

Why Sleep and Leptin are Yoked?

Reader Summary

1. How does sleep begin?
2. Is there a disease that helps us understand how diet and sleep are linked?
3. Neuroanatomical reasons to reject the “set point” theory of obesity.
4. Why are addiction, metabolism and sleep all linked?
5. Did you know that one cause of central leptin resistance maybe autoimmune damage similar to celiac?

To begin to understand how sleep interacts with metabolism, we need to understand a bit about neuroanatomy. In sleep, the cerebral cortex is in a state of cortical synchronization. In wakefulness, several subcortical regions of the brain stimulate the cortex to remove this synchronization. When DHA is lacking cortical synchronization is not able function optimally. When we undergo slow wave non REM sleep (drowsiness) there are a small group of neurons in the hypothalamus called VLPO neurons that are GABAergic (inhibitory) and they fire on the subcortical areas that are stimulating the cortex. In doing so, these VLPO neurons bring about cortical synchronization. After sleep begins, NREM sleep gives way to REM sleep. During REM sleep there is a coordination of cross talk between the grey matter brainstem nuclei while cortical synchronization is maintained. This is quite complex coordination of events that occurs in the brain while we sleep. A common disease of dis-coordination of sleep is narcolepsy. In other words, the tracts that normally control the stages of sleep occur out of sequence and cause people to fall asleep and lose muscle control in wakefulness. Narcolepsy occurs because we lose a specific set of neurons in

the hypothalamus that effects this coordination of signals. These neurons are called the hypocretin neurons (HC). These neurons are found in the ventral lateral hypothalamus in a small area that also control appetite and feeding. These neurons also effect loops that effect feeding. There is no set point. When we lose HC neurons we set up the neurochemistry that becomes resistant obesity. The dopamine tracts are the direct targets of the HC neurons. We don't see obesity as a common phenotype when we see tumors of surgical ablation of these dopamine outflow tracts. This is the main reason many do not believe there is a set point for obesity. The hypocretin neurons sit scattered through many MSH cells (also involved in obesity). The HC neurons make two peptides called (hypocretin 1 and 2)HCrT1 and HCrT2. In the literature, these peptide hormones are also known as the orexins so you do not get confused. These peptides are remarkably similar to gut incretin hormones that help tell the brain what type of foods (electrons) are present in the gut. Another remarkable trait of the hypocretin neurons is that in the human brain there is only 50,000 total HC neurons in an organ with over one trillion cells. And they appear to be very new in mammalian phylogeny. It appears mammals handle sleep and energy metabolism very differently than the rest of the living. The small amount of HC neurons, however, project widely all over the brain. We now know that the hypocretin neurons control the stability of wakefulness or our arousal. It appears they may also control energy metabolism via leptin function.

The HC neurons also stimulate appetite. So they control two vital behaviors in humans simultaneously. This is called pleiotrophic behavior of the neuropeptides. This is where the story gets interesting between sleep, metabolism, and addiction. The HC neurons are excited by Leptin, glucose, and gherlin hormones. They are also stimulated by NPY, NYY, and cortisol releasing factor (a glucocorticoid). Remember that high cortisol levels chronically are generally a bad thing for

the brain. We saw that in my [Hormone 101 blog](#) in relation to obesity and leptin resistance. Leptin resistance long term ALWAYS leads to hyper-cortisolism. This also increases the excitation of the HC neurons. Drug addiction also begins with hyper-cortisolism and causes the nucleus accumbens to make higher amounts of dopamine while the rest of our brain has lower levels of serotonin. Obesity begins with inflammation but once it is firmly established in humans they become centrally leptin resistant. Long term this causes high cortisol levels to be made chronically as well. Those high levels of cortisol appear to knockout HC neurons where leptin signal transduction occurs in the brain. This effect maybe mediated by a leaky gut due to molecular mimicry. [In effect, we become centrally leptin resistant.](#)

The outflow of the HC neurons directly feeds to the dopamine tracts and receptors that were thrown about (Median forebrain bundle and ventral segmental area) in Stephen Guyenet's series on food reward. They also are excitatory to the Acetylcholine tracts of the pre frontal cortex and to histaminergic system in the brain. While I enjoyed Stephen's series, I think it missed the obesity target because it did not focus in on the effect of leptin on the small numbers of HC neurons. This is precisely where central leptin resistance effects are felt. Leptin resistance knocks out hypocretin neuronal function. There is also current research being done to see if the effects of chronically lowering hypocretin neuron numbers could cause a lack of coordination of tracts involving leptin function and food seeking behavior. This has biologic plausibility because there exists another human disease with hypocretin neuron losses effect its targeted behavior. That disease is narcolepsy-cataplexy.

It appears that leptin, and other metabolic cues, stimulate the 50,000 HC cells to lead to a coordinated response in the arousal centers of the brain. This has huge implications for sleep, eating and drug seeking behavior. [George Koob](#) is a very

famous addiction researcher found that when he placed mice in an operant conditioning cage with an active button that delivered a cocaine dose and an inactive one that did not, the animals learned to push the cocaine button quickly. The behavior of pressing the active button was then extinguished to cocaine but yoked to cues that could be described as drug seeking behavior in the mice. This learning occurred quickly. Then, Luis de Lecea from Stanford University, tested these animals with HCrT1 peptide instead of cocaine and he found that HCrT1 also caused continuation of drug seeking behaviors without any cocaine in the experiment. Moreover, the infusion of HCrT1 peptide also caused the animals to have higher levels of cortisol present which also seemed to independently drive their drug seeking behaviors without any cocaine being present. A second experiment was done to see if an HCrT1 receptor antagonists would diminish the drug seeking behavior and diminish the stress response. This is precisely what occurred in the Stanford experiments

It is also well known in psychiatry and sleep literature that patients with narcolepsy-cataplexy are extremely resistant to all forms of drug abuse but not to obesity! It is clear that the HC neurons are extremely important in energy balance and sleep. It appears this is the tract in the brain where dual control funnels down to. It also helps explain why most people who are obese also tend to have central sleep apnea. Central administration of orexin A/hypocretin-1 strongly promotes wakefulness, increases body temperature, locomotion, and elicits a strong increase in energy expenditure. This is what one sees in extreme leptin sensitivity with UCP1 and UCP3 uncoupling. Sleep deprivation also increases orexin A/hypocretin-1 transmission. The orexin/hypocretin system may thus be more important in the regulation of energy expenditure than food intake. In fact, orexin/hypocretin-deficient narcoleptic patients have increased obesity rather than decreased BMI, as would be expected if orexin/hypocretin were primarily an appetite stimulating peptide. In humans,

narcolepsy is associated with a specific variant of the human leukocyte antigen (HLA) complex. Furthermore, genome-wide analysis shows that, in addition to the HLA variant, narcoleptic humans also exhibit a specific genetic mutation in the T-cell receptor alpha locus. In conjunction, these genetic anomalies cause the autoimmune system to attack and kill the critical hypocretin neurons. Hence the absence of hypocretin-producing neurons in [narcoleptic humans](#) may be the result of an autoimmune disorder. This could occur via a defect in molecular mimicry as seen in the leaky gut due to toll receptor proteins. When DHA is deficient, so are electrons and toll receptor proteins do not not work well and the gut becomes more leaky. Similar mechanisms are seen in Celiac disease, Hashimoto's thyroiditis, Crohn's disease, and psychiatric disorders such as GAPS.

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