Arousal neurons – neurons located in the brainstem that when active keep us awake and alert.

Ventrolateral preoptic nucleus (VLPO) – nucleus in the hypothalamus that when active, puts us to sleep.

For a complete list of defined terms, see the Glossary.

So far we've discussed the nature of sleep, its functions, and problems associated with it. Now, let's examine what researchers have discovered about the neural circuits that are responsible for sleep and its counterpart, alert wakefulness.

**Control of the sleep-wake cycle**

Our sleep-wake cycles are controlled by two main factors:

- The length of time we've been awake and active
- The time of day

**The Flip-Flop Switch**

When we are awake and alert, most of the neurons in our brain – especially those in our forebrain – are active, which enables us to pay attention to sensory information, to think about what we are perceiving, to retrieve and think about memories, and to engage in the variety of behaviors that we have to do during the day. The level of brain activity is largely controlled by the **arousal neurons** located in our brainstem (Figure 12). A high level of activity of these neurons keeps us awake, and a low level puts us to sleep.

But what controls the activity of the arousal neurons? What causes this activity to fall, and put us to sleep? We know that a region of the hypothalamus, usually referred to as the **ventrolateral preoptic nucleus (VLPO)**, is critically important for controlling when we fall asleep (Figure 12). If this area is destroyed total insomnia results. On the other hand, stimulating this area electrically can induce sleep.

**Figure 12: Neural control of sleep and wakefulness.**

Arousal neurons in the brainstem keep us awake. VLPO neurons in the hypothalamus put us to sleep.
LESSON READING

The VLPO contains sleep neurons. Their axons form inhibitory synaptic connections with the brain’s arousal neurons, and inhibit them. When our VLPO sleep neurons become active and suppress the activity of our arousal neurons, we fall asleep. The sleep neurons in the VLPO themselves receive inhibitory inputs from some of the same regions they inhibit, including the arousal neurons in the brainstem. Thus, when arousal neurons are active, they inhibit the VLPO sleep neurons and we remain awake. It is important to understand that the VLPO sleep neurons need to be active to inhibit the arousal neurons and vice versa – inhibition is an active process, just like excitation.

The fact that the sleep neurons inhibit the arousal neurons and vice versa is called a flip-flop switch that sets periods of sleep and waking. As you might imagine the flip-flop switch can only be in one of two states ‘on’ or ‘off’. If the sleep neurons are active and inhibit the arousal neurons we will be asleep. Conversely, if the arousal neurons are active and inhibit the sleep neurons, we are awake (Figure 13). Also because the two switches are mutually inhibitory, it is impossible for the neurons in both sets of regions to be active at the same time.

A flip-flop switch has one important advantage – when it switches from one state to another, it does so quickly. Clearly, it is to our advantage to be either asleep or awake. A state that has some of the characteristics of both sleep and wakefulness would be quite problematic!

Controlling the switch

There is one problem with flip-flop switches however – they can be unstable. In fact, people with narcolepsy exhibit just this characteristic. They have difficulty staying awake and they also have trouble remaining asleep for an extended amount of time.

We know from examining animals with narcolepsy that the problem lies in damage to a set of neurons called orexin neurons. The orexin neurons are located in the hypothalamus and are so named because they use the neurotransmitter orexin. Orexin neuron are connected to the arousal neurons in the brainstem and help stabilize the sleep-wake flip-flop switch (Figure 14).

DEFINITIONS OF TERMS

Orexin neurons – neurons located in the hypothalamus that use the neurotransmitter orexin. When active, these neurons activate the arousal neurons in our brainstem to keep us awake. Damage to these neurons has been implicated in narcolepsy.

For a complete list of defined terms, see the Glossary.
LESSON READING

How do orexin neurons connect to the flip-flop switch?

But how do orexin neurons stabilize the flip-flop switch? Orexin neurons are activated by light, energy balance, and the limbic system (which you’ll remember regulates emotion). These inputs cause the orexin neurons to activate the arousal neurons, tipping the activity of the flip-flop switch toward the waking state, thus promoting wakefulness and inhibiting sleep. When input to the orexin neurons from light, energy balance and limbic system stops, the orexin neurons stop activating the arousal neurons. Now the balance is shifted, allowing the VLPO sleep neurons to inhibit the arousal neurons, thus promoting sleep and inhibiting wakefulness (Figure 15).

Figure 14: The orexin neurons. Orexin neurons in the hypothalamus send projections to the arousal neurons in the brainstem to further control the flip-flop switch regulating our sleep-wake circuit.

What turns orexin neurons on? What turns them off?

Figure 15: The orexin neurons are the actual switch between being awake and being asleep. (A) When orexin neurons are stimulated by light, emotional cues or energy balance they activate the arousal neurons, which in turn inhibit the VLPO and we remain awake. (B) When input to the orexin neurons from light, energy balance and limbic system stops, the orexin neurons stop activating the arousal neurons. Now the balance is shifted and the VLPO can inhibit the arousal neurons and we fall asleep.
So what causes narcolepsy?

Narcolepsy is a relatively uncommon condition — only one case per 2,500 people — but it is a great example of a defect in the flip-flop switch that controls the transition between wakefulness and sleep, particularly REM sleep.

Narcoleptics have sleep attacks during the day, in which they suddenly fall asleep. This is socially disruptive, as well as dangerous — for example, if it strikes while they are driving. They tend to enter REM sleep very quickly, and may even enter a dreaming state while still partially awake. They also have attacks during which they lose muscle tone — similar to what occurs during REM sleep only while they are awake. These attacks of paralysis, known as cataplexy, can be triggered by emotional experiences, even by hearing a funny joke.

You can watch a profile of a patient with narcolepsy online — see this unit on the student website or click below:

Video: Narcolepsy

Narcolepsy has been traced to defects in the orexin neurons (Figure 16). For instance, two dog species that have narcolepsy naturally have an abnormality in the gene that will make a receptor for the orexin neurotransmitter. Also, if we remove the gene for orexin from mice, they immediately become narcoleptic. These mice also move directly from wakefulness to REM sleep — which is also a characteristic of patients with narcolepsy (Figure 17). Since signaling between the orexin neurons and the arousal neurons requires both the orexin neurotransmitter and the orexin receptors on the arousal neurons that recognize the transmitter, removing either of the two partners in orexin signaling between the neurons can cause narcolepsy.
Human cases of narcolepsy also show problems with the orexin signaling pathway, and have abnormally low orexin levels in the brain and spinal fluid. However human patients don’t have the genetic defects we saw in the dogs. Humans develop the disorder in their teens or 20s, and we think its because the immune system attacks the orexin neurons (like we saw in multiple sclerosis). Using brain tissues postmortem (after people have died), researchers have shown that humans with narcolepsy have far fewer orexin neurons than humans without narcolepsy (Figure 18).

Figure 18: Narcolepsy in humans is triggered by actual loss of orexin containing neurons in the hypothalamus. The pictures are data from normal patients (left panel) and narcoleptic patients (right panel). The pictures are of brain tissue after the orexin neurons have been marked with an antibody against them. Then the antibody itself is marked with a dark brown color. The dark brown spots represent neurons that contain orexin. The narcoleptic patient has far fewer orexin containing neurons than the control patient.

How did scientists realize that the orexin neurons were affected in narcoleptic humans?

You can watch a video of a narcoleptic dog online — see this unit on the student website or click below:

- Video: Snoozy the Narcoleptic Dog!
Given what you know about the causes of narcolepsy, how do you think you could treat the disorder?