

Neurotransmitters and Sleep

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Acetylcholine: Sleep and Thermoregulation

In the first part of this lesson we discussed the characteristics of the stages of sleep, the sleep cycle, and the functions of sleep. We will now explore sleep at the level of neurotransmitters and brain structures, beginning with the neurotransmitter that plays, perhaps, the largest role in sleep **acetylcholine (ACh)**.

The acetylcholine neurons that are most important in the sleep process have cell bodies in the Pons and the Basal Forebrain. The pons is located at the base of the brain just above the medulla. As we will see, structures at the base of the brain, particularly those located in the Pons, play a very big role in sleep and biological rhythms. The basal forebrain is located just in front of and above the hypothalamus (in a standing human). The ACh neurons in these two different areas, as we will see, play slightly different roles in sleep.

The activity of ACh neurons, in general, is associated with cortical arousal (increase in wave frequency) and desynchrony, as measured by an EEG. As you might suspect this plays an important role in REM sleep. There is much evidence that supports this role of acetylcholine. For example, in laboratory animals, lesions to brain areas that contain ACh cell bodies decrease cortical arousal and desynchrony, and stimulation of these areas has the opposite effect.

Before we discuss the role of ACh in REM sleep, it is important to note that the cell bodies in the basal forebrain area also play an important role in temperature regulation in the body. Interestingly, sleep and thermoregulation are strongly tied together. For example, one of the results of inhibiting sleep in lab animals is that they lose the ability to regulate their body temperature. In addition, brain and body temperature vary across stages of sleep. The basal forebrain area forms an important sleep and thermoregulation circuit with two nuclei in the hypothalamus, the **anterior hypothalamus** and the **preoptic area**. These three structures and the connections among them constitute the **POAH**. Evidence that the POAH plays a combined role in these two important processes comes from experiments that indicate that: a) lesions of the basal forebrain create insomnia, while stimulation creates drowsiness and sleepiness; b) Warming the POAH induces delta sleep; and c) POAH nerve firing increases during sleep and in response to an increase in body temperature.

Acetylcholine: REM

There is a great deal of evidence that acetylcholine is associated with REM sleep. For example, release of ACh in the cortex is highest during waking and REM sleep, and lowest during delta sleep. Further, drugs that act as ACh agonists increase REM, and antagonists decrease REM. In terms of brain structure, it appears that REM sleep initiation begins in the ACh neurons located in the pons, in one particular area called the

Peribrachial Area. In one sense, the ACh neurons in this area of the brain are "REM headquarters".

Researchers have found that this area of the brain initiates the effects of all of the principle components of REM sleep (i.e., cortical desynchronization, rapid eye movement, and skeletal paralysis). This is illustrated in Figure 1. The peribrachial area controls cortical desynchronization directly via pathways that pass through areas of the **thalamus**, and, indirectly, through ACh neurons in the basal forebrain. Rapid eye movement is initiated and maintained via ACh pathways that go to the **tectum** at the back of the brain stem. It is interesting to note that the Tectum contains two small bumps known as **superior colliculi**. The superior colliculi have been implicated as playing an important role in visual tracking and spatial location. It is not surprising, then, that such a pathway would be associated with the jerky rapid eye movement which may, very possibly, represent the pseudo-tracking of objects occurring during dreams.

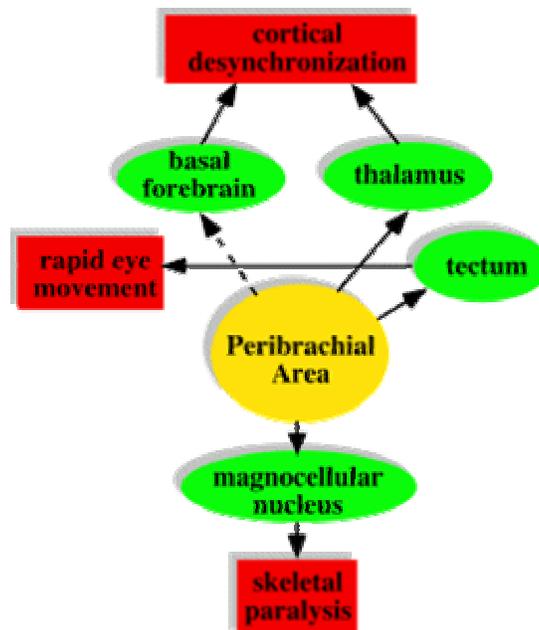


Figure 1. Peribrachial Area and Connections

The peribrachial pathway responsible for skeletal muscle paralysis is between this area and the **magnocellular nucleus** in the medulla. This nucleus sends projections to the spinal cord, which have an inhibitory effect on motor neurons. This function can be illustrated dramatically when the magnocellular nucleus of a laboratory animal is lesioned. This creates a phenomenon known as **REM without atonia**. The animals with such a lesion will apparently "act out" their dreams, due to the lack of skeletal paralysis.

Norepinephrine and Serotonin

The other two neurotransmitters that have been implicated as playing an important role in sleep are **norepinephrine (NE)** and **serotonin (5-HT)**. The cell bodies that are most

important in sleep with these two neurotransmitters are located in the **locus coeruleus** and the **raphe nuclei** for NE and 5-HT respectively. Again, both of these areas are located near the bottom of the brain stem. The locus coeruleus is located in the dorsal pons, and the raphe nuclei is a part of the reticular formation located in both the pons and the medulla. Both of these nuclei project diffusely throughout the brain, so that they have a wide reaching and general effect when stimulated.

As with ACh, both of these neurotransmitters, and the corresponding brain structures play an important role in cortical activation in general, though their specific effects are more complex. Experiments with lab animals have found that stimulation of NE neurons in the locus coeruleus or 5-HT neurons in the raphe nuclei will result in cortical arousal, and lesions to these areas will decrease cortical arousal. However, unlike ACh, this effect does not carry over into cortical arousal associated with REM. Further, the function of this arousal during waking appears to be different and specialized for NE and 5-HT. The differential function of the two neurotransmitters in cortical arousal in waking is illustrated in Figure 2. Research indicates that NE levels increase most when novel stimuli are introduced to a situation, especially when some sort of focused cognitive effort is interrupted. Thus, it has been suggested that NE plays a role in vigilance or attention, encouraging the organism to notice unusual and important stimuli. 5-HT levels, on the other hand, vary in the exact opposite manner, with levels increasing during sustained levels of cortical activation, and decreasing in response to novel stimuli. For this reason, 5-HT is thought to play a role in maintenance of cortical arousal, concentration, and suppression of distracting stimuli.

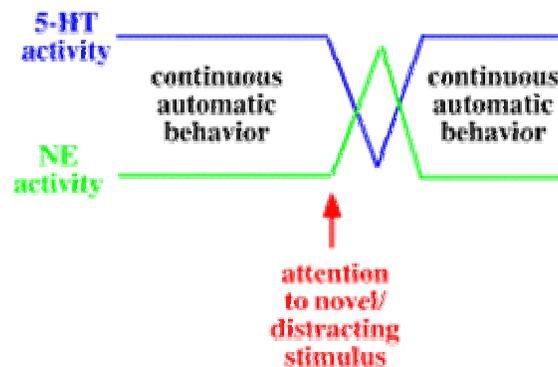


Figure 2. Differential Effect of NE and 5-HT on Cortical Arousal in Waking

As mentioned, NE and 5-HT levels do not increase with the cortical arousal and desynchronization that accompanies REM sleep. In fact, the exact opposite is the case. Both of these neurotransmitters are at their lowest levels during REM. Further NE and 5-HT agonists repress REM activity, and antagonists increase it. Thus, it appears that these two neurotransmitters play a complimentary role with ACh, in that they act to control and suppress REM activity, while ACh acts to initiate and maintain REM. In fact, NE neurons in the locus coeruleus and 5-HT neurons in the raphe nuclei both send projections, which synapse on ACh neurons in the peribrachial area.