantly, the findings in hypocretin neurons suggest that synaptic strength modification across the sleep-wake cycle may be regulated in an activity-dependent manner and that cellular and molecular mechanisms underlying the expression of LTP (or LTD) may be responsible for synaptic potentiation (or de-potentiation) across the sleep-wake cycle. In summary, experience-dependent synaptic plasticity may serve as a potential mechanism underlying changes in synaptic efficacy across the wake-sleep cycle.

If experience-dependent synaptic plasticity in hypocretin neurons serves as the mechanism underlying the normal sleep-wake cycle and prolonged wakefulness in animals, it is likely that this process can be usurped by physiological and psychological factors, triggering changes similar to experience-dependent synaptic plasticity in hypocretin neurons. Since the generation of action potentials in neurons depends on their intrinsic excitability and synaptic inputs, experience-dependent synaptic potentiation of glutamatergic synapses on hypocretin neurons might facilitate the activation of hypocretin neurons and lead to the enhanced sensitivity of the hypocretin system to environmental cues promoting arousal and wakefulness (a hyperactive hypocretin system). Although it has not been directly demonstrated that LTP at glutamatergic synapses leads to changes in the pattern of activity in hypocretin neurons, the functional implications of this process are significant. On one

hand, the hyperactive hypocretin system may lead to a lowered threshold of activation, which may be translated into a lowered arousal threshold. On the other hand, hyperactive hypocretin neurons may require a higher level of inhibitory (sleep-promoting) inputs to antagonize the arousal-promoting effects. Therefore, the threshold for inducing sleep may be elevated. These postulations will still need to be examined; however, evidence supporting these possibilities is emerging.

Previous data have shown that action potential firing in hypocretin neurons requires glutamatergic inputs (Li et al 2002). Our recent results indicate the facilitation of action potential generation in hypocretin neurons in genetically altered mice with up-regulated glutamatergic transmission to these neurons (Rao et al 2008). The neuropeptide melanin-concentrating hormone (MCH), which is released exclusively from a group of neurons adjacent to hypocretin neurons, has been implicated in an inhibitory role in the modulation of hypocretin neurons (Rao et al. 2008, Gao 2009). Deficiency in MCH receptor-1 (MCHR1) leads to the up-regulation of mEPSC amplitude and AMPAR/NMDAR ratio in hypocretin neurons compared with wild type (WT) littermates (Rao et al. 2008). It has also been shown that hypocretin-induced action potential firing is facilitated in MCHR1 KO mice as compared with WT littermates, suggesting a lowered threshold for activation of hypocretin neurons in KO mice (Rao et al. 2008). Interestingly, MCHR1 KO mice are hyperactive and more sensitive to modafinil-induced wakefulness than their WT littermates (Marsh et al. 2002, Rao et al. 2008). In a recent report, Kim et al (2007) has shown that one episode of long-lasting sleep deprivation (20 hrs) led to an increase in sleep intensity (NREM delta power) and REM sleep during a 4-hour recovery sleep following SD in rats. However, after the repeated exposure to 20-hr SD for 2–5 days, rats failed to show the increment in NREM delta power, NREM and REM sleep time. The rats did not regain their sleep during the following 3-day recovery period in spite of the sleep debt accumulated during 2–5 days of SD (Kim et al 2007). The authors suggested that repeated sleep deprivation induced an allostatic process posing direct effects on sleep/wake regulatory circuitry in the brain. It is intriguing to know if the allostatic process involves experience-dependent plasticity in wake/arousal-promoting systems including hypocretin neurons in these animals.

6. Conclusion and future direction

In summary, recent results by our group and others have indicated that the history of activity rendering in the hypocretin neuron-centered neural circuitry results in synaptic plasticity in these neurons. The consequence of these changes is to re-shape the output of the hypocretin system. If the output of hypocretin neurons contributes to the determination of arousal threshold of animals (Sutcliffe & de Lecea 2002), experience-dependent synaptic potentiation in hypocretin neurons would be able to enhance this output, increase the weight of hypocretin in the wake-promoting process, re-set the threshold for arousal and eventually contribute to hyperarousal and sleep disturbance (such as insomnia) in humans and animals. Mechanisms underlying experience-dependent plasticity in hypocretin neurons are emerging but remain to be addressed. Current data suggest that well-established molecular and cellular pathways involving the induction of LTP in other brain areas (e.g the hippocampus, cortex, etc.) participate in the development of plasticity in hypocretin neurons. However, the physiological, psychological and environmental factors that exert their effects on hypocretin neurons through LTP-inducing pathways are still missing. Future studies aiming to delineate specific neuronal pathways involving in plastic changes underlying altered animal behaviors in hypocretin neurons will be greatly appreciated.

Since experience-dependent synaptic plasticity in hypocretin neurons is an adaptive change in response to various acute and chronic external and internal stimuli, one might wonder if

hypocretin neurons provide a fundamental mechanism underlying the adaptive changes in wake/arousal-promoting neurons in the central nervous system. It may be possible that changes in the hypocretin system are only the tip of the iceberg and that other arousal-relevant centers undergo similar adaptive changes as reported in the cortex (Vyazovskiy et al. 2008). Therefore, it remains to be examined whether experience-dependent synaptic plasticity occurring in hypocretin neurons discussed here takes place in other wake/arousal-promoting brain areas, such as the prefrontal cortex, TMN and locus coeruleus, etc. The answer to this question might lead this research to a new avenue to explore the dysregulation of the sleep/wake cycle in animals and sleep disorders in humans. Since the arousal-promoting circuitry in the brain is a redundant system with many integrated nuclei and regions including hypocretin neurons, it is still not clear to what extent a potentiated hypocretin system will do to the arousal-promoting process. Nevertheless, further investigations into adaptive changes in brain arousal centers induced by arousal-promoting stimuli are strongly warranted.

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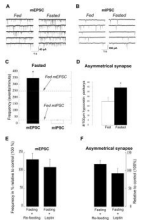

Figure 1.
Synaptic potentiation of excitatory synapses on hypocretin neurons after one episode of 24-hour food deprivation in mice. Representative traces of mEPSC and mIPSC recorded in hypocretin neurons are presented in A and B. C, statistical results of electrophysiological recordings show that the frequency of mEPSCs but not mIPSCs is significantly enhanced in fasted mice. D, ultrastructural analyses indicate that the number of asymmetrical (excitatory) synapses increases in fasted mice. E and F, statistical results from electrophysiological and ultrastructural studies show that re-feeding reverses and leptin application abolishes the effects of fasting on synaptic plasticity in hypocretin neurons. This figure was reproduced with permission from Horvath and Gao (2005).

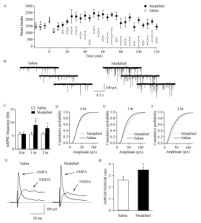

Figure 2.

One episode of sustained wakefulness induced by administration of modafinil induces long-lasting potentiation of glutamatergic synapses on hypocretin neurons. A, locomotor activity recorded in mice show that modafinil administration induces a prolonged wakefulness (>2 hr) during the light phase in mice. B, representative traces of mEPSCs recorded in hypocretin neurons from control and modafinil-treated mice. C–F, the analyses of frequency and amplitude of mEPSCs indicate that glutamatergic synaptic transmission onto hypocretin neurons is enhanced in mice exhibiting prolonged wakefulness after administration of modafinil. G and H, further experiments show that AMPA-type glutamatergic receptors are up-regulated in hypocretin neurons in mice exposed to prolonged wakefulness. This figure was reproduced with permission from Rao et al. (2007).

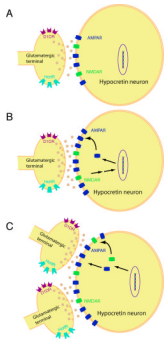

Figure 3.

Schematic diagram summarizing experience-dependent synaptic plasticity in hypocretin neurons. A, glutamatergic synapses on hypocretin neurons before synaptic potentiation. B, synaptic potentiation of glutamatergic synapses on hypocretin neurons triggered by an acute exposure to adaptive cues occurs in an activity-dependent manner as observed in the induction of LTP. Synaptic potentiation may occur at both pre- and postsynaptic sites, e.g. enhanced release of glutamate from presynaptic terminals and up-regulation of glutamate receptors in hypocretin neurons. C, repeated exposure to adaptive cues leads to re-organization of synaptic architecture in hypocretin neurons, which includes the increased number of excitatory (glutamatergic) synapses on hypocretin neurons. AMPAR, AMPA receptor; NMDAR, NMDA receptor; D1DR, D1 dopamine receptor; HcrtR, hypocretin receptor.