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Mini-Review

The Hypocretins: Excitatory Neuromodulatory Peptides for Multiple Homeostatic Systems, Including Sleep and Feeding

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The hypocretins are two neuropeptides of related sequence that are produced from a common precursor whose expression is restricted to 1,100 large neurons of the rat dorsal-lateral hypothalamus. The hypocretins have been detected immunohistochemically in secretory vesicles at synapses of fibers that project to areas within the posterior hypothalamus that are implicated in feeding behaviors and hormone secretion and diverse targets in other brain regions and in the spinal cord, including several areas implicated in cardiovascular function and sleep-wake regulation. The hypocretin-producing cells have receptors for leptin and receive input from arcuate neuropeptide Y neurons. The peptides are excitatory when applied to cultured hypothalamic, cortical, or spinal cord neurons. Two G protein-coupled receptors for the hypocretins have been identified, and these have different distributions within the CNS and differential affinities for the two hypocretins. Administration of the hypocretins stimulates food intake; affects blood pressure, hormone secretion, and locomotor activity; and increases wakefulness while suppressing REM sleep. The hypocretin mRNA accumulates during food deprivation. An inactivating insertion into the hypocretin receptor 2 gene in dogs results in narcolepsy. Mice whose hypocretin gene has been inactivated exhibit a narcolepsy-like phenotype. Human patients with narcolepsy have greatly reduced levels of hypocretin peptides in their cerebral spinal fluid. One aspect of hypocretin activity is the direct excitation of noradrenergic neurons in the locus coeruleus to prevent entry into REM sleep. These peptides appear to be part of a complex circuit that integrates aspects of energy metabolism, cardiovascular function, hormone homeostasis, and sleep-wake behaviors. J. Neurosci. Res. 62:161–168, 2000.

Key words: orexins; leptin; narcolepsy; REM sleep

THE HYPOTHALAMUS: A CENTER FOR HOMEOSTATIC REGULATION

The hypothalamus is a phylogenically ancient region of the mammalian brain. In contrast to laminar cortical structures such as the cerebellum and hippocampus whose final functions rely on input from the thalamus and brainstem, the hypothalamus is organized as a collection of distinct, autonomously active nuclei with discrete functions. Ablation and electrical stimulation studies and medical malfunctions and misadventures have implicated several of these nuclei as central regulatory centers for major autonomic and endocrine homeostatic systems mediating processes such as reproduction, lactation, fluid balance, blood pressure, thermoregulation, metabolism, and aspects of behaviors such as circadian rhythmicity, basic emotions, the sleep-wake cycle, feeding and drinking, mating activities, and responses to stress as well as normal development of the immune system. Distinct hormones and releasing factors have been associated with some of these nuclei, but, at best, the organizations and molecular operations of these structures are only partially understood.

A substantial portion of a mammal's genetic endowment is dedicated to the function of its central nervous system, as evidenced by the substantial number of mRNAs selectively expressed in the brain (Sutcliffe, 1988). Many of these have been observed to be associated with distinct neural subsets. A survey of the most prevalent mRNAs selectively associated with the hypothalamus found that as many as 40% encoded hormones and releasing factors (Gautvik et al., 1996).

HYPOCRETIN MRNA IN 1,100 PERIFORNICAL NEURONS

In a search for additional undiscovered homeostatic regulatory peptides, a systematic subtractive hybridization study was conducted aimed at identifying mRNA species whose expression was restricted to discrete nuclei within the hypothalamus (Gautvik et al., 1996). One novel

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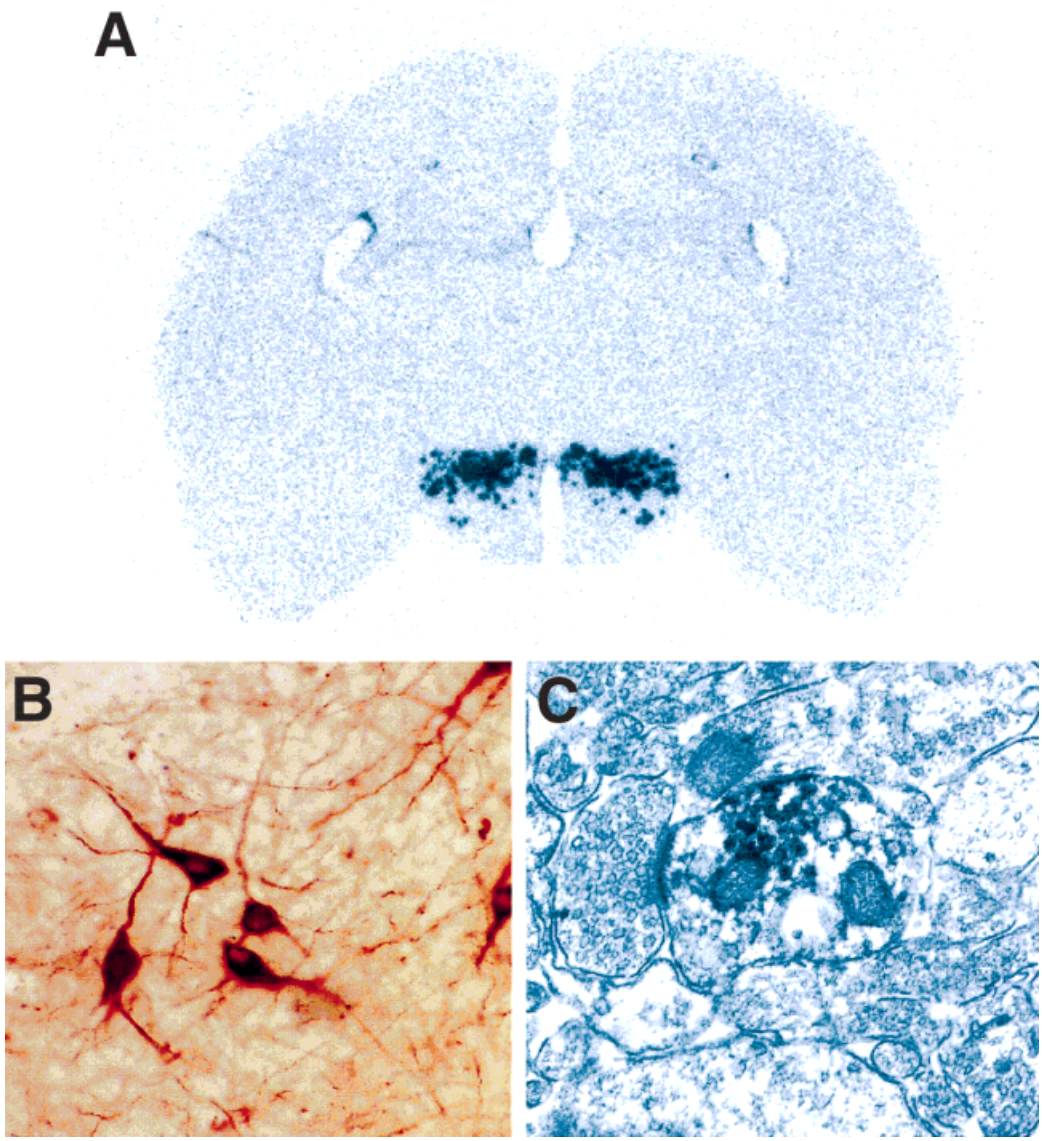

Fig. 1. The hypocretins are expressed in 1,100 neurons in the rat brain. **A:** Detection of hypocretin mRNA in large neurons in the dorsal-lateral hypothalamus by in situ hybridization to a coronal section from rat brain. **B:** Photomicrograph of the perifornical area in the lateral hypothalamus stained with antibody 2123 to preprohypocretin. All hypocretin-immunoreactive cell bodies are located in approximately 1 mm^3 of the fornix. Fiber projections are clearly visible with this antibody. **C:** Electron micrograph showing electron-dense hypocretin-immunoreactive material in large dense core vesicles of a hypothalamic axon terminal.

mRNA (Fig. 1A) found in that study exhibited a striking bilaterally symmetric distribution in approximately 1,100 neurons of the dorsal-lateral portion of the rat hypothalamus (Gautvik et al., 1996; de Lecea et al., 1998; Peyron et al., 1998). Colocalization studies (Peyron et al., 1998; Broberger et al., 1998; Elias et al., 1998; Hakansson et al., 1999) have shown these to represent a distinct but spatially overlapping collection of perifornical neurons from those that express melanin-concentrating hormone. Northern blot analysis detected the mRNA only within the brain (Gautvik et al., 1996; de Lecea et al., 1998), although a subsequent study detected expression of hypocretin in a subset of neurons in the gut (Kirchgessner and Liu, 1999). The mRNA was not detectable before postnatal day 5.

PREPROHYPOCRETIN CONTAINS TWO PEPTIDES

The respective cDNA sequences of the rat and homologous mouse mRNAs encoded a 130-residue putative secretory protein with an apparent signal sequence and one additional phylogenically conserved site for potential proteolytic maturation. This structure (Fig. 2A) suggested that the product of this novel hypothalamic mRNA served as a preprohormone for two C-terminally amidated, secreted peptides. One of these, hypocretin 2 (hcrt2), was,

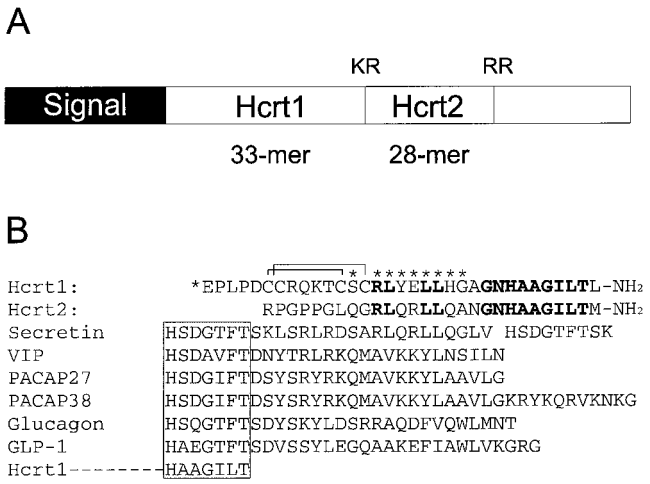

Fig. 2. Alignment of the two hypocretin peptides with members of the secretin peptide family. **A:** Diagram of preprohypocretin, indicating the dibasic residues that may be used as substrates for prohormone convertases. The C-terminal glycines of hcrt1 and hcrt2 are amidated by peptidylglycine α-amidating monoxigenase. **B:** Amino acid alignment of incretin family members. Identical residues between hypocretin 1 (hcrt1) and hypocretin 2 are indicated in boldface. Identities between at least one of the hypocretins and at least one of the secretin family members (secretin, PACAP27, glucagon, GLP-1) are indicated by asterisks. The N-terminal regions of the secretin family members (shaded box) have been aligned with the C-terminal hypocretin residues to extend the region of identity. Disulfide bridges between cysteine residues and the pyroglutamate derivatization in hcrt1 were determined by Sakurai et al. (1998).

based on the putative preprohormone amino acid sequence, predicted to contain precisely 28 residues. The other, hypocretin 1 (hcrt1), had a defined predicted amidated C-terminus but, because of uncertainties regarding how the N-terminus might be proteolytically processed, an undefined N-terminal extent (de Lecea et al., 1998). The C-terminal 19 residues of these two putative peptides shared 13 amino acid identities (Fig. 2B). This region of hcrt2 contained a 7/7 match with secretin, suggesting that the preprohormone gave rise to two peptide products that were structurally related both to each other and to secretin. These putative peptides were named the *hypocretins* to reflect their hypothalamic origin and the similarity to secretin. Their precursor is, thus, preprohypocretin.

The actual presence of the two hypocretin peptides within the brain was demonstrated, and the exact structures of these endogenous peptides were determined by mass spectroscopy (Sakurai et al., 1998). The structure of hcrt2 was the same as that predicted from the cDNA sequence. The N-terminus of hcrt1 was defined and was found to correspond to a genetically encoded glutamine derivatized as pyroglutamate. The two intrachain disulfide bonds within hcrt1 were also defined. The exact structures of these novel peptides are shown in Figure 2B. The three-dimensional solution structure of hcrt2 has been determined by NMR and reveals a stable α-helix in the middle portion of the peptide (Lee et al., 1999).

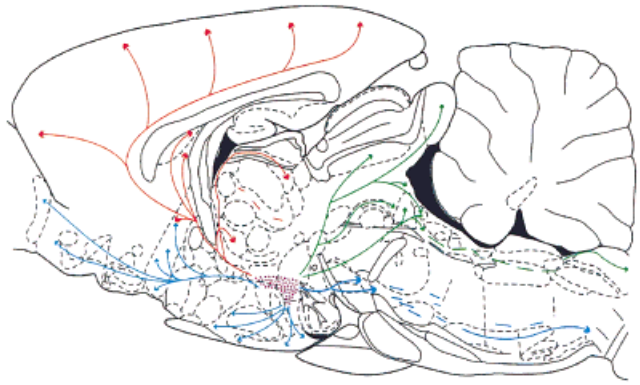

Fig. 3. Hypocretin cells project throughout the brain. Four main hcrt-ergic central afferents can be recognized from anatomical studies: an intrahypothalamic field, an ascending pathway through the basal ganglia, septum and cerebral cortex, a medial pathway that connect a variety of thalamic nuclei, and a descending pathway that reaches the locus coeruleus, dorsal raphe, and spinal cord. These widespread projections suggest multiple modulatory roles for the hypocretins. Reproduced with permission from the Journal of Neuroscience (Peyron et al., 1998).

HYPOCRETIN-CONTAINING CELLS PROJECT THROUGHOUT THE BRAIN

Anatomic analysis of neuropeptide distribution is an important step towards understanding physiological function. Indeed, examination of the immunoreactivity of antisera generated against both chemically synthesized and recombinant hypocretin fragments has given key information about possible roles of these peptides in the brain (de Lecea et al., 1998; Peyron et al., 1998; Date et al., 1999; van den Pol, 1999).

Approximately 1,100 cell bodies immunoreactive for the hypocretins were observed in the rat brain between the fornix and the mammillothalamic tracts (Fig. 1B). Additionally, the antisera detect a prominent network of axons that project from these neurons to the perifornical and posterior hypothalamus and beyond. Prominent fiber projections were observed in apparent terminal fields within septal nuclei in the basal forebrain, the preoptic area, the paraventricular nucleus of the thalamus, the central gray, the locus coeruleus, and the spinal cord. A thorough mapping (Fig. 3) of these extensive projections from a relatively small number of neurons in the rat is given by Peyron and colleagues (1998). Similar immunoreactivity of cell bodies and terminals has been found in primates (Horvath et al., 1999a).

HYPOCRETINS IN SYNAPTIC VESICLES

The deposition of the immunoreactivity along axons was clearly grainy. Electron microscopic examination revealed that hypocretin immunoreactivity is associated with dense core vesicles (de Lecea et al., 1998; Peyron et al., 1998; Horvath et al., 1999a). Not only were vesicles observed along myelinated axons but they were seen traversing the Golgi network and at presynaptic terminals opposed to dendritic shafts (Fig. 1C).

HYPOCRETINS ARE NEUROEXCITATORY

The putative structures of the hypocretins, their expression within the dorso-lateral hypothalamus, and their accumulation within dense core vesicles at axon terminals suggested that they might have intercellular signaling activity. Indeed, bath application of nanomolar concentrations of synthetic hcrt2 to mature hypothalamic neurons evoked a substantial, but reversible, increase in the frequency of postsynaptic currents (de Lecea et al., 1998). More detailed studies have shown that approximately 33% of hypothalamic neurons respond to hcrt2, whereas 5% of cerebral cortex neurons and 15% of spinal cord neurons are responsive (van den Pol et al., 1998; van den Pol, 1999). Similar results have been obtained when hcrt1 was applied on locus coeruleus slices (Hagan et al., 1999). Hcrt2 has a potent effect at both presynaptic and postsynaptic receptors. Most synaptic activity in hypothalamic circuits is attributable to axonal release of GABA or glutamate. Hypocretin, acting directly at axon terminals, can increase the release of each of these amino acid transmitters, as seen with whole-cell patch-clamp recording (van den Pol et al., 1998).

Van den Pol and colleagues (1998) have studied the second messenger systems involved in hypocretin signaling. Both hcrt1 and hcrt2 evoke rises in Ca^{2+} as measured by fura-2 imaging, in about one-third of hypothalamic neurons, probably by opening a plasma membrane calcium channel. Hypocretin responses are completely blocked by the PKC-specific inhibitor bisindolylmaleide, suggesting that hypocretin may work via G_q-activated PKC, resulting in phosphorylation of Ca^{2+} channels that has been reported to increase Ca^{2+} conductance (Yang and Tsien, 1993).

TWO HYPOCRETIN RECEPTORS

Sakurai and collaborators (1998) prepared transfected cell lines stably expressing each of 50 orphan G protein-coupled receptors and measured calcium fluxes in response to fractions from tissue extracts. One of these transfected cell lines responded to a brain peptide whose sequence was that of the endogenous hcrt1. The initial orphan receptor, hcrtr1, bound hcrt1 with high affinity but bound hcrt2 with 100- to 1,000-fold lower affinity. However, a related receptor, hcrtr2, identified by searching database entries with the hcrtr1 sequence, had high affinity for both hcrt2 and hcrt1. The mRNAs encoding the two receptors are both enriched in the brain and moderately abundant in the hypothalamus (Trivedi et al., 1998) but display remarkably different distributions (Table I). The combined pattern of expression of these receptors is consistent with the map of hcrt-containing fibers and suggests that the hypocretins modulate multiple neuronal circuits.

ARE THE HYPOCRETINS OREXIGENIC?

Stereotactic ablation and physiological studies have previously implicated the dorsal lateral hypothalamus in several homoeostatic processes, including feeding behavior, blood pressure, thermoregulation, and arousal (Satinoff and Shan, 1971; Levitt and Teitelbaum, 1975; Gilbert and Blatteis, 1977; Trojniar et al., 1987). Sakurai and

TABLE I. mRNA Distribution of the Hypocretin Receptors

Hypocretin receptor 1	Hypocretin receptor 2
Ventromedial hypothalamus	Cerebral cortex (layers IV–VI)
Locus coeruleus	Medial thalamus
Median raphe	Paraventricular hypothalamus
Hippocampus	Nucleus accumbens
Taenia tecta	Subthalamic and paraventricular thalamus
	Anterior pretectal nucleus

colleagues (1998) demonstrated that intracerebroventricular administration of either hcrt1 or hcrt2 increased food consumption in rats. Furthermore, rats fasted for 48 hr increased the concentration of hypocretin mRNA and peptides (Sakarai et al., 1998; Mondal et al., 1999). Based on these observations, they proposed the alternative name *orexins* for the hypocretin peptides. Hcrt1-elicited feeding was observed after local administration to the paraventricular nucleus, the dorsomedial nucleus, the lateral hypothalamus, and the perifornical area (Dube et al., 1999).

Hcrt-immunoreactive fibers make synaptic contacts with neurons in the arcuate nucleus that contain NPY, an important orexigenic peptide, and with POMC neurons, which produce γ-MSH (Broberger et al., 1998; Elias et al., 1998; Horvath et al., 1999a). Hcrt-positive cells also show leptin receptor (*ob*-r) immunoreactivity (Horvath et al., 1999a; Hakansson et al., 1999), and preprohypocretin mRNA expression is reduced in *ob/ob* mice (Yamamoto et al., 1999). Hcrt neurons receive inputs from NPY- and AGRP-positive neurons in the arcuate nucleus, which themselves express leptin receptors, and NPY receptor antagonists block the feeding effect of hypocretins (Jain et al., 2000; Yamanaka et al., 2000). Intracerebroventricular injection of antibodies to hcrt1 reduces feeding activity (Yamada et al., 2000). Also supporting the idea that the hypocretins neurons are involved in feeding is the observation that these neurons express STAT3, a transcription factor known to be activated by leptin (Hakansson et al., 1999). These results suggested a complex circuitry of appetite-controlling signaling molecules in the arcuate and lateral hypothalamus, in which hypocretin may play a major integrating role.

The effects of hypocretin on feeding, however, remain controversial. Ida and colleagues (1999) could not observe significant changes in food intake upon infusion of hcrt1. Other groups could not find any effect with hcrt2 (Lubkin and Stricker-Krongrad, 1998; Edwards et al., 1999). One paper reported increases in food intake only with intracerebroventricular infusion and not with local intrahypothalamic injections of hcrtr2 (Sweet et al., 1999). Taheri and colleagues (1999) measured no alteration in hcrt1 concentration in the rat hypothalamus in response to either fasting or high-fat diet. As was already pointed out (van den Pol et al., 1998), it is difficult to attribute physiological effects to intracerebroventricular administration of high doses of hypocretin, which may activate circuits other than those that would be activated by local axonal release of the transmitter. Alternatively, it may be that the hcrts are orexigenic only under some physiological states

(e.g., related to circadian rhythms or stress). Continuous administration of hcrt1 for 7 days in rats did not significantly affect food intake per day, body weight, blood glucose, total cholesterol, or free fatty acid levels, suggesting that its effects may be limited to short-term, immediate regulation of feeding behavior (Yamanaka et al., 1999).

MULTIPLE ACTIVITIES OF THE HYPOCRETINS

The presumptive function of the hypocretins based on the cumulative evidence is as peptide neurotransmitters or neuromodulators. The 1,100 hypocretin neurons project widely within the brain, suggesting that these peptides might affect several systems (de Lecea et al., 1998; Peyron et al., 1998). Indeed, the finding that hcrt2 is excitatory for 33% of cultured hypothalamic neurons is consistent with a widespread dispatch arising from a limited set of neurons. The location of the neuronal soma and their major projections to the posterior hypothalamus are consistent with one of the roles involving regulation of food intake, and the feeding-fasting studies certainly support this notion. The location of hypocretin-producing cells in the perifornical and lateral hypothalamus and their projections (considered in detail by Peyron et al., 1998) indicated that the peptides might have roles in other homeostatic processes. These cells receive inputs from brainstem areas associated with cardiovascular function and output to the ventrolateral medulla, the locus coeruleus, the lateral paragigantocellular nucleus, the nucleus of the solitary tract, and other areas that are consistent with a role in the regulation of blood pressure and heart rate (Dampney, 1994). The projections to the arcuate nucleus suggest a role in the regulation of hormone release. The projections to the raphe magnus and subcoeruleus suggest a role in the regulation of body temperature. The dense hypocretinergic projections to the ventrolateral preoptic area, tuberomammillary nucleus, pontine reticular formation, laterodorsal tegmental area, and locus coeruleus suggest involvement in states of arousal (Sherin et al., 1996; Peyron et al., 1998; Hagan et al., 1999). Very strong hypocretin-immunoreactive projections have been described in regions of the spinal cord related to modulation of pain (van den Pol, 1999).

In accordance with the wide distribution of hcrt terminals, intracerebroventricular administration of the hypocretins has been shown to affect not only feeding but also several other systems. Both hcrt1 and hcrt2 elevate mean arterial blood pressure and heart rate (Samson et al., 1999; Shirasaka et al., 1999; Chen et al., 2000). Both peptides also were found to stimulate the secretion of luteinizing hormone in ovarectomized rats (Pu et al., 1998). Hcrt1 decreased the concentrations of circulating growth hormone and prolactin, the latter to below limits of detection, while increasing corticosterone and insulin levels (Hagan et al., 1999; Malendowicz et al., 1999; Nowak et al., 2000; Ida et al., 2000). Central administration of hcrt1 increased water consumption and stimulated gastric acid secretion in the gut (Kunii et al., 1999; Takahashi et al., 1999). Hcrt1 increased locomotor activity and increase wakefulness, almost exclusively at the expense of REM sleep (Hagan et al., 1999; Piper et al., 2000; Bourgin et al., 2000).

THE HYPOCRETINS AND NARCOLEPSY

Sleep is characterized by complex patterns of neuronal activity in thalamocortical systems (Jones, 1994; Steriade et al., 1993; McCormick and Bal, 1997). The fast, low-amplitude activity of the aroused state is replaced by synchronized high-amplitude waves that characterize deep sleep. This pattern develops further into fast-frequency waves that define paradoxical, or REM, sleep. The dramatic differences that characterize each stage of sleep, together with the discovery of associated cellular systems and the selective actions of sleep stages on brain functions (e.g., memory consolidation), indicate that sleep oscillations are highly regulated (Buzsaki, 1998; Siapas and Wilson, 1998). Theoretical and experimental reviews have proposed interlinked anatomic and neurotransmitter systems, with multiple neuromodulators involved in the regulation of the sleep state (Inoue, 1986; Shiromani et al., 1987; Jones, 1994; McCormick and Bal, 1997). However, the molecular mechanisms of the natural processes underlying sleep initiation, sleep maintenance, and sleep stage alternation and their associated pathologies remain largely unknown.

Recent papers have placed the hypocretinergic neurons as the system responsible for narcolepsy and the regulation of REM sleep. Narcolepsy is a sleep disorder that strikes 1 in 2,000 adults, appears between the ages of 15 and 30 years, and shows four characteristic symptoms: 1) excessive daytime sleepiness, with irresistible sleep attacks during the day; 2) cataplexy (brief episodes of muscle weakness or paralysis precipitated by strong emotions, such as laughter or surprise); 3) sleep paralysis, a symptom considered to be an abnormal episode of REM sleep atonia, in which the patient suddenly finds himself unable to move for a few minutes, most often upon falling asleep or waking up; and 4) hypnagogic hallucinations, or dream-like images that occur at sleep onset. It has been known for some time that the disabling symptoms of narcolepsy are pathological equivalents of REM sleep.

Genetic studies of a form of narcolepsy that occurs in a colony of doberman pinschers had shown it to be inherited as an autosomal recessive, fully penetrant gene. Fine mapping and cloning of the defective canine narcolepsy gene showed it to be the gene encoding hcrtr2 (Lin et al., 1999). The mutation is an insertion of a short interspersed repeat (SINE element) into the third intron of this gene that causes aberrant splicing of the hcrtr2 mRNA and results in a truncated receptor protein. Analysis of the gene in a colony of narcoleptic Labradors revealed that hcrtr2 contained a distinct mutation that also resulted in the premature termination of the protein.

Chemelli and colleagues (1999) described the phenotype of mice in which the hypocretin gene had been inactivated by homologous recombination in embryonic stem cells. Continuous recording of the behavior of hcrt knockout mice revealed periods of ataxia, which were especially frequent during the dark period. EEG recordings showed that these episodes were not related to epi-

lepsy and that mice suffered from cataplectic attacks, a hallmark of narcolepsy. In addition, the mutant mice spent almost twice the amount of time in REM sleep compared to wild-type littermates, and their EEGs showed episodes of wakefulness/REM sleep transition, another event unique to narcolepsy.

It was unlikely, a priori, that human narcolepsy would have as straightforward an explanation as the canine disorder. Studies with monozygotic twins have shown that human narcolepsy is weakly penetrant: Only 35% of monozygotic twins develop the disease. Approximately two-thirds of narcoleptic patients carry a particular class II HLA haplotype, but most people with this haplotype are not narcoleptic. Nishino and colleagues (2000) studied hypocretin concentrations in the cerebral spinal fluid (CSF) of normal control and patients with HLA-linked narcolepsy by radioimmunoassay. In control CSF, hypocretin concentrations were highly clustered between 250 and 285 pg/ml, suggestive of an importance to the tight regulation of the substance. However, among nine patients with narcolepsy, only one had a hypocretin concentration within the normal range. One patient had a greatly elevated concentration, whereas seven patients had no detectable circulating hypocretin. These findings leave no doubt about the central role that the hypocretin system plays in this sleep disorder. However, it is unlikely that mutations in the hypocretin gene per se account for these observations on HLA-linked narcolepsy, given the genetic considerations mentioned above. Other narcolepsies may find explanation in mutations in the genes for hypocretin or its receptors. The narcolepsies are likely a collection of disorders caused by defects in the production or secretion of the hypocretins or in their signaling, and these could have numerous genetic, viral, and/or autoimmune causes.

HYPOCRETINS REGULATE REM

Based on the characterized dense hcrt projections in rats to the locus coeruleus (LC; Horvath et al., 1999b), a likely mechanism would be excitation of LC neurons that fire constantly during wakefulness to inhibit the cholinergic REM generator neurons that project to the pons (Hobson et al., 1975; Aston-Jones and Bloom, 1981). Indeed, local administration of hcrt1, but not hcrt2, to the LC suppressed REM in a dose-dependent manner and increased wakefulness (Bourgin et al., 2000). These effects were neutralized by an antibody that prevented hcrt1 binding to hcrt receptor 1, the only hcrt receptor expressed in the LC. The hcrt1 administration increased the firing rate of LC neurons and induced expression of *c-fos* in these cells. Thus, hcrt1 acting at hcrtr1 accounts for at least some of the REM sleep-inhibiting activity of the hypocretinergic system. The mRNA distribution of this receptor is fully consistent with a role in REM sleep regulation, because it is highly expressed in the locus coeruleus and other brainstem nuclei that have long been shown to have a function in arousal.

These results are, at least superficially, paradoxical. The hcrtr2 receptor that is defective in dogs with narcolepsy is not, at least in rats, expressed in the LC or in other regions classically associated with arousal or EEG desynchronization (i.e., cholinergic brainstem nuclei). Rather, hcrtr 2 mRNA is abundantly expressed in the rat nucleus accumbens. Dopamine neurons that originate in the ventral tegmental area and project to the nucleus accumbens, olfactory tubercle, and frontal cortex have long been implicated in reward and motivational processes (Koob, 1996). The nucleus accumbens may be relevant to the pathology of narcolepsy, because cataplectic attacks are triggered by emotions and increased motivation. In addition, narcolepsy has been associated with deficits in the dopaminergic system (Foutz et al., 1981; Mefford et al., 1983; Bowersox et al., 1987). An important role for the amygdala, which is also involved in emotions and which contains dense hcrt fibers, cannot be ruled out.

WHICH FACTORS MODULATE HCRT CELLS?

From the feeding studies it is known that hcrt cells are sensitive to glucose and food deprivation (Griffond et al., 1999; Moriguchi et al., 1999; Bayer et al., 2000). Hcrt-cells are innervated by NPY cells from the arcuate, contain leptin receptors, and respond to circulating leptin by reducing hcrt1 concentrations (Beck and Richy, 1999; Lopez et al., 2000). This may be relevant to the very significant changes of glucose metabolism that accompany the sleep-wake cycle, as seen on positron emission tomography (Maquet, 1997). Thus, hcrt cells seem to integrate information about the energy balance and release the neuromodulators in key areas for arousal. The two peptides are also involved in central regulation of essential neuroendocrinological parameters and in blood pressure regulation.

How should we view these findings about a very small number of neurons that modulate many physiological and behavioral modalities? Higher organisms must integrate the demands of internal metabolism and external environment, both natural and social. Overlapping neuromodulatory systems that receive input from multiple sensors and with multiple output responses allow conflicting demands to be valued and the resulting calculation to be acted upon. The calculus of systems such as the hypocretin system provides much greater flexibility over matching demand with response than would one system–one output strategies. Thus, we might expect that this strategy will be most favored by complex organisms.

HYPOCRETIN NOMENCLATURE

The term *hypocretin* was originally coined to reflect the exclusively hypothalamic origin of the peptides and their sequence relationship to the secretin peptide family. With a number of functional possibilities, few of which had been tested at the time, the name *hypocretin* was selected from a list of candidate terms by a vote of neuroscientists attending the posters first describing these peptides (Sutcliffe et al., 1997; Peyron et al., 1997) at the 1997 Society for Neuroscience Meeting. The term has been adopted by the OMIM and MGD genetic databases, largely because of the temporal priority in the absence of a singular biological or biochemical function. Sakurai and associates (1998) subsequently proposed the term *orexins*

because of evidence for a role in feeding behavior, a clever term reflecting one activity of the hypocretins, at least in rats. However, experimental support for additional functions, including roles in hormone secretion, blood pressure, and REM sleep, has emerged, as discussed above. Thus, the term *orexin* seems unnecessarily restrictive for a peptide system involved in multiple homeostatic mechanisms. Given the burgeoning literature about these fascinating peptides (more than 200 citations in 2 years), we suggest a homogenous nomenclature.

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