Function and Dysfunction of Hypocretin/Orexin: An Energetics Point of View

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Abstract

The basic elements of animal behavior that are critical to survival include energy, arousal, and motivation: Energy intake and expenditure are fundamental to all organisms for the performance of any type of function; according to the Yerkes-Dodson law, an optimal level of arousal is required for animals to perform normal functions; and motivation is critical to goal-oriented behaviors in higher animals. The brain is the primary organ that controls these elements and, through evolution, has developed specialized structures to accomplish this task. The orexin/hypocretin system in the perifornical/lateral hypothalamus, which was discovered 15 years ago, is one such specialized area. This review summarizes a fast-growing body of evidence discerning how the orexin/hypocretin system integrates internal and external cues to regulate energy intake that can then be used to generate sufficient arousal for animals to perform innate and goal-oriented behaviors.

Contents

INTRODUCTION

Locomotion is a fundamental characteristic of the kingdom Animalia and is essential for individuals and species within the kingdom to survive. For example, movement is required for most animals to perform such tasks as foraging for food, escaping predators, and reproducing, among others. Several elements are essential to execute locomotive functions, first among these elements being energy. Energy is required for biochemical reactions and biophysical activities to sustain the normal functionality of every cell, but it is also needed for animals to overcome environmental factors (e.g., gravity, air or water resistance) to execute locomotor activity. Second among the essential elements is the maintenance of a sufficient level of arousal for animals to perform daily activities. The shift between rest (sleep) and active (wake) states occurs in both lower animals such as *C. elegans* and higher animals such as mammals (Mackiewicz et al. 2008). According to the Yerkes-Dodson law, both hypo- and hyperarousal will compromise normal animal behaviors (Yerkes & Dodson 1908). The third important component is motivation (desire to achieve a certain behavior) to initiate and sustain locomotion in animals. This is particularly true in goal-oriented behaviors.

In the mammalian brain, many neuronal systems are responsible for one or all of the elements required for locomotor activity in animals. A small number of nerve cells in the perifornical/lateral hypothalamus (LH) that synthesize the neuropeptide hypocretin/orexin participate in neural mechanisms underlying all three elements critical to animal behavior. Hypocretin/orexin (Hcrt) was discovered independently by two groups of investigators 15 years ago (de Lecea et al. 1998, Sakurai et al. 1998). Hcrt comprises two peptides, Hcrt-1 (orexin A) and Hcrt-2 (orexin B) derived from a common 130–amino acid precursor peptide (preprohypocretin) by proteolytic cleavage (de Lecea et al. 1998, Sakurai et al. 1998). In mammals, Hcrt is synthesized only by neurons in the LH, and investigators have estimated that rodents have a few thousand Hcrt cells and humans have about 50,000–90,000 (Peyron et al. 1998, Thannickal et al. 2000, Sutcliffe & de Lecea 2002). Even though this population of neurons is small, studies have detected the nerve fibers containing Hcrt all over the central nervous system and even in peripheral organs (Peyron et al. 1998, Trivedi et al. 1998, van den Pol 1999, Marcus et al. 2001, Adeghate et al. 2010). At the cellular level, Hcrt generally acts as an excitatory transmitter to enhance synaptic transmission, neuronal activity, and intracellular calcium levels in central neurons (van den Pol et al. 1998, Hagan et al. 1999, Davis et al. 2003, Korotkova et al. 2003).

BIDIRECTIONAL ROLES OF Hcrt IN THE REGULATION OF ENERGY BALANCE

The intake and use of energy are fundamental characteristics of all organisms and are essential to their performance of basic functions. The hypothalamus of the brain is a classic structure that participates in the regulation of food intake in animals. Hetherington & Ranson (1940) incidentally found that lesions of the LH resulted in decreased food intake. Their work was extended by Anand & Brobeck (1951a,b), who demonstrated that circumscribed lesions in the LH at tuberal levels of the hypothalamus led to a remarkable reduction in food intake and to death by starvation. These pioneering observations led investigators to consider the LH as a feeding center (Stellar 1954, Sawchenko 1998). A large body of evidence subsequently supported this concept. Delgado & Anand (1953) showed that electrical stimulation of the LH induced food intake. Ungerstedt (1971) demonstrated that selective chemical lesions of dopamine neurons projecting rostrally through the LH led to hypophagia. Stricker et al. (1978) found that chemical lesions with glutamate agonists depressed feeding and body weight regulation. And still other studies showed that neurons in the LH fired spontaneously during naturally occurring feeding behavior and hypoglycemia (Katafuchi et al. 1985, Himmi et al. 1988). However, the exact identity of the cells responsible for the role of the LH in positive energy balance was not clear until the end of the twentieth century.

Hcrt Promotes Energy Intake in Animals

Hcrt's role in food intake originates back to when it was first discovered (Sakurai et al. 1998). Investigators found that the application of Hcrt and antagonists of Hcrt receptors modulates food intake. The intracerebroventricular administration of Hcrt (either Hcrt-1 or -2) leads to a short-term increase in food consumption in rats (Sakurai et al. 1998). Local administration of Hcrt-1 to brain areas such as the paraventricular nucleus, the dorsomedial nucleus, or the LH/perifonical area triggers food intake in rats (Dube et al. 1999, Thorpe et al. 2003). Applying the selective Hcrt-1 receptor antagonist, SB-334867, suppresses food intake (Haynes et al. 2000, Rodgers et al. 2002). Additionally, the activity level of the Hcrt neurons is closely related to the amount of food intake. Fasting enhances expression of Hcrt mRNA and peptides in rats (Sakurai et al. 1998, Mondal et al. 1999, Yamamoto et al. 2000). Acute hypoglycemia induces upregulation of Hcrt mRNA and c-Fos expression in Hcrt neurons in rats when food is not available (Cai et al. 1999, Griffond et al. 1999, Moriguchi et al. 1999), whereas leptin treatment decreases the concentration of Hcrt in the LH and fasting-induced upregulation of Hcrt mRNA (López et al. 2000, Beck et al. 2001). Hcrt may also be involved in intense hyperphagia produced by $GABA_A$ receptor stimulation in the nucleus accumbens shell (Baldo et al. 2004). Finally, Hcrt helps control peripheral organs essential to feeding behavior. Some evidence indicates that Hcrt neurons innervate the dorsal motor nucleus of the vagus (DMV) (Peyron et al. 1998), which is a key region that controls gastric acid secretion and gut motility. The activation of Hcrt neurons by hypoglycemia triggers c-Fos expression in the DMV (Cai et al. 2001), and the central application of Hcrt increases both gastric acid secretion and gastric motor function in rats (Takahashi et al. 1999, Krowicki et al. 2002). The current consensus is that Hcrt may promote positive energy balance by promoting arousal or mediating the rewarding aspects of feeding (Yamanaka et al. 2003, Harris et al. 2005). However, the mechanisms underlying these two processes are still largely unclear.

Hcrt Regulates Energy Expenditure

Hcrt's ability to increase energy expenditure in animals was reported shortly after the discovery of the peptide. Lubkin & Stricker-Krongrad (1998) were the first to show that microinjection of

Hcrt-1 into the third ventricle stimulated the metabolic rate in mice. They also showed that the effect of Hcrt-1 was more potent in the dark cycle than in the light cycle. This observation was later confirmed in mice and rats (Asakawa et al. 2002, Wang et al. 2003, Semjonous et al. 2009). By microinjecting Hcrt-1 into various brain structures, Wang and colleagues (2003) showed that a direct infusion of Hcrt-1 into the arcuate nucleus (ARC) led to an enhancement in whole-body O_2 consumption (VO_2) in urethane-anesthetized rats, whereas Kiwaki et al. (2004) showed that Hcrt-1 microinjection into the paraventricular nucleus of hypothalamus (PVH) and LH increased thermogenesis in conscious rats. The discrepancy in action sites of Hcrt in rats may reveal new aspects of Hcrt-mediated effects on energy expenditure because Hcrt promotes physical activity when microinjected into many brain areas, including the PVH and LH (España et al. 2001; Kotz et al. 2002, 2006, 2008; Kiwaki et al. 2004). Research clearly shows that Hcrt enhances energy expenditure by promoting cardiovascular functions and thermogenesis, which is mediated by the sympathetic nervous system (see reviews by Samson et al. 2005, Székely 2006, Teske et al. 2010). In addition, new evidence has shown that Hcrt is required to mediate the mobilization of brown adipose tissue (BAT) (Sellayah et al. 2011). Compared with their wild-type littermates, Hcrt knockout mice expressed higher levels of preadipocyte markers, fewer mitochondria, and lowered levels of BAT thermogenic proteins (such as PPAR-γ1/γ2, PGC-1α/β, and UCP-1) in brown fat cells (Sellayah et al. 2011). These defects led to a compromised thermogenesis induced by high-fat diet and cold exposure (Sellayah et al. 2011, Sellayah & Sikder 2012). These results are supported by a recent study showing the direct innervation of the raphe pallidus by Hcrt-containing nerve fibers of the LH to promote BAT thermogenesis in rats (Tupone et al. 2011). The most recent study supporting this argument is by Kotz and colleagues (2012), who found that Hcrt is critical in obesity resistance in animals.

Earlier studies have shown that Hcrt may be an important player in the regulation of glucose metabolism (Cai et al. 1999, 2001; Jöhren et al. 2006; Paranjape et al. 2007; Tsuneki et al. 2010). Most recent developments further reveal how the Hcrt system may be involved in the regulation of glucose metabolism and the development of diabetes. First, both Hcrt and its receptors have been found in peripheral tissues, including the endocrine pancreas, and studies in vitro and in vivo have demonstrated that Hcrt modulates insulin and glucose levels (reviewed by Heinonen et al. 2008, Chandra & Liddle 2009). Second, locally applying Hcrt into brain structures directly affects glucose metabolism in the peripheral organs. During the light phase, disinhibition of Hcrt neurons by microinjecting bicuculline, the $GABA_A$ receptor antagonist, into the perifornical area increased basal endogenous glucose production (EGP) in rats, which was prevented by pretreating the HcrtR1 antagonist and hepatic sympathetic denervation (Yi et al. 2009). In addition, plasma insulin clamped at severalfold of the basal level did not counteract the effects of disinhibition of Hcrt neurons on glucose production, suggesting hepatic insulin resistance (Yi et al. 2009). The local infusion of Hcrt into the ventromedial hypothalamus (VMH) enhanced glucose uptake in skeletal muscles by activating beta-2-adrenergic receptors (Shiuchi et al. 2009). Third, a role for Hcrt and the HcrtR1 pathway in the regulation of glucose metabolism and the development of diabetes mellitus (DM) is strengthened by a report that HcrtR1-immunopositive nerves were found in the pancreas of normal and DM rats (Adeghate et al. 2010). The number of HcrtR1-positive cells increased significantly in the islets after DM was induced by streptozotocin (STZ) in this species (Adeghate et al. 2010). In line with these results, Hcrt knockout mice showed more efficient glucose use in glucose tolerance tests and reduced hyperglycemia after the STZ treatment (Adeghate et al. 2010).

Hcrt System Serves as a Sensor of Energy Status in Animals

Unlike many other neuropeptides, which promote energy intake and decrease energy expenditure [such as neuropeptide Y (NPY) and agouti-related protein (AgRP) or vice versa (such as α-MSH)

(Semjonous et al. 2009)], the actions of the Hcrt system are bidirectional. The mechanisms through which Hcrt modulates energy homeostasis are not clear and are still emerging. To promote energy intake, the Hcrt system must be able to sense the animal's energy status. The Hcrt system should be activated to promote food/energy intake when the energy state is low, whereas it should be inhibited when the energy status is high, as it would be after a meal. However, as a promoter of energy expenditure, the Hcrt system is expected to do the opposite. Although it seems paradoxical, the evidence supports the existence of both situations. Yamanaka et al. (2003) originally showed that the activity in isolated Hcrt neurons could be inhibited by molecules encoding cues for energy status, such as glucose, insulin, and leptin. However, this report suffered from limitations originating from the approaches used in their experiments. The acutely isolated Hcrt neurons led to a compromised internal cellular content and external environment. The concentration of glucose used in the study was not at physiological levels either.

Later, Burdakov and colleagues (2006) showed in brain slices that Hcrt neurons could be inhibited by an elevated glucose level resembling the physiological levels in the cerebrospinal fluid (CSF) after a meal through the opening of tandem-pore K^+ channels. However, a later report argued that in mice with a deficiency in tandem-pore K^+ channels, Hcrt neurons could still be inhibited by elevated glucose levels in the artificial cerebrospinal fluid (Guyon et al. 2009). Surprisingly, two of the most recent reports demonstrated that with an intact intracellular content, the Hcrt neurons did not respond to an increase in the ambient glucose levels when cell-attached extracellular or perforated whole-cell recordings were performed in Hcrt neurons (Parsons & Hirasawa 2010, Liu et al. 2011). In fact, a lowered level of ambient glucose inhibited Hcrt neurons, owing to lowered intracellular ATP levels and the opening of K-ATP channels in the Hcrt neurons (Liu et al. 2011). The difference between the responses to extracellular glucose may lie within the experimental conditions used in the above experiments. When conventional whole-cell recording was used, in which the original intracellular content was compromised by the pipette solution, Hcrt neurons were inhibited by high glucose levels and activated by low glucose amounts (Yamanaka et al. 2003; Burdakov et al. 2006). When the intracellular content was kept intact with extracellular or perforated whole-cell recording, Hcrt neurons were inhibited by low levels of glucose (Parsons & Hirasawa 2010, Liu et al. 2011). These results suggest that the Hcrt neurons' response to the changes in ambient glucose levels may involve heterogeneous mechanisms. Identifying key molecule(s) missing during the conventional whole-cell recording may provide critical insight into the understanding of mechanisms underlying the sensing of ambient energy status by Hcrt neurons.

Hcrt AS A POTENT PLAYER IN AROUSAL/WAKE MAINTENANCE

The role of the hypothalamus in sleep regulation was originally proposed by von Economo on the basis of his observations in human patients that lesions in the posterior hypothalamus and midbrain junction lead to sleepiness, whereas anterior hypothalamic inflammation leads to insomnia and chorea (von Economo 1930). Later, the sleep-promoting effect of lesions and inhibition of the posterior LH was confirmed in monkeys, rats, and cats (Ranson 1939, Nauta 1946, Swett & Hobson 1968, Lin et al. 1989). How the LH participates in sleep regulation, however, remained elusive until Hcrt was discovered in this brain area.

Hcrt is a potent arousal/wake promoter in the brain (reviewed by de Lecea & Sutcliffe 2005; Sakurai 2005; Saper 2006, 2013). First, a deficiency in Hcrt itself and its receptor (HcrtR2 or OXR2) leads to narcolepsy in dogs, mice, and human patients (Chemelli et al. 1999, Lin et al. 1999, Nishino et al. 2000, Thannickal et al. 2000, Ripley et al. 2001). Second, the concentration of Hcrt fluctuates in animals depending on the behavioral state. The Hcrt-1 level in CSF is high

during the active period and low during the inactive period in rodents and squirrel monkeys (Fujiki et al. 2001, Yoshida et al. 2001, Zeitzer et al. 2003). The activity in these neurons changes along with the rats' behavioral state. The c-Fos expression increases in Hcrt neurons during the dark phase and sleep deprivation (Estabrooke et al. 2001). Also, Hcrt neurons are generally active in the dark phase (awake) and silent in the light phase (sleep) (Lee et al. 2005, Mileykovskiy et al. 2005). Direct and selective stimulation of Hcrt neurons with the optogenetic approach increases the probability of the subject's transition to wakefulness from either slow-wave sleep or rapid-eye-movement sleep (Adamantidis et al. 2007). Last, by projecting to major arousal areas such as the locus coeruleus and the basal forebrain, Hcrt neurons promote arousal and antagonize sleep and muscle atonia by integrating various sensory and homeostatic inputs (Bourgin et al. 2000, España et al. 2001, van den Pol et al. 2002, Lee et al. 2005, Yoshida et al. 2006). Thus, in the flip-flop switch model of sleep regulation, Hcrt neurons consolidate wakefulness by setting the threshold for state transitions (Saper 2006, 2013; Selbach & Haas 2006). Under the physiological condition, the Hcrt system is closely regulated by a network of negative feedbacks to maintain an optimal output (Burt et al. 2011). It is not clear, however, whether the closely regulated output of the Hcrt system and/or other arousal system underlies the optimal arousal levels required for animals to perform normal functions as described by the Yerkes-Dodson law, an interesting phenomenon that has not been well understood.

The latest development in understanding the role of Hcrt in the regulation of the sleep and wake cycles provides a more complicated picture than previously described. One of the hypothesized functions of sleep is to preserve energy, which is crucial to animals in the natural environment where food is not always accessible. Therefore, the study of the integration of the sleep/wake cycle and energy balance regulation is essential to the overall understanding of the homeostatic regulatory processes in animals. The original reports by Yamanaka et al. (2003) on the regulation of Hcrt neuron activity by molecules encoding ambient energy supplies such as glucose provided a critical clue that the Hcrt system may be a node where the neuronal systems controlling energy balance and sleep/wake status converge. Liu & Gao (2007) later showed that adenosine, a substance resulting from cellular activity and metabolism, inhibited Hcrt neurons. On the one hand, adenosine is usually considered a potent sleep-promoting substance (Porkka-Heiskanen & Kalinchuk 2011). On the other hand, a main source of extracellular adenosine comes from the energy metabolism of cells (Porkka-Heiskanen & Kalinchuk 2011). This particular piece of evidence not only shows the sleep-promoting effects of adenosine on Hcrt neurons, but also suggests that energy use can be translated into a mechanism used by the Hcrt system as a cue to limit energy expenditure and modulate the behavioral state. Shulman et al. (2003) showed that the animals' energy status is highly correlated with their behavioral state. The brain utilizes more energy in the activated state than it does in the anesthetized state, and a low-energy state leads to unconsciousness in animals (Shulman et al. 1999, 2009). Insufficient energy may attenuate wakefulness and promote sleep in animals (Benington & Heller 1995, Scharf et al. 2008). The evidence supporting this hypothesis is emerging, particularly from the studies on Hcrt neurons. Parsons & Hirasawa (2010) have shown that lactate, but not glucose, is required to maintain the firing of Hcrt neurons in vitro, and Gao and colleagues (Liu et al. 2011) have further shown that the intracellular levels of ATP are a key factor to maintain the membrane potential and firing of action potential in Hcrt neurons. More importantly, the intracellular levels of ATP are lower in Hcrt neurons in sleeping mice than in sleep-deprived animals (Liu et al. 2011). This finding is consistent with the results indicating that the cerebral consumption of glucose and oxygen and glucose uptake fluctuate across the sleep/wake cycle in humans and animals (Boyle et al. 1994, Vyazovskiy et al. 2008). The correlation between activity and the intracellular levels of ATP in Hcrt neurons may serve as a mechanism underlying the energy hypothesis of sleep; i.e., the decrease in ATP levels may limit arousal/wakefulness

and promote sleep in animals (Benington & Heller 1995, Scharf et al. 2008). In summary, research on the relationship between energy and behavioral states is revealing new avenues for understanding the sleep/wake cycle and behavioral states in the context of energy metabolism in animals. The role of the Hcrt system is no doubt critical to deciphering the mystery behind these processes.

Hcrt IN REWARDING/MOTIVATIONAL BEHAVIORS

The perifornical/LH area is a brain structure known to be responsible for reward-seeking behaviors. In rats, electrical stimulation of the LH induces marked reinforcement activity: Investigators observed a robust self-administration of electric current when the stimulating electrodes were implanted within the LH area (Olds & Milner 1954, Olds 1958). Many drugs of abuse, such as morphine and amphetamine, modulate the self-reinforcement induced by stimulation of the LH area (Adams et al. 1972, Goodall & Carey 1975). Drugs of abuse, in addition to electrical stimulation, induce self-administration in rats when applied to the LH directly. For instance, administering D-Ala2-Met-enkephalin, a long-lasting analogue of encephalin, through a cannula implanted in the LH area triggers self-administration in rats, which can be blocked by naloxone (Olds & Williams 1980). Similar results have been reported in self-administration of morphine and morphine-induced place preference in mice (Cazala et al. 1987).

Hcrt neurons are clearly required in the development of drug addiction in animal models and human patients (see reviews by Baimel & Borgland 2012, España 2012, Mahler et al. 2012). First, Hcrt neurons are activated when rodents are exposed to drugs of abuse, and the expression of c-Fos in Hcrt neurons is enhanced by opiates, cocaine, amphetamine, and nicotine in various animal models of drug-seeking behavior (Georgescu et al. 2003, Harris et al. 2005, Pasumarthi et al. 2006, McPherson et al. 2007, Plaza-Zabala et al. 2011). Second, direct applications of Hcrt to reward centers in the brain promote drug-induced plasticity in these brain areas and drug-seeking behavior in animals. Activation of Hcrt neurons or administration of Hcrt directly into the ventral tegmental area (VTA) reinstates extinguished morphine-seeking behavior and increases the break point in a progressive ratio task for cocaine (Boutrel et al. 2005, Harris et al. 2005, Hamlin et al. 2008, España et al. 2011). Also, a central application of Hcrt [intracerebroventricular (i.c.v.)] reinstates extinguished nicotine-seeking behavior in mice (Plaza-Zabala et al. 2011). The findings that Hcrt induces synaptic plasticity in the VTA and that Hcrt receptor antagonists abolish cocaine or amphetamine-induced locomotor sensitization, potentiation of glutamatergic currents, and expression levels of genes associated with synaptic plasticity in the VTA in rats may provide mechanisms underlying the role that Hcrt plays in reward centers of the brain (Borgland et al. 2006, Winrow et al. 2010). Third, the disruption of Hcrt receptor–mediated pathways attenuates or blocks drug-seeking behavior in animals. The development of morphine dependence is attenuated by systemic application of the selective Hcrt-1 receptor antagonist, SB334867 (Georgescu et al. 2003). SB334867 blocks the acquisition of cocaine sensitization, attenuates cocaine and amphetamine conditioned place preference (CPP), and reduces break points for cocaine under a progressive ratio (PR) schedule of reinforcement (Harris et al. 2005; Borgland et al. 2006, 2009; España et al. 2010). SB334867 significantly decreases nicotine reinforcement in rats as well (Hollander et al. 2008, LeSage et al. 2010). Drug-seeking behaviors are attenuated or abolished in animals with a deficiency in Hcrt peptide or receptors (Georgescu et al. 2003, Hollander et al. 2012). In human narcoleptic patients (who have a deficiency in Hcrt peptide or neurons), the tendency toward drug abuse is significantly low (Guilleminault et al. 1974).

Despite the growing body of evidence on the Hcrt system's participation in reward-seeking behavior, the Hcrt system's role in the development of motivational behaviors is not yet clear.

Harris et al. (2005) proposed that the Hcrt system may be responsible for cue-induced seeking conduct (i.e., CPP) for cocaine and morphine. The Hcrt system may contribute to psychostimulatory effects of drugs (such as cocaine and amphetamine) (Borgland et al. 2006). Borgland et al. (2009) recently suggested that the Hcrt system may be involved not in the rewarding aspect of drugs of abuse but rather in the motivational aspect of drug-seeking behavior, as indicated in cocaine self-administration experiments. Ho & Berridge (2013) showed that activating Hcrt signaling in the ventral pallidum (VP) generated hedonic (liking) responses to sweetness in rats. The Hcrt system may also be responsible for sleep disorders in drug addicts (Rao et al. 2013). Additionally, the Hcrt system may mediate the effects of metabolic states on rewarding and motivational behaviors in animals. Carroll et al. (1979) showed that food restriction increases sensitivity to drug reward. According to the current framework, stimulation of D1 receptors, upregulation of protein kinases, and activation of epigenetic mechanisms in the NAc are responsible for the effects of food restriction on drug reward (reviewed by Carr 2011). The latest progress in the field suggests that not only food restriction but also metabolic status may shape drug reward in animals. Consistent with the effects of food restriction on drug use, overnutrition or obesity decreases the subject's sensitivity to drug reward (reviewed by Kenny 2011). Emerging evidence proposes that D2 dopamine receptor–mediated mechanisms in striatal neurons underlie this process (Kenny 2011). Because food and calorie restriction and diet-induced obesity represent two opposite sides of the same coin, a common mechanism is likely responsible for the effects of metabolic status on drug reward. Is the Hcrt system one of the converging points where metabolic status interacts with motivational behaviors in animals? Studies have demonstrated that cues encoding hunger and food restriction increase the expression of Hcrt mRNA in animals (Sakurai et al. 1998; Cai et al. 1999, 2001; Kurose et al. 2002), whereas obesity leads to the downregulation of Hcrt expression in rats and mice (Cai et al. 2000, Beck et al. 2001, Stricker-Krongrad et al. 2002). We have also shown previously that an acute food restriction leads to the reorganization of the neural circuitry onto Hcrt neurons (Horvath & Gao 2005). These data clearly implicate the adaptation of Hcrt neurons induced by changes in metabolic status. Therefore, an important question arises about whether the effects of the metabolic status on motivational behaviors in animals require the Hcrt system, an issue that has not yet been thoroughly explored.

DYSFUNCTION OF Hcrt IN ALTERED ANIMAL BEHAVIORS AND HUMAN DISEASES

Deficiency in the Hcrt system in narcolepsy is well addressed in human patients and animal models (Chemelli et al. 1999, Lin et al. 1999, Nishino et al. 2000, Thannickal et al. 2000, Ripley et al. 2001). Although in animal models, the loss of Hcrt peptide, its receptors (particularly OXR2), and Hcrt-containing neurons produce a narcolepsy-like phenotype (Lin et al. 1999, Hara et al. 2001, Willie et al. 2003), in most human narcolepsy cases, the mutation does not occur in either the Hcrt ligand or Hcrt receptor genes. The low (or undetectable) level of Hcrt in the CSF in patients with narcolepsy–cataplexy is likely due to the loss of Hcrt-containing neurons (Thannickal et al. 2000). The mechanisms underlying the selective loss of Hcrt-containing neurons in narcoleptic patients are not yet clear, but the latest evidence suggests an autoimmune process may be involved in this pathological condition (Han 2012, Mahlios et al. 2013). The replacement of Hcrt in narcoleptic animal models is currently being tested as a potential treatment for narcolepsy (Blanco-Centurion et al. 2013, Kantor et al. 2013).

In an animal model of narcolepsy, obesity is one of the phenotypes observed in the study (Hara et al. 2001). In fact, historic records have shown an increased body weight in narcoleptic patients (Schuld et al. 2000, Akinnusi et al. 2012). The exact link between obesity and narcolepsy in human

patients is uncertain, but in mice with genetically ablated Hcrt neurons, hypophagia was observed in conjunction with obesity. This piece of evidence implies that the balance may tilt toward energy expenditure when the Hcrt system functions normally in intact animals.

Although research has not yet established a direct association, dysfunction in the Hcrt system has been seen in many other diseases and pathological conditions. For instance, the dual Hcrt receptor antagonists SB649868 and suvorexant have been effective treatments for insomnia in clinical trials (Winrow & Renger 2013). This evidence may shed new light on the development of treatments for insomnia. In patients with Prader–Willi syndrome (PWS), the loss of muscle tone in infancy and sleep disturbances with excessive daytime sleepiness (EDS) at later developmental stages imply a similarity between this disease and narcolepsy caused by a deficiency in the Hcrt system (Camfferman et al. 2008). Some evidence indicates that impaired levels of Hcrt-1 in the CSF correlate with the severity of EDS in PWS patients (Nevsimalova et al. 2005), whereas the total number of Hcrt neurons is not significantly different in PWS patients as compared with age-matched controls (Fronczek et al. 2005). Thus, the reduced CSF levels of Hcrt in PWS patients may very likely be due to impaired functions in neurons expressing this neuropeptide.

PERSPECTIVE

The Hcrt system is only one part of an ever-evolving network controlling the most fundamental functions in animals. The intake and use of energy are the basis of all biological activities. The Hcrt system may be a critical hub of the brain positioned to control energy intake and expenditure and, at the same time, may contribute significantly to the control of behavioral (rest versus active) states and motivational behaviors in animals (**Figure 1**). Several lines of research are still needed. First, investigators must discern just how the Hcrt system monitors the ambient energy state and nutritional stores. To this end, new evidence must materialize and inconsistencies in published reports must still be addressed. Determining the molecular and cellular mechanisms that underlie the sensing of cues encoding energy status and nutritional stores is also essential to improving our

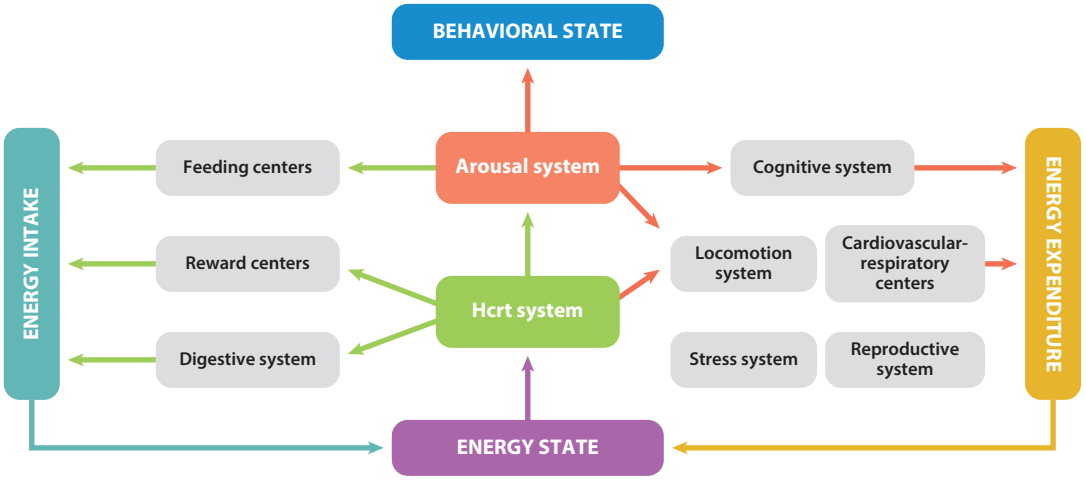

Figure 1

A theoretical scheme of how the Hcrt system regulates animal behaviors depending on animals' energy states. As proposed in this diagram, the Hcrt system promotes both energy intake and expenditure. The energy state based on the available energy store in animals may fine-tune the activity in the Hcrt system and help determine animals' behavioral states. In this simplified diagram, the interaction of the Hcrt system with other homeostatic centers and feedbacks from environmental cues are not included.

understanding. Second, we need to understand the connectomics of Hcrt neurons with an emphasis on the brain structures and peripheral organs responsible for energy intake and expenditure. Interactions between the Hcrt neurons and the NPY, melanin-concentrating hormone (MCH) and other neuronal populations have been reported previously (Horvath et al. 1999, Guan et al. 2002, van den Pol et al. 2004, Rao et al. 2008); however, the contribution of these interactions in the context of bidirectional effects of Hcrt on energy homeostasis has not been shown. Third, and most important, a comprehensive understanding of how an animal's energy state shapes the Hcrt system, and in turn modulates other homeostatic, motivational, and cognitive functions, is critical.

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