REM SLEEP MECHANISMS AND NEUROANATOMY

REM sleep is the state in which our most vivid dreams occur. REM sleep in humans and animals can be recognized by the presence of rapid eye movements during sleep. These rapid eye movements are accompanied by "PGO waves," electrical currents resulting from bursts of neuronal activity (see REM SLEEP PHYSIOLOGY). The ponto-geniculo-occipital (PGO) waves originate in the brainstem region called the pons, and then ascend through a nucleus in the thalamus called the lateral geniculate, to the occipital cortex (see PGO WAVES). Another sign of REM sleep is low-voltage brain waves, resembling those seen during waking. The brain waves of waking and REM sleep contrast with the slower and higher-voltage brain waves seen in NREM sleep. The high-voltage waves of NREM sleep are a result of synchronized "idling" activity in adjacent cortical neurons that produces a bigger signal even though less information processing is going on. During waking, adjacent neurons tend to be active at different times so that the currents produced by the neurons cancel each other out. Therefore, the electrical signals that can be recorded from large groups of neurons in waking are smaller (see AROUSAL).

Whereas muscle tone is low in NREM sleep, it is completely absent in many muscles during REM sleep. This loss of muscle tone is thought to prevent the "acting out" of dreams. The loss of muscle tone results from the action of an inhibitory system that blocks activity in the motor neurons in the spinal cord, even while the higher motor systems within the brain are intensely active (see ATONIA).

Since its discovery, sleep researchers have attempted to localize the areas in the brain that generate the REM sleep state. Some evidence has come from brain-damaged humans; however, most has been derived from experiments on rats and cats. Two profound conclusions emerge from this work. One is that the REM sleep is substantially similar in animals and humans. The second is that the generation mechanisms for REM sleep are in the brainstem and not in the cerebral cortex. Both of these conclusions seem to be at variance with the complex symbolic representations and highly imaginative nature of dreams. One might expect that this state would be generated by higher nervous system structures and perhaps be unique to humans.

The localization of REM sleep mechanisms within the brain derives from three kinds of evidence. The first kind can be termed "lesion" evidence. The experimenter studies animals with certain brain regions removed or disconnected. If REM sleep is present after this removal, it can be concluded that the removed region is not required for generating this state.

A second kind of evidence comes from "stimulation" studies. Electrical and chemical stimulation is administered to see if REM sleep can be induced or blocked. If the critical brain area is identified and the right chemical chosen, it should be possible to control REM sleep.

A third type of evidence comes from recording. Microscopically fine electrodes can be placed near or even within neurons in the brain regions that are believed to have an important role in REM sleep control. The presence of recording electrodes does not disturb the normal pattern of sleep-wake states. The experimenter can not only observe whether the electrical activity of the recorded neurons changes in REM sleep, but also determine the neurotransmitters the cells respond to and what the connections of the cells are.

As explained below, all of these kinds of evidence indicate that a portion of the brainstem called the PONS (Figure 1) is the brain area most critical for REM sleep. It had been known since the work of the English physiologist Charles SHERRINGTON that animals could survive removal of the entire forebrain in front of the midbrain (Figure 1). After the discovery of REM sleep, Michel JOUVET analyzed the sleep and waking states in these "decerebrate" (without cerebrum) animals. He found that they had periods of muscle tone suppression with rapid eye movements PGO spikes, similar to those seen in REM sleep

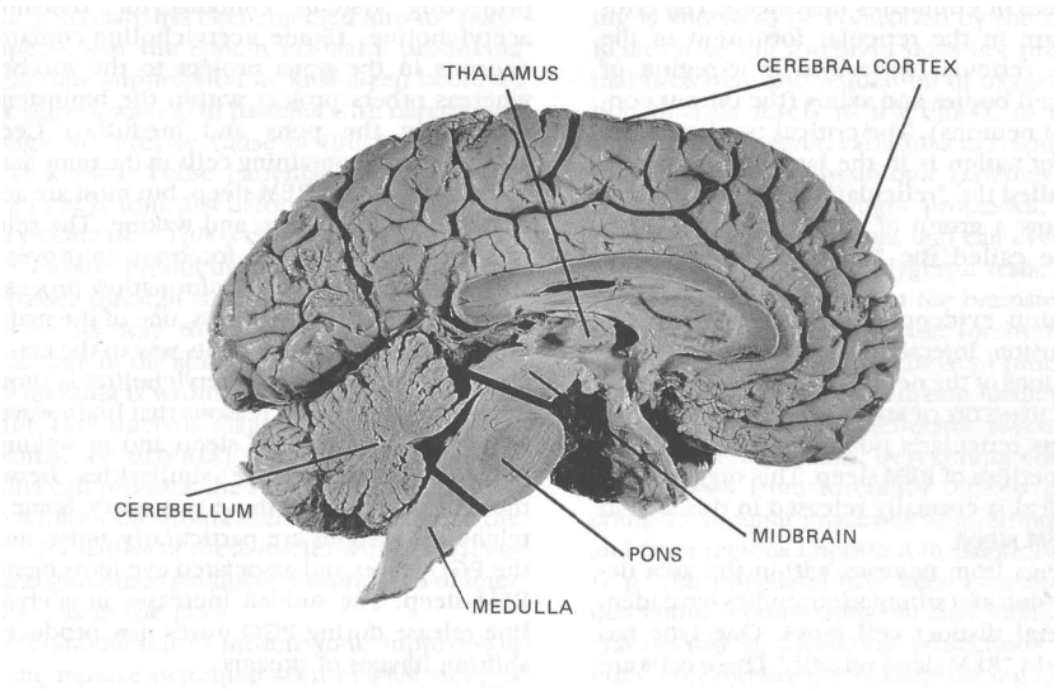

Figure 1. Midline, or "sagittal," section of the human brain, showing the medial part of the left half. The major subdivisions of the brain have been labeled.

occurred along with the eye movements. The REM sleep state (or PARADOXICAL SLEEP, as Jouvet named it) had a duration similar to that seen in the intact animal. It also recurred cyclically, as it does in the intact animal. This experiment proved that the forebrain was not essential to REM sleep.

Further work showed that REM sleep would occur in animals in which a transection was made just in front of the pons, demonstrating that most of the midbrain was not required for REM sleep. The REM sleep phenomena that can be recorded after such a transection include rapid eye movements, PGO spikes, and suppression of muscle tone. It was also shown that the spinal cord is not required for REM sleep control. Therefore, the pons and MEDULLA alone are sufficient to generate REM sleep.

It is possible to localize the brain regions responsible for REM sleep further by separating the brainstem at the junction of the pons and medulla (Figure 1). We can then look on both sides of the transection to determine which portion of the brain has REM sleep. The medulla of such an animal does not have REM sleep: periods of rapid eye movement and neuronal activity resembling that seen in REM sleep do not occur, and muscle tone is never completely suppressed. Therefore, unlike the midbrain decerebrate brain, the medullary decerebrate brain is not capable of generating REM sleep.

Whereas the disconnected medulla is not capable of generating REM sleep, the forebrain and pons, when disconnected from the medulla, produce several of the signs of REM sleep. PGO spikes can be observed in the thalamus in association with low-voltage brain waves, as in REM sleep. At these times, the activity of single neurons in the forebrain resembles that seen during REM sleep. These transection studies, therefore, led to the conclusion that the pons contains neurons critical for generating REM sleep. When the pons is connected to the medulla, REM sleep signs occur in the pontine and medullary regions. When the pons is connected to the forebrain, several REM sleep signs are seen in the pons and forebrain.

If the pons is critical for REM sleep control, then damage to it should prevent REM sleep. A number of studies have shown that damage to the

pons reduces or eliminates REM sleep. The critical areas are in the reticular formation of the pons. The reticular formation is a region of neuronal cell bodies and axons (the output connections of neurons). The critical portion of the reticular formation is in the lateral regions of a nucleus called the "reticularis pontis oralis" and is just below a group of cells containing norepinephrine called the "locus coeruleus" (see PONS).

Stimulation evidence confirms and extends this conclusion. Injections of chemicals mimicking the actions of the neurotransmitter acetylcho-line (see CHEMISTRY OF SLEEP; ACETYLCHOLINE) into the nucleus reticularis pontis oralis can trigger very long periods of REM sleep. This suggests that this chemical is normally released in this area to initiate REM sleep.

Recordings from neurons within the area defined by lesion and stimulation studies have identified several distinct cell types. One type has been called a "REM sleep-on cell." These cells are inactive (i.e., they do not release their neurotransmitter) during waking and NREM sleep, but they are extremely active during REM sleep. Some of these cells may be the ones releasing acetylcholine to trigger REM sleep. It has been shown that most of the REM sleep-on cells do not contain acetylcholine, however, indicating that other neurotransmitters are also important in REM sleep control.

A second major cell type in the critical regions of the pons is the REM sleep off cell. These cells are continuously active in waking but become inactive in REM sleep. Some of these REM sleep-off cells contain the neurotransmitter serotonin (see PONS) . These cells are located on the midline of the brainstem in an area called the "raphe" nucleus. Their activity blocks the expression of PGO waves. The inactivity of these raphe cells in REM sleep allows the PGO waves to appear. Other REM sleep-off cells located in the locus coeruleus nucleus contain the neurotransmitter norepinephrine. While these cells are not essential for generating REM sleep, they may have some role in inhibiting REM sleep. The cessation of activity in REM sleep-off cells may also "rest" the neurons with which REM sleep-off cells connect. This "rest" may be one of the functions of REM sleep (see FUNCTION OF REM SLEEP).

Certain neurons located in the pontine region important in REM sleep control project forward to affect the forebrain. One of these forward-projecting systems contains the transmitter acetylcholine. (Some acetylcholine-containing neurons in the pons project to the forebrain, whereas others project within the brainstem to regions in the pons and medulla.) Certain acetylcholine-containing cells in the pons maybe active only during REM sleep, but most are active during both REM sleep and waking. The release of acetylcholine in the forebrain improves the speed and efficiency of information processing (particularly in the THALAMUS, one of the main relays for sensory activity on its way to the cerebral cortex). The release of acetylcholine is thought to be one of the main reasons that brain wave activity is similar in REM sleep and in waking. It may also underlie the similarities between thought processes in these two states. Some acetylcholine systems are particularly active during the PGO waves and associated eye movements of REM sleep. The sudden increases in acetylcholine release during PGO waves may produce the shifting images of dreams.

By activating or inactivating particular cell groups, it is possible to impair or elicit parts of the REM sleep state. For example, damage to a small portion of the nucleus reticularis pontis oralis can disrupt the muscle tone suppression of REM sleep without preventing the rest of the state from occurring. The result is an animal that appears to act out its dreams, a syndrome called REM sleep without atonia (see ANIMALS' DREAMS; ATONIA) . A cat with REM sleep without atonia will appear to chase imaginary mice, confront imaginary foes, and explore its environment, while other aspects of its brain activity demonstrate that it is in REM sleep. Humans with damage to this system will in the same way make violent movements during REM sleep as they act out their dreams (see REM SLEEP-BEHAVIOR DISORDER) .

Small injections of acetylcholine or of glutamate, another neurotransmitter implicated in REM sleep control, into these same pontine regions can produce a complete suppression of muscle tone without the other aspects of REM sleep. Such animals appear to be fully awake, but cannot move until the chemicals wear off.

This state induced by injections of acetylcholine resembles a state seen in human patients with NARCOLEPSY. Humans with this sleep disorder will collapse when suddenly excited, a condition called CATAPLEXY. During these cataplectic attacks, the patients are awake but are unable to move, just like the animals in which acetylcho-

line or glutamate has been injected into the pons. It appears that the system normally producing muscle tone suppression in REM sleep becomes active during waking in patients with narcolepsy, although the precise cause of this triggering is not yet known. These patients also experience loss of muscle tone just before going to sleep and when waking up. (This is called SLEEP PARALYSIS.)

The circuit producing muscle tone suppression passes through the pons to the medial medulla on its way to produce suppression of muscle tone in the spinal cord. The critical relay in the medulla is within two cell groups near the midline (the nucleus magnocellularis and paramedianus; see MEDULLA). Damage to the medial medulla can produce the same syndrome of REM sleep without the atonia seen after damage to the pons. Stimulation of these nuclei with acetylcholine and glutamate produces suppression of muscle tone, as in the pons.

The combination of muscle tone suppression with the muscle twitching seen in REM sleep is what makes this state so "paradoxical." Recent work sheds light on how this combination of excitation and inhibition might be generated. Glutamate activates two kinds of receptors in the pons and medulla. One type of receptor ("non-NMDA receptors") produces suppression of muscle tone, while the other type ("NMDA receptors") produces increased motor activity. The simultaneous release of glutamate during REM sleep onto neurons with each of these receptor types may be responsible for this combination of motor excitation, producing rapid eye movements and twitches, with the simultaneous inhibition of motoneurons. The inhibition allows us to have the motor excitation accompanying our dreams, while at the same time protecting us from the injuries that would occur if we actually made these movements while we slept.

If REM sleep is generated in the brainstem, how can it produce dreams with all of their complexity? While REM sleep is present after damage to the forebrain, it is not completely normal. The patterns of eye movements in REM sleep are changed to simpler, more stereotyped sequences after forebrain damage. Studies in humans show that eye movement patterns and intensity are highly correlated with dream content. Therefore, forebrain lesions that change eye movement are likely to have altered dream content. An analogy between forebrain control of breathing and forebrain control of REM sleep can be made. Breathing is known to be controlled by the brainstem. Removal of the forebrain does not prevent normal breathing and regulation of oxygen and carbon dioxide levels in the blood. In the intact individual, however, variations in respiration and related brainstem physiologic variables are sensitive indicators of thought processes, fear, surprise, and other emotions, and can even be used to detect lying, as in polygraph tests. Although respiration is organized in the brainstem, it can clearly be controlled by the forebrain. In the same way, our highest intellectual processes can affect the physiology and dream imagery of REM sleep, even while the generator mechanism resides in the brainstem. Descending connections to the pons from forebrain regions governing complex thought processes (e.g., frontal cortex) and from regions important in emotional control (e.g., the amygdala) have been identified. These descending connections can alter REM sleep generation just as ascending projections from the pons alter forebrain processes during REM sleep. In this way our most subtle thoughts, our most intense fears and desires can interact with brain-stem mechanisms to generate our dreams.

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