proteinspotlight
> ONE MONTH, ONE PROTEIN <

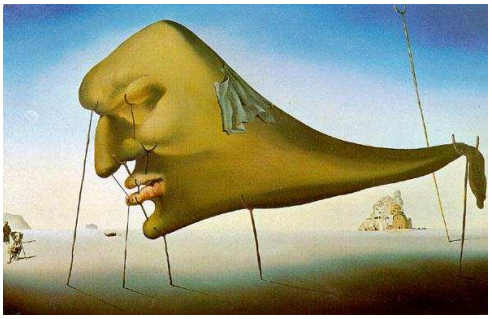
Issue 15, October 2001

www.proteinspotlight.org

«Qui dort dîne»

Vivienne Baillie Gerritsen

In China, there is an old legend which says that Buddha (?563-483 BC) slit his eyelids off in a struggle to stay awake. They fell to the moist ground below, from which grew a red flower, the opium poppy. Opium was used as a narcotic as early as 4'000 BC in Sumerian and European cultures. In 1753, the Swedish botanist Linnaeus classified the poppy as *Papaver somniferum*, a sleep-inducing plant. Would it not be handy to discard one's eyelids to fight off somnolence? Patients suffering from narcolepsy would certainly agree. Narcolepsy is an inconvenient sleep disorder where those afflicted with it fall asleep at any time of the day. Since 1998, much research has been made in this field following the discovery of a small protein that has a role in our state of wakefulness: hypocretin.



'The Dream', Salvador Dali

What exactly is narcolepsy? The French neuropsychiatrist Jean Gélineau first described the state as a human pathology in 1880. He had observed patients who experienced bouts of "irresistible sleep without apparent cause, and curious attacks on emotion in which the muscles relax suddenly, so that the victim sinks to the ground fully conscious but unable to move". The latter condition, which can be set off by mere laughter, describes what is now known as cataplexy.

Narcoleptics suffer from both conditions. In the second half of the 20th century it became apparent that there was a link between narcolepsy, cataplexy and rapid eye movement (REM) sleep. REM sleep is the period of sleep in which we dream and in which muscle tone is completely abolished. Narcoleptics fall into REM sleep much faster than normal individuals and muscle atonia characterises cataplexy. This is why it is thought that hypocretins may have a key role in the onset of REM sleep.

Hypocretins are neuropeptides and were first discovered in 1998 by two independent teams. J.G. Sutcliffe from the Scripps Research Institute in California was looking into the hypothalamus where processes such as eating, reproduction and sleep are controlled. His attention was drawn to a cluster of cells situated in the lateral hypothalamus, where he observed the synthesis of exclusive proteins: the hypocretins. So named because they are made and secreted in the hypothalamus.

M. Yanagisawa from the University of Texas set off in a more drug-oriented direction. His attention was focused on G protein-coupled receptors, which are key drug targets. If we know what effect is generated by a molecule hitting its receptor then we are on the way to finding how the said effect is blocked or enhanced. Yanagisawa's team stumbled upon a couple of peptides which stimulated two orphan receptors located in the lateral hypothalamus. Since the hypothalamus is known to direct a number of bodily functions that includes food intake, Yanagisawa – perhaps rather rashly – termed the peptides orexins, from the Greek 'orexis' meaning appetite. Indeed, when his team injected the peptides into the brains of rats, they ate more. But when they spied on the mice overnight, they discovered that their behaviour was comparable to narcolepsy: while walking or grooming, the mice would suddenly collapse apparently fast asleep.

Hypocretins/orexins are synthesized in specialised neurons of the dorsal and lateral hypothalamic areas, and are found in secretory vesicles in fibres which project within the

hypothalamus and to other parts of the brain. They come in pairs processed from a common precursor, preprohypocretin. The role of hypocretin in normal sleep is uncertain. It has a wake-promoting effect, which could be mediated by complementing the monoaminergic and cholinergic systems in the sleep cycle via excitatory hypocretin receptors. Maximum hypocretin activity occurs during wakefulness and REM sleep. However, the link between hypocretin abnormalities and narcolepsy is now established. In dogs, narcolepsy seems to be the result of mutations of one of the hypocretin receptors. Human narcolepsy, on the other hand, is caused by a lack of hypocretin. Indeed, hypocretin levels were almost non-existent in post-mortem brains of human narcoleptics. Instead, scar tissue was found indicating that hypocretin-producing cells are most likely destroyed. Hence, human narcolepsy could be an auto-immune disease.

In 1998, the news that orexins had a role in the regulation of appetite swept around the world. Here could be a remedy to obesity, anorexia and other forms of eating disorders. Since then, their involvement in sleep has also been shown, thus demonstrating the direct involvement of orexins in metabolic regulation. Classic experiments were carried out in the 1980s where it was shown that animals with lateral hypothalamic lesions ate less but put on weight nevertheless, thus suggesting a shift in overall energy homeostasis. How this works on the molecular level is still unknown. One interesting application is being carried out in the field of agriculture. One in ten piglets dies shortly after birth because of poor food intake. What if this food intake were boosted? Some researchers in Missouri did just this. Orexin was injected into a number of piglets whose appetite was indeed increased, though only over a short period. Trials at regular intervals could be a solution, or even transgenic pigs.

The development of drugs that could mimic hypocretin or clog its receptors would help to fight against disorders such as narcolepsy, insomnia, obesity and anorexia. However, as more and more research is being carried out, hypocretins are beginning to bear a rather heavy burden. Researchers have also reported a role in the transmission of pain, cardiovascular activity and hormone secretion. In effect, hypocretins seem to be involved in a far larger and more complex system which regulates major bodily functions. And the question is will any dabbling with this system not have undesired side effects? Will the pursuit of sleep and appetite not upset some other vital function?

Cross-references to Swiss-Prot

Orexin, *Bos taurus* (Bovine) : P56717
Orexin, *Canis familiaris* (Dog) : Q9GLF6
Orexin, *Homo sapiens* (Human) : O43612
Orexin, *Mus musculus* (Mouse) : O55241
Orexin, *Sus scrofa* (Pig) : O77668
Orexin, *Rattus norvegicus* (Rat) : O55232

References

1. Hungs M., Mignot E.
   Hypocretin/orexin, sleep and narcolepsy
   Bioessays 23:397-408(2001)
   PMID: 11340621

2. Willie J.T., Chemelli R.M., Sinton C.M., Yanagisawa M.
   To eat or to sleep? Orexin in the regulation of feeding and wakefulness
   Ann. Rev. Neurosci. 24 :429-458(2001)
   PMID: 11283317

3. Chicurel M.
   The sandman's secrets
   Nature 407:554-556(2000)
   PMID: 11034181

Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).