An appetite for sleep?

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Rapid eye movement (REM) sleep is one of the least understood aspects of neuroscience. Much of the mechanisms and purposes behind this extraordinary brain state remain unknown, but it has been associated with sensorimotor development (Rio-Bermudez et al. 2017), consolidation of memories (Li et al. 2017), and dreaming (Perogamvros et al. 2013). As opposed to the dominating stage of sleep, non-REM, REM sleep is characterized by its signature behavior of rapid eye movement during sleep, which is remarkably similar to eye movement during wake states (Figure 1).

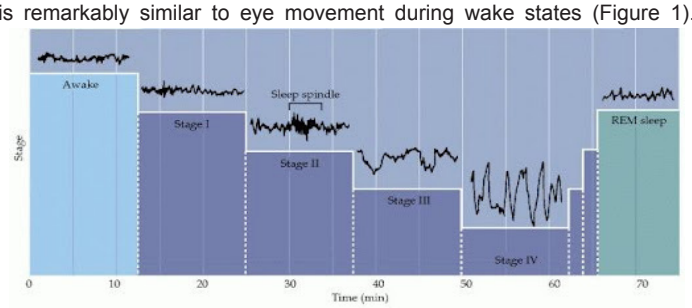

Figure 1. EEG recordings during first hour of sleep, showing wakefulness, REM, and the four stages of nREM sleep. (Purves 1970)

Among the areas in the brain that are most active during this sleep stage is the hypothalamus (Siegel 2005). It has been found that the hypothalamus plays an important role in sleep-wake cycles, and recent studies show that certain neurons in the hypothalamus are maximally active during REM sleep specifically (Hassani et al. 2010). The hypothalamus is also known to regulate a range of different functions, but it is most important for maintaining homeostasis and regulating behavior and metabolism in the brain and body (Zhou et al. 2020). One of these homeostatic behaviors is feeding habits and food consumption (Jennings et al. 2015). However, it is still unknown if REM sleep contributes to the hypothalamic control of food consumption. Answering this central question is important for understanding the role of REM sleep in maintaining certain biological functions and for the development of new treatments for disorders linked with sleep. A study by Oesch et al. (2020) reported in *PNAS* indicates there is a relationship between REM sleep and feeding in which REM sleep regulates and stabilizes the hypothalamic control of short- and long-term food intake. The authors first looked at the neuronal activity in the lateral hypothalamus (LH) of mice by assessing the calcium transients during feeding, food approach, and non-feeding. A neuron's activity is based off the concentrations of calcium inside and outside of the cell and can be calculated by measuring the influx and efflux of calcium. The more calcium flowing into the cell, the greater the activity. The mice began the trial deprived of food so they would have a high motivation to eat and then were given a free-feeding period, during which their LH neuronal activity was measured. The authors found that the LH neurons were most active during feeding and less active during food approach and non-feeding (Figure 2).

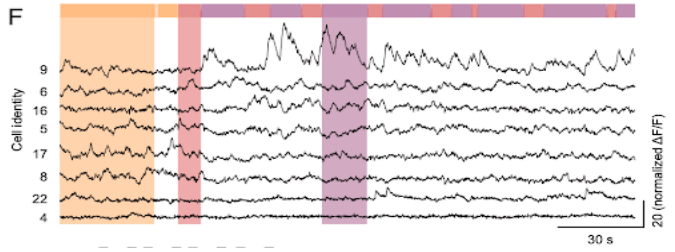

Figure 2. Calcium transients in eight LH neurons during non-feeding (orange), food approach (red), and feeding (purple). (Oesch et al. 2020)

Next, Oesch et al. (2020) turned to measuring LH activity during REM sleep. During the same trial, neuronal activity was also measured while the mice were sleeping. By comparing the calcium transients during both feeding and REM sleep, any evidence of a pattern in LH activity could be identified. The results showed that the LH activity pattern during REM sleep was similar to the activity during feeding but not any other stage (Figure 3). Not only did this finding suggest a connection between REM sleep and feeding, but it also showed that the relationship is unique to only those two stages.

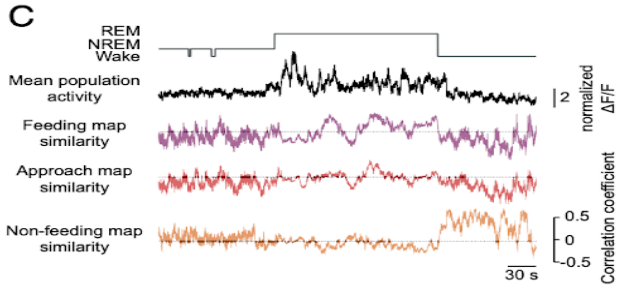

Figure 3. Feeding-associated activity compared to sleep-wake cycles. Colored graphs represent activity during different feeding patterns with black graph (lower) showing mean activity across all patterns. Corresponding sleep-wake cycles represented by black line (upper) (Oesch et al. 2020).

To test the significance of this relationship, Oesch et al. (2020) used optogenetics to ablate the LH neurons (Figure 4). Optogenetics is used to control neurons in a way similar to how a light switch controls a light bulb. While this method originated in neuroscience, it is used across many fields to study biological functions. Optogenetics is modeled off the ability of certain microorganisms to regulate ion flow across a membrane by harnessing visible light energy, and in 1971, researchers found that certain protein channels that transport these ions can be swiftly activated by light photons (Deisseroth 2011). Using this idea, scientists were able to rapidly activate or inactivate individual neurons using light. In the authors' experiment, a special light-sensitive gene was injected into the LH of mice that then allowed those select LH neurons to be activated or inactivated by light.

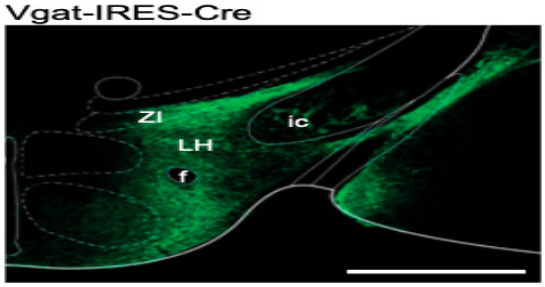

Figure 4. LH neurons infected with light-sensitive virus for optogenetic manipulation of neuronal activity (Oesch et al. 2020).

While the mice were in REM sleep, stagnant light was given in 30-second intervals during the duration of the REM sleep stage. This meant that while they were in REM sleep, those select neurons in the mice's LH were ablated and activity was inhibited for 30 seconds at a time. Following the optogenetic inhibition, Oesch et al. (2020) then observed the amount of food intake that occurred during a free-feeding period. They found that after the time of LH neuronal inhibition during REM sleep, the mice ate less food, spent less time feeding, and still had decreased levels of food intake four days after LH inhibition (Figure 5). This strongly suggests that neuronal activity in the LH during REM sleep is important for regulating short- and long-term food intake.

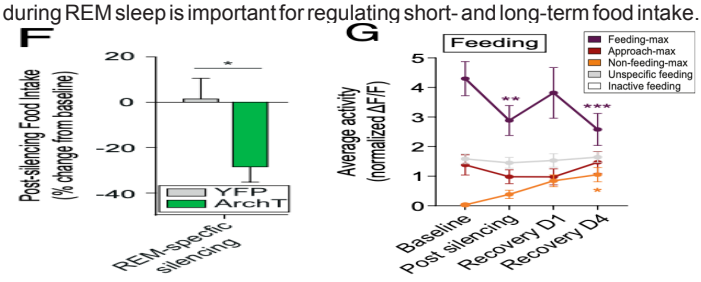

Figure 5. Average food intake post-silencing of LH neurons during

REM sleep (left). Feeding behavior across 4 days post-silencing (right) (Oesch et al. 2020).

Oesch et al. (2020)'s finding provides previously unknown functions of REM sleep and its association with LH neurons and feeding. Their discovery supports hypotheses surrounding how intuitive behaviors are modified during REM sleep as it shows its role in maintaining a necessary biological function. The continuation of the effects of the LH inhibition suggests that the impacts of LH synapses are preserved over multiple days and multiple changes in homeostasis. However, the study does not go into other possible behaviors controlled by REM sleep. The next step after considering Oesch et al. (2020)'s study is to follow up this question and investigate if REM sleep is responsible for regulation and stabilization of other homeostatic behaviors besides feeding, such as thirst or mating cycles. Additionally, the support of the idea that REM sleep plays a role in behavior modification and homeostasis is important for understanding possible implications for individuals who do not regularly reach REM sleep. Individuals suffering from sleep disorders may be at a greater risk of developing eating disorders associated with low intake of food, which could lead to other severe health implications such as loss of weight, hypothyroidism, and slow metabolism (NCEED 2018). The new connection between REM sleep and stabilized feeding behaviors could offer new therapies and treatments for those affected by sleep and eating disorders. Yet, there is still so little known about the functions of REM sleep, who knows what other treatments can be linked with this mysterious sleep stage. Understanding the relationships between REM sleep, behavior, and homeostasis is vital to fully understanding how the human brain and body are interconnected. Further research on REM sleep should help shed light on whether we are what we sleep.