A propos d'un nouveau neuromédiateur, l'hypocretin. Sa place dans la neurophysiologie du sommeil, du bâillement, et de l'appétit (7)

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Il est réconfortant de penser qu'on ait récemment, en 1998, découvert un nouveau neuromédiateur et d'imaginer qu'il en reste d'autres à découvrir pour éclairer les fonctionnements inexpliqués de notre cerveau.

En 1998, deux groupes de chercheurs, sans lien entre eux, découvrent simultanément le même neuropeptide, baptisé "hypocretins" par de Lecea (2) et "orexins" par Sakurai (12). Le plus étonnant reste la découverte en elle-même, car les cellules sécrétrices, peu nombreuses, sont localisées dans une infime partie de l'hypothalamus latéral. Les première observations ont montré un rôle dans la stimulation de la satiété, d'où son appellation orexin (injections dans les ventricules cérébraux du cerveau de rats (3,4,6).

La découverte, en 1999, que la narcolepsie (1,5) canine était due à une mutation d'un gêne codant pour un des récepteurs à l'hypcretin (Hcrt2), a encouragé d'étendre les recherches du contrôle de l'appétit à la régulation du sommeil. Il apparut rapidement que l'absence d'hypocrétine chez la souris avait d'importants effets sur le comportement et le sommeil rappelant la narcolepsie ou maladie de Gélineau (7,10).

D'autres études indiquèrent les importantes projections des cellules hypophysaires sécrétrices d'hypocrétinee vers toutes les cellules monoaminergiques, et l'effet de stimulation de l'éveil ainsi engendré (3).

Des mesures récentes ont indiqué que les patients atteints de narcolepsie avaient des taux effondrés d'hypocrétinee dans le système nerveux central. A l'heure présente, il semble que la principale cause de la narcolepsie soit une destruction par auto-immunité des cellules hypophysaires sécrétrices. Les gênes déterminant l'apparition des récepteurs à l'hypocrétinee sont identifiés, ainsi que deux types de petides actifs sur deux types de récepteurs (10,11).

La neuroanatomie montre que les cellules hypothalamiques sécrétrices projettent sur tout le cortex, le tronc cérébral, le système limbique, le thalamus, et vers la moelle épinière. Des projections denses et monosynaptiques vers le locus coeruleus (3,8) indiquent l'importance de ce peptide dans la régulation de l'éveil. Autre constat crucial, la répartition des deux types de récepteurs à l'hypocrétinee ont des distributions anatomiques différentes : le locus coeruleus noradrénergique est couplé de façon dense avec le type Hcrt1 et ne contient pas de Hcrt2; le nucleus tubero-mammillaire histaminergique contient exclusivement des Hcrt2. L'effet semble essentiellement excitateur, surtout au niveau du locus coeruleus, des noyaux du raphé, de la substantia nigra, des noyaux tuberomammillaires (10,11,13)

La différence d'expression de Hctr1 et Hctr2 peut expliquer le rôle primordial de Hctr2 dans la narcolepsie. Chez l'animal, la destruction des récepteurs Hctr2 engendre un tableau de blocage d'activité motrice comparabale à la cataplexie et des accès de sommeil paradoxal. D'autre part, des animaux porteurs de mutations de Hctr1 ont des perturbations de leur sommeil lent profond sans cataplexie (7,10,11,13)

Il n'existe à ce jour aucune donnée répertoriée étudiant le bâillement dans la narcolepsie. La place de l'hypocrétinee dans la neurophysiologie du bâillement reste à décrire mais ne peut pas ne pas exister.

L'effet orexigène de l'hypocrétinee, avec un rythme circadien confirmé, semble jouer un rôle central dans la régulation homéostasique de l'apport alimentaire (2,12). L'obésité est associée à une réduction d'activité, un excès de somnolence mais aucune donnée actuelle ne permet d'attribuer à un déficit d'hypocrétinee une cause à certaines obèsités. L'injection intraventriculaire cérébrale d'hypocrétine chez l'animal (6), potentialise la stimulation adrénergique avec libération de cortisol,

réduction de la prolactine et de l'hormone de croissance. Chez l'homme la prolactine et l'hormone de croissance sont au plus bas pendant le sommeil; le cortisol ne varie pas au cours de la narcolepsie (7).

En général, les carnivores bâillent plus que les herbivores, comme les variations du niveau de leur vigilance le laissent prédire (Baenninger). En effet, le rythme de vie des carnivores est caractérisé par d'importantes variations du niveau de vigilance, depuis la tranquilité somnolente, à la marche, la course après une proie, la chasse, le dépeçage. Au contraire, la vie des herbivores est relativement monotone, et ils passent la plupart de leur temps à brouter; la difficulté à fabriquer des protéines à partir de l'herbe obligent ces mammifères à passer beaucoup plus de temps de leur éveil à en ingérer. On peut supposer ici un rôle régulateur de l'hypocrétine sur le sommeil et l'homéostasie énergétique et donc sur la fréquence des bâillements.

Les observations de patholologie humaine montrent le bâillement par excès comme signe sémiologique d'une éventuelle pathologie hypophysaire. Par exemple, l'acromégalie, excès de fabricaton d'hormone de croissance, se révèle par des troubles osseux classiques mais aussi par une asthénie, une somnolence associée à des bâillements répétés. L'adénome hypophysaire peut comprimer les cellules sécrétrices d'hypocrétinee, perturber leur sécrétion; l'augmentation d'hormone de croissance circulante peut engendrer un rétrocontrôle négatif sur la sécrétion de d'hypocrétinee. Tout reste à découvrir.

Les très intenses interactions de l'hypocrétinee avec le système aminergique tant moléculaire que cellulaire lui font jouer un rôle dans la régulation de l'éveil. Comment ne pas penser que l'hypocrétinee a sa place dans la neurophysiologie du bâillement ?

1. **Chemelli R M, JT Willie et al. (1999).** "Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation." Cell 98(4): 437-51.... Neurons containing the neuropeptide orexin (hypocretin) are located exclusively in the lateral hypothalamus and send axons to numerous regions throughout the central nervous system, including the major nuclei implicated in sleep regulation. Here, we report that, by behavioral and electroencephalographic criteria, orexin knockout mice exhibit a phenotype strikingly similar to human narcolepsy patients, as well as canarc-1 mutant dogs, the only known monogenic model of narcolepsy. Moreover, modafinil, an anti-narcoleptic drug with ill-defined mechanisms of action, activates orexin-containing neurons. We propose that orexin regulates sleep/wakefulness states, and that orexin knockout mice are a model of human narcolepsy, a disorder characterized primarily by rapid eye movement (REM) sleep dysregulation.
2. **de Lecea L, TS Kilduff et al. (1998)**. "The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity." Proc Natl Acad Sci U S A 95(1): 322-7.... We describe a hypothalamus-specific mRNA that encodes preprohypocretin, the putative precursor of a pair of peptides that share substantial amino acid identities with the gut hormone secretin. The hypocretin (Hcrt) protein products are restricted to neuronal cell bodies of the dorsal and lateral hypothalamic areas. The fibers of these neurons are widespread throughout the posterior hypothalamus and project to multiple targets in other areas, including brainstem and thalamus. Hcrt immunoreactivity is associated with large granular vesicles at synapses. One of the Hcrt peptides was excitatory when applied to cultured, synaptically coupled hypothalamic neurons, but not hippocampal neurons. These observations suggest that the hypocretins function within the CNS as neurotransmitters.
3. **Hagan J J, R A Leslie et al. (1999)**. "Orexin A activates locus coeruleus cell firing and increases arousal in the rat." Proc Natl Acad Sci U S A 96(19): 10911-6.... The localization of orexin neuropeptides in the lateral hypothalamus has focused interest on their role in ingestion.

The orexigenic neurones in the lateral hypothalamus, however, project widely in the brain, and thus the physiological role of orexins is likely to be complex. Here we describe an investigation of the action of orexin A in modulating the arousal state of rats by using a combination of tissue localization and electrophysiological and behavioral techniques. We show that the brain region receiving the densest innervation from orexinergic nerves is the locus coeruleus, a key modulator of attentional state, where application of orexin A increases cell firing of intrinsic noradrenergic neurones. Orexin A increases arousal and locomotor activity and modulates neuroendocrine function. The data suggest that orexin A plays an important role in orchestrating the sleep-wake cycle.

4. **Hakansson M, L de Lecea et al. (1999).** "Leptin receptor- and STAT3-immunoreactivities in hypocretin/orexin neurones of the lateral hypothalamus." J Neuroendocrinol 11(8): 653-63. ... Hypocretins/orexins are recently characterized peptides that are synthesized in neurones of the lateral hypohalamus and stimulate food intake in rats. To clarify whether leptin may interact with hypocretin/orexin to reduce ingestive behaviour, the presence of leptin receptor-immunoreactivity in hypocretin/orexin-containing neurones was examined. Many leptin receptor-and hypocretin/orexin-immunoreactive neurones were demonstrated in the lateral hypothalamic area and perifornical region. Both direct double-labelling and elution-restaining methods showed that leptin receptor-immunoreactivity was present in the vast majority of hypocretin/orexin-containing neurones. Immunoreactivity for STAT3, a transcription factor activated by leptin, was also demonstrated in hypocretin/orexin-containing neurones. Isolated hypocretin/orexin cell bodies in the dorsal part of the lateral hypothalamic area and the ventral perifornical region were shown to contain immunoreactivity for galanin, another peptide known to affect feeding. Galanin neurones were also seen to contain leptin receptor-and STAT3-immunoreactivity. Melanin-concentrating hormone (MCH)-containing neurones constituted a cell population within the lateral hypothalamus distinct from the one containing hypocretin/orexin-immunoreactivity, as shown by elution-restaining methodology. The presence of leptin receptor-and STAT3-immunoreactivities in hypocretin/orexin-containing neurones of the lateral hypothalamus suggests that leptin may directly regulate these hypothalamic neurones, most likely via an inhibitory action on hypocretin/orexin expression and/or secretion resulting in reduced food intake.
5. **Lin L, J. Faraco et al. (1999).** "The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene." Cell 98(3): 365-76....Narcolepsy is a disabling sleep disorder affecting humans and animals. It is characterized by daytime sleepiness, cataplexy, and striking transitions from wakefulness into rapid eye movement (REM) sleep. In this study, we used positional cloning to identify an autosomal recessive mutation responsible for this sleep disorder in a well-established canine model. We have determined that canine narcolepsy is caused by disruption of the hypocretin (orexin) receptor 2 gene (Hcrtr2). This result identifies hypocretins as major sleep-modulating neurotransmitters and opens novel potential therapeutic approaches for narcoleptic patients.
6. **Lubkin M and A Stricker-Krongrad (1998).** "Independent feeding and metabolic actions of orexins in mice." Biochem Biophys Res Commun 253(2): 241-5.... Orexin-A and orexin-B (OX peptides) are two putative products of a newly discovered secreted protein encoded by a mRNA restricted to neuronal cell bodies of the lateral hypothalamus (LH). Because the activation of the LH can induce changes in energy balance, we wanted to investigate the actions of OX peptides on energy metabolism in mice. We injected male C57BL/6J mice with different doses (1, 3, and 10 nmol) of orexin-A and orexin-B into the third ventricle (i3vt). A single i3vt injection of orexin-A 3 h into the light period slightly stimulated feeding at the lowest dose only over the following 4 h (11 +/- 09 mg/mouse vs 80 +/- 13 mg/mouse, $p < 0.05$). Orexin-B showed

no effects at any dose. We therefore investigated the effects of 3 nmol orexin-A on energy utilization using indirect calorimetry. Single i3vt injection 3 h after light on, or just before dark onset, or in 4-h fasted mice resulted in increases in the metabolic rate. These effects were associated with decreases or increases in the respiratory quotient regarding the time of injection or the underlying metabolic state of the mice. The present findings provide direct evidence that OX peptides are more likely to be involved in the control of energy metabolism than of food intake in mice.

7. **Mignot E. (2001).** "A commentary on the neurobiology of the hypocretine/orexin system." Neuropsychopharmacology 25(5 Suppl): S5-13... hypocrtin/orexins are rapidly emerging as functionally important neurotransmitters. Two related neuropeptides (Hcrt-1/OXA, Hcrt-2/OXB) encoded by the same precursor gene and two G-protein coupled receptors (Hcrtr1/OXR1, Hcrtr2/OXR2) are currently known. hypocrtinee-containing cells are discretely localized within the perifornical hypothalamus but have widespread projections, with generally excitatory postsynaptic effects. Dense excitatory projections to all monoaminergic cell groups have been reported. A major emerging function for this system is likely to be the regulation of sleep. Alterations in hypocretin neurotransmission causes the sleep disorder narcolepsy in mice, dogs and humans. Effects on appetite, neuroendocrine and energy metabolism regulation are also suggested by other studies. hypocrétines are uniquely positioned to link sleep, appetite and neuroendocrine control, three behaviors of major importance in psychiatry. The potential role of this system in regulating the sleep cycle, modulating wakefulness at selected circadian times and in mediating the deleterious effects of sleep deprivation is discussed.
8. **Moore R Y, E A Abrahamson et al. (2001).** "The hypocretin neuron system: an arousal system in the human brain." Arch Ital Biol 139(3): 195-205... hypocretin are recently discovered neuropeptides produced by a small group of posterior hypothalamic neurons which project widely over the neuroaxis. In this study, we note that hypocretin neuron perikarya in the human brain are localized to the perifornical region of the posterior hypothalamus, extending into the lateral hypothalamus. These neurons lightly innervate all areas of cerebral cortex studied in a variable pattern with denser innervation of association cortex than primary motor or sensory cortex. There is a dense innervation of hypothalamus, locus coeruleus, raphe nuclei, midline thalamus and nucleus of the diagonal band-nucleus basalis complex of the forebrain. This pattern of projections from the hypocrétinee neurons is compatible with an important role in arousal and the maintenance of the waking state.
9. **Nishino S, B Ripley et al. (2000).** "Hypocretin (orexin) deficiency in human narcolepsy." Lancet 355(9197): 39-40. Alterations in the hypocretin receptor 2 and preprohypocretin genes produce narcolepsy in animal models. Hypocretin was undetectable in seven out of nine people with narcolepsy, indicating abnormal hypocretin transmission.
10. **Overeem S, E Mignot et al. (2001).** "Narcolepsy: clinical features, new pathophysiologic insights, and future perspectives." J Clin Neurophysiol 18(2): 78-105.... Narcolepsy is characterized by excessive daytime sleepiness and abnormal manifestations of rapid eye movement sleep such as cataplexy. The authors review the clinical features of narcolepsy, including epidemiology, symptoms, diagnosis, and treatment, in detail. Recent findings show that a loss of hypocretin-producing neurons lies at the root of the signs and symptoms of narcolepsy. The authors review the current state of knowledge on hypocretin anatomy, physiology, and function with special emphasis on the research regarding the hypocretin deficiency in narcolepsy, which may also explain associated features of the disorder, such as obesity. Lastly, they discuss some future perspectives for research into the pathophysiology of sleep/wake disorders, and the potential impact of the established hypocretin deficiency on the diagnosis and treatment of narcolepsy.

11. **Peyron C, J Faraco et al. (2000).** "A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains." Nat Med 6(9): 991-7... We explored the role of hypocretins in human narcolepsy through histopathology of six narcolepsy brains and mutation screening of Hcrt, Hcrtr1 and Hcrtr2 in 74 patients of various human leukocyte antigen and family history status. One Hcrt mutation, impairing peptide trafficking and processing, was found in a single case with early onset narcolepsy. In situ hybridization of the perifornical area and peptide radioimmunoassays indicated global loss of hypocretins, without gliosis or signs of inflammation in all human cases examined. Although hypocretin loci do not contribute significantly to genetic predisposition, most cases of human narcolepsy are associated with a deficient hypocretin system.
12. **Sakurai T, A Amemiya et al. (1998).** "Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior." Cell 92(4): 573-85... The hypothalamus plays a central role in the integrated control of feeding and energy homeostasis. We have identified two novel neuropeptides, both derived from the same precursor by proteolytic processing, that bind and activate two closely related (previously) orphan G protein-coupled receptors. These peptides, termed orexin-A and -B, have no significant structural similarities to known families of regulatory peptides. prepro-orexin mRNA and immunoreactive orexin-A are localized in neurons within and around the lateral and posterior hypothalamus in the adult rat brain. When administered centrally to rats, these peptides stimulate food consumption. prepro-orexin mRNA level is up-regulated upon fasting, suggesting a physiological role for the peptides as mediators in the central feedback mechanism that regulates feeding behavior.
13. **Salin-Pascual R, D Gerashchenko et al. (2001)**. "Hypothalamic regulation of sleep." Neuropsychopharmacology 25(5 Suppl): S21-7... The recent discovery linking narcolepsy, a sleep disorder characterized by very short REM sleep latency, with a neuropeptide that regulates feeding and energy metabolism, provides a way to understand how several behaviors may be disrupted as a result of a defect in this peptide. In this chapter we review the evidence linking hypocrétinee and sleep, including our own studies, and propose that a defect in the lateral hypothalamus that also involves the hypocrétinee neurons is likely to produce a disturbance in sleep, mood, appetite, and rhythms.
14. **Sato-Suzuki I, I Kita, et al. (2002)**. "Cortical arousal induced by microinjection of orexins into the paraventricular nucleus of the rat." Behav Brain Res 128(2): 169-77.. Orexin-A is a neuropeptide which has been suggested to be involved in sleep and arousal mechanisms. Orexin-A, for example, stimulates arousal when administrated intracerebroventricularly to rats. We attempted to identify specific neural sites of orexin-A and orexin-B action. Orexin-A and orexin-B were microinjected into the medial parvocellular subdivision of the paraventricular nucleus (PVN) in anesthetized, spontaneously breathing rats, and cortical arousal and yawning responses were assessed. Cortical arousal responses were monitored with the electrocorticogram (ECoG), and yawning responses were evaluated by monitoring intercostal electromyograms as an index of inspiratory activity and digastric electromyograms as an indicator of mouth opening. We also measured blood pressure and heart rate during yawning responses, since yawning is accompanied by changes in autonomic activity. Microinjection of orexin-A into the PVN elicited an arousal shift in the ECoG to lower voltage and faster rhythms. This cortical arousal response was followed by a single large inspiration with mouth opening, i.e. a yawning response. On the other hand, microinjection of orexin-B into the PVN elicited an arousal shift in the ECoG without yawning responses. These results demonstrate that an orexin receptive site for triggering arousal/yawning responses exists in the PVN, and suggest that the PVN is involved in arousal mechanisms.