

## SLEEP-WAKE NEUROANATOMY

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In this review, we will discuss thalamocortical circuits, which generate EEG rhythms; the wake-promoting cells; the sleep center; the flip-flop switch; sleep-promoting-substances; circadian influences on sleep; and a current model for REM sleep anatomy.

### THALAMOCORTICAL CIRCUITS

Richard Caton, a physiologist at the Royal Infirmary in Liverpool, is attributed with the birth of electroencephalography. He first published his findings on the observation of cortical currents in rabbits and monkeys in the *British Journal of Medicine* in 1875. Caton writes that he discovered the currents when he placed electrodes on "two points of the external surface, or one electrode on the grey matter and one on the surface of the skull." Using a mirror galvanometer, Caton observed an increase in cortical amplitudes during states of sleep as opposed to a decrement in cortical amplitudes during wakefulness, and thus Caton was the first person to detect electroencephalographic sleep (Brazier 1963).

In the late 1960's, an understanding of the role of the thalamocortical networks in the generation of sleep spindles and slow-wave sleep emerged. The major cell populations involved in this network are the gamma-aminobutyric acid (GABAergic) reticular thalamic neurons, the cortical pyramidal cells, and the T-type calcium channel thalamocortical neurons. The reticular thalamic nuclei gate the flow of information between the thalamus and cortex and the thalamocortical neurons drive cortical EEG patterns.

The low threshold spike is a phenomenon that has gained much attention over the past forty years because of its role in the firing patterns of thalamocortical neurons. The low threshold spike occurs in T-type calcium channels, which have a low voltage threshold for firing; considerable evidence points to specifically to the  $Ca_v3.1$  ( $\alpha 1G$ ) channel subunit as being responsible for the low-threshold currents. The low threshold spike involves a slowly rising and falling membrane depolarization accompanied by a burst of low-voltage threshold action potentials. In the classic model, the low threshold spike occurs when thalamocortical neurons are hyperpolarized more negatively than  $-65mV$ , causing a burst firing pattern. When the neurons are depolarized more than positively than  $-65mV$ , single action potential firing occurs, instead, producing a tonic firing pattern; this occurs during wakefulness, when wake-promoting cells excite the thalamic reticular neurons and maintain the membrane potential at a more positive state than  $-65mV$  (Steriade 1993).

Recent evidence suggests that the firing states of thalamocortical neurons are more complicated than this bistate model predicts and that high threshold bursts along with slow ( $<1Hz$ ) oscillations also occur, providing a polystate model of firing patterns. These states generate the various EEG patterns observed during sleep (Crunelli 2006).

Excitation of the reticular thalamic nuclei causes GABAergic inhibition of thalamocortical cells. With repeated inhibitory post-synaptic potentials in thalamocortical neurons, eventually the thalamocortical membrane hyperpolarizes more negatively than  $-65mV$ , and a low threshold spike occurs. As mentioned, the low threshold spike is accompanied by a burst of action potentials. The thalamocortical burst acts both on the reticular thalamic cells to facilitate their rhythmic oscillation and also acts on the cortex to

induce excitatory postsynaptic potentials in the cortical pyramidal cells; these potentials generate the observable EEG pattern.

The hyperpolarization of thalamocortical neurons that occurs after a low-threshold spike is conjectured to suppress relay signals from the thalamus to the cortex and induce a state of sensory gating during sleep. Sensory gating is the deprivation of sensory stimuli within the cortex, which occurs when the thalamocortical neurons fire in a burst pattern. In support of this hypothesis, it has been shown that during burst firing there is reduced responsiveness from lateral geniculate neurons to their receptive fields (Livingstone & Hubel 1981), and it has also been shown, albeit in limited studies, that  $Ca_v3.1$  ( $\alpha 1G$ ) T-type calcium channel knock-out mice have poorer amounts of non-REM sleep (Anderson 2005). Tonic firing of wake-promoting cells, which we will discuss next, results in the inactivation of the burst pattern of reticular thalamic GABAergic firing and causes a tonic firing pattern, instead. This tonic pattern inhibits the production of sleep EEG rhythms and inactivates thalamic sensory gating.

### WAKE-PROMOTING CELLS

Before the center for sleep was proven, the center for wakefulness was discovered. In the 1940s and 1950s neurophysiologists Giuseppe Moruzzi and H. W. Magoun performed a series of electroencephalographic studies to prove the existence of a wakefulness center. They described an active arousal generator in the brainstem reticular formation, coined the ascending reticular activating system, which was shown to directly and indirectly activate the cerebral cortex by way of diffuse projection fibers directly to the cortex and indirectly through the thalamus.

In their 1949 paper "Brain Stem Reticular Formation and Activation of the EEG," Moruzzi and Magoun write:

*The evidence given above points to the presence in the brain stem of a system of ascending reticular relays whose direct stimulation activates or desynchronizes the EEG, replacing high-voltage slow waves with low-voltage fast activity. This effect is exerted generally upon the cortex and is mediated, in part, at least, by the diffuse thalamic projection system.*

Over the past 50 years, discovery of the specific brainstem, hypothalamic, and basal forebrain cell populations responsible for arousal system has elaborated and shaped our understanding of wakefulness anatomy. Numerous neurotransmitters and neuronal populations have been discovered to be responsible for wakefulness. They are the cholinergic pedunculopontine and lateral dorsal tegmental nuclei in the upper brainstem and the cholinergic nuclei in the basal forebrain; the histaminergic neurons of the tuberomammillary nuclei in the middle nuclear group of the hypothalamus; and the catecholamine-producing neurons, which include the dopaminergic neurons of the substantia nigra and ventral tegmental area in the midbrain; noradrenergic neurons in the locus ceruleus of the pons; and the upper brainstem group of serotonergic raphe nuclei. The role of the neuropeptide orexin (aka hypocretin) has most recently gained attention. It is excreted from the posterior hypothalamus and serves as a stabilizer of the "flip-flop switch," which is a bistate circuit that coordinates abrupt transitions in sleep-wake states.

As a pharmacologic corollary to the list of neurotransmitters involved in wakefulness: amphetamines are adrenergic reuptake inhibitors and are stimulatory

(presumably by increasing the amount of circulating monoamines), and anti-histamines, such as diphenhydramine (Benadryl), cause drowsiness as do anticholinergic agents.

### THE SLEEP CENTER

As late as 1914, renowned French neurologists Joseph Dejerine and Jacques Lhermitte emphatically denied the possibility of an active brain sleep center. They, and most others at the time, did not deny that brain changes occurred during sleep but that sleep was not an active process, rather it was simply a result of the absence of sensory input to the brain. In 1916–1917, however, Baron Constantin von Economo documented pathologic–anatomic correlations of patients who had died from encephalitis lethargica (aka von Economo's encephalitis), and for the first time, he demonstrated clear sleep and wake central nervous system centers. Encephalitis lethargica causes a myriad of clinical manifestations. RR Dourmashkin, in his paper "What caused the 1918-30 epidemic of encephalitis lethargica?", summarized the accounts of several physicians who observed the clinical manifestations of encephalitis lethargica as follows:

*The afflicted individuals became ill suddenly with only slight prodromal upper respiratory signs and low-grade fever. In the acute 'oculo-lethargic' stage, most common early in the epidemic, the presenting features were: somnolence, at times deep, but from which the patient could be roused; mask-like facies accompanied by mental apathy; tired, expressionless, toneless speech, often thick and slurred; eye signs (e.g. oculogyric crises, diplopia, ptosis, squint, nystagmus, pupil irregularity); convulsive seizures, and stroke.*

Additional parkinsonian features were tremor, which was coarse (but not pill-rolling as in Parkinson's disease), rigidity, loss of equilibrium, and shuffling gait. The parkinsonian features and the oculogyric crisis suggested a midbrain/diencephalic localization for the encephalitis, which pathologic observations confirmed. Von Economo observed pathological differences in the cases of severe hypersomnia (excessive sleepiness) and those of insomnia (inability to fall or stay asleep). He formalized them into a construct of sleep–wake anatomy that resembles our model of it today.

In his 1931 paper entitled "Sleep as a Problem of Localization," von Economo writes:

*the inflammation in cases associated with insomnia is localized anteriorly in the lateral wall of the third ventricle, near the corpus striatum, while it is localized in cases showing disturbances of ocular muscles with sopor (stupor) in the posterior wall of the third ventricle near the nuclei of the oculomotorius in the cap of the interbrain.*

In this statement, he proposes that the center for sleep lies in the anterior hypothalamus and the center for wakefulness lies in the posterior hypothalamus and upper brainstem. Von Economo's work held little sway in his time, however, and many decades passed before the premise of his hypothesis was proven.

In the 1980's and 1990's, investigators found that the predominant neuronal population activated during sleep lies within the anterior hypothalamus, specifically in the ventrolateral preoptic nucleus of the preoptic area. Sherin et. al, in 1996, were the first to show this cell population had enhanced Fos immunoreactivity after periods of sleep; they

demonstrated that the amount of Fos reactivity was directly proportional to the amount of sleep achieved. Sherin et. al proposed that the ventrolateral preoptic area exerted its sleep inducing effect through its inhibition of the tuberomammillary nucleus (the major histaminergic, wake-promoting nucleus of the hypothalamus) and they demonstrated a neuronal relationship between the ventrolateral preoptic area and the tuberomammillary nucleus by injecting retrograde tracer cholera toxin subunit B into the tuberomammillary nucleus. Five to seven days later, when the animals were sacrificed and the preoptic area was sectioned, ventrolateral preoptic sites ipsilateral to the injected tuberomammillary nucleus demonstrated retrograde cholera toxin. Other sites surrounding the tuberomammillary nucleus were also injected but did not produce retrograde cholera toxin in the ventrolateral preoptic area, proving the specificity of the relationship between the ventrolateral preoptic area and the tuberomammillary nucleus.

In 2000, Gong et. al expanded the breadth of the sleep center to include the median preoptic nucleus when they demonstrated the production of c-Fos production during sleep versus wake periods in rat median preoptic nuclei. They further sub-divided the median preoptic area into rostral and caudal divisions (they defined the rostral median preoptic nucleus as forming "a 'cap' around the rostral end of the third ventricle just anterior to the decussation of the anterior commissure") and examined both subdivisions during sleep periods in ambient temperature (control sleep) and warm temperature (heat sleep). Both subdivisions were activated during control sleep and also during heat sleep, but the rostral median preoptic nucleus (and not the caudal) expressed even further amounts of c-Fos during heat sleep as compared to control sleep, suggesting a specific heat-related activation of the rostral median preoptic nucleus.

Four years later, in 2004, Gong et. al, proved that the neurotransmitter used by the median preoptic nucleus in the promotion of sleep is gamma-aminobutyric acid (GABA), based on Fos-immunoreactive staining of glutamate acid decarboxylase (GAD) positive neurons in the median preoptic nucleus. In their experiments, Gong et. al sleep deprived rats. After 24 hours of sleep deprivation, both before and after sleep recovery, the animals demonstrated greater amounts of total GAD neuronal Fos-immunoreactive staining and a higher percentage of GAD staining cells became Fos-immunoreactive.

### OREXIN & THE FLIP-FLOP SWITCH

In 1998, two different research groups concurrently but independently identified a pair of hypothalamic-produced neuropeptides; the neuropeptides were named orexins by Sakurai et. al and hypocretins by de Lecea et. al (here-to-forward they will be referred to as orexins). Orexins are produced by a discrete neuronal population within the lateral hypothalamus and their role in the nervous system came as great surprise.

A decade and a half prior to the identification of the orexins, in 1982, Baker et. al identified a candidate gene for narcolepsy in a colony of Doberman Pinschers with canine narcolepsy, which was designated canarc-1. Despite extensive study of this gene and the canine narcoleptic colony, researchers failed to identify a singular neuropeptide responsible for narcolepsy. In 1999, when the first orexin knock-out mouse was bred, investigators believed the effects would relate to energy metabolism because the lateral hypothalamus had been shown to be dedicated to energy homeostasis. However, study of homozygote orexin knock-out mice, demonstrated that the mice expressed a phenotype consistent with narcolepsy, instead, and rather than play a role in energy metabolism (in the way it was

hypothesized to) orexin was discovered to play a critical role in the maintenance of wakefulness.

Orexin knockout mice displayed the following features of narcolepsy. Consistent with cataplexic events, the mice demonstrated "the abrupt cessation of purposeful motor activity associated with a sudden sustained change in posture that was maintained throughout the episode, ending abruptly with complete resumption of purposeful motor activity". As well, twenty-four hour EEG/EMG recording showed "unanticipated disruption of REM sleep regulation" typical of narcolepsy. And it also showed transitions from wakefulness to REM sleep without passing through non-REM sleep, which again is consistent with narcolepsy.

In humans, it has been observed that loss of orexin production through gliosis or other pathology to the perifornical hypothalamic area in the posterior-lateral hypothalamus results in narcolepsy with cataplexy. In 2005, Saper et. al published a paper entitled "Hypothalamic Regulation of Sleep and Circadian Rhythms," which popularized the concept of the flip-flop switch. They proposed that mutual inhibition between the sleep-wake states allows for coordinated transitions in sleep-wake states through a flip-flop switch. A flip-flop circuit is an electrical engineering term for a switch that avoids transitional states; the circuit is in either one of two states but not in a blend of both. If you are tired when you lie down, you quickly fall asleep, and when you're ready to rise, you suddenly wake up.

In the flop-flop switch model, the arousal center inhibits the sleep center and the sleep-center inhibits the wake-promoting cells. Orexin stabilizes the transition between states. Orexigenic neurons in the lateral hypothalamus send excitatory projections to wake-promoting cells, stabilizing their activation. In the wake-state, orexin stabilizes the wake-promoting cells. In the sleep-state, the sleep center inhibits the wake-promoting cells and the orexigenic cells of the lateral hypothalamus.

### SLEEP PROMOTING SUBSTANCES

At the beginning of the twentieth century, Kuniomi Ishimori in Japan and Henri Piéron in France, independently but concurrently, performed experiments wherein they transferred cerebrospinal fluid or brain tissue from sleep-deprived dogs to well-rested dogs and observed that the well-rested dogs went to sleep. Jerome Siegel, in his book The Neural Control of Sleep and Waking, describes Ishimori and Piéron's experiments as follows.

*(Ishimori) deprived (the dogs) for up to 113 hours. Their brains were removed, processed, and desiccated, with the dry substance then rehydrated and injected subcutaneously into recipient dogs. The dogs exhibited a number of effects, one of which was excess sleep. Control dogs that received brain extracts from non-sleep deprived animals showed some of the same effects, but not increased sleep (Ishimori, 1909).*

*Piéron and Legendre, according to Jouvet (1972), deprived dogs of sleep by walking them through the streets of Paris, after which the experimenters removed a small amount of CSF and injected it into a cerebral ventricle of non-sleep deprived dogs. The recipient animals promptly fell asleep. Control animals, receiving CSF from non-sleep deprived dogs, did not fall asleep.*

Similar experiments, using blood and cerebrospinal fluid were performed on other animal types, such as goats, rats, and rabbits, with similar results. This body of evidence led

researchers to search for the individual substances responsible for the promotion of sleep (sleep-promoting substances).

Experiments over the past thirty years have identified several sleep-promoting substances. Tumor necrosis factor  $\alpha$  and interleukin 1 are the two most clear-substances with sleep-promoting properties. They have been shown to cause sleepiness and fatigue as well as other somatic symptoms commonly associated with sleepiness: cognitive dysfunction, sensitivity to pain, impaired glucose tolerance, and chronic inflammation.

Of special interest is the sleep-promoting-substance adenosine, because caffeine, which is second only to oil in its importance as a global commodity, is believed to perform its wake-promoting effects through actions on adenosine receptors. Evidence suggests that both  $A_1$  and  $A_{2A}$  receptors are involved in adenosine's sleep-promoting effects. In multiple studies in the late 1990's, Satoh et. al demonstrated the potency of  $A_{2A}$ -agonists in the promotion of sleep and in 2003, Urade et. al demonstrated that  $A_{2A}$ -knock-out mice demonstrated less rebound sleep than did normal mice.

In 2005, Gallopin et. al demonstrated that direction activation of  $A_{2A}$ -expressing neurons in the ventrolateral preoptic area promotes sleep. Specifically, they demonstrated that a subset of ventrolateral preoptic nuclei (Type-2) neurons showed excitation with  $A_1$  blockade (from the additional activation of adenosine on  $A_{2A}$ -adenosine receptors) and with a using direct  $A_{2A}$ -agonist, Gallopin et. al showed excitation of Type 2 neurons.

In 2008, Thakkar et. al demonstrated the role of adenosine on  $A_1$ -receptors in orexigenic neurons in the lateral hypothalamus. They showed that bilateral injections of a selective  $A_1$ -receptor antagonist (DPX) increased rat wakefulness and in sleep-deprived rats both reduced overall sleep-recovery and the latency to sleep.

Other substances with sleep-promoting properties are growth hormone-releasing hormone, prostaglandin  $D_2$ , and nitric oxide for non-REM sleep, and vasoactive intestinal peptide and prolactin for REM sleep (Basics of Sleep 2009).

### CIRCADIAN INFLUENCES ON SLEEP

In 1729, Jean-Jacques d'Ortois de Mairan conducted an experiment to determine whether a heliotrope flower's 24-hour of cycle of opening and closing its leaves would persist in a place devoid of light. The flower is known for its inclination for the sun; its name translates to "turning towards the sun". He placed the plant in a dark room and found that the plant's 24-hour cycle of opening and closing its leaves persisted. De Marian's experiment is recognized as the first modern demonstration of the circadian rhythm, the internal timing system, which exists across species of flora and fauna, alike.

As a byproduct of 3.5 billion years of the Earth's daily rotation around its axis, all of us have a circadian rhythm of approximately 24-hours. The central master timekeeper of this internal clock is the suprachiasmatic nucleus of the anterior hypothalamus; it regulates the timing of sleep-wake periods, feeding and satiety, and core body temperature fluctuations, amongst other behaviors. Because of this internal clock, we maintain a 24-hour cycle of behavioral activities even when we are placed in non-24-hour environments. However our internal clock can be adjusted through certain environmental cues, called zeitgebers.

In regards to sleep-wake cycles, light is commonly considered the most robust zeitgeber. It passes from the retinae along the retinohypothalamic pathway to the suprachiasmatic nucleus. Sadun et. al first published findings demonstrating this pathway in

humans in 1984. Using autopsy specimens and a previously unavailable stain, paraphenylenediamine (PPD), they stained the optic nerves, optic chiasm, optic tracts, and suprachiasmatic nuclei of normal controls and individuals who during their lives had undergone either unilateral or bilateral optic nerve damage. They found degenerated nerves in the bilateral suprachiasmatic nuclei in specimens from individuals who had a history of bilateral optic nerve damage but also from individuals who had a history of unilateral optic nerve damage. Thus, they concluded that the retino-hypothalamic tract passes from the retinae, along the optic nerves, through the optic chiasm (to spread both unilaterally and bilaterally), and subsequently sends projections to the bilateral suprachiasmatic nuclei.

The suprachiasmatic nucleus projects, most notably, to the dorsomedial hypothalamic nucleus and the paraventricular hypothalamic nucleus. The dorsomedial hypothalamic nucleus is involved in the control of many circadian features. The paraventricular hypothalamic nucleus governs the pineal gland's production of melatonin, and melatonin, amongst other things, helps facilitate our transition to sleep. Pinealocytes produce melatonin through a multi-step pathway. Alkylamine N-acetyltransferase (AA-NAT) is responsible for the first step in this pathway: the acetylation of serotonin. The paraventricular hypothalamic nucleus acts indirectly on the pineal gland through the superior cervical ganglion, the most rostral ganglion of the sympathetic chain. The superior cervical ganglion innervates the pinealocytes and triggers the production of alkylamine N-acetyltransferase, which sets in motion the production of melatonin from serotonin.

During daytime, light is perceived in the retinae and passes down the retinohypothalamic pathway and then triggers the suprachiasmatic nucleus, which inhibits the paraventricular nucleus from its stimulation of the pinealocytes. The suprachiasmatic inhibition of the paraventricular nucleus shuts off the production and release of melatonin. Through this circadian mechanism, plasma melatonin levels rise two hours before our anticipated bedtime and help us transition to sleep (Benarroch 2008).

### REM SLEEP

In 1959, Jouvet and Michel discovered a sleep phase in cats that comprised muscle atonia, cortical activation, and rapid-eye movements. Through chemical and electrolytic studies, they demonstrated that the brainstem region responsible for this sleep state (called paradoxical sleep) lies within the pontine reticular formation in the peri-locus coeruleus (dorsal pontis oralis and caudalis). Chemical studies used cholinergic agonists to excite the area, and from this body of evidence, acetylcholine was believed to be the primary neurotransmitter responsible for REM sleep. In the 1970's, Hobson et. al discovered that monoaminergic neurons ceased firing during REM sleep and later it was also demonstrated that histaminergic and orexigenic neurons also ceased firing during REM sleep. Accordingly, cholinergic neurons became known as REM-on neurons and monoaminergic, histaminergic, and orexigenic neurons became known as REM-off neurons.

Currently, the importance of acetylcholine in the promotion of REM sleep is less clear. With the discovery of the sublaterodorsal nucleus in the rat (an anatomical equivalent to the feline peri-locus coeruleus), the production of REM sleep has been shown to predominantly involve glutamate and gamma-Aminobutyric acid (GABA).

Regulation of the sublaterodorsal/peri-locus coeruleus is believed to involve inhibition by the ventrolateral periaqueductal grey and dorsal deep mesencephalic reticular nucleus. These structures have been shown to send inhibitory projections to the

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sublaterodorsal/peri-locus coeruleus. Activation of the ventrolateral periaqueductal grey and dorsal deep mesencephalic reticular nucleus are believed to be gated by the ventrolateral periaqueductal grey's own internal circuits, the dorsal paragigantocellular nucleus (in the medullary reticular formation), and the melanin-concentrating hormone nuclei of the lateral hypothalamus (Fort et. al 2009, Vetrivelan et. al 2009, Hassani 2009).

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## REFERERNCES

- Basics of Sleep Guide, Second Edition*. 2nd ed. Westchester, IL: Sleep Research Society, 2009.
- M.P. Anderson, T. Mochizuki, J. Xie, W. Fischler, J.P. Manger, E.M. Talley, T.E. Scammell, S. Tonegawa. "Thalamic Cav3.1 T-type Ca<sup>2+</sup> channel plays a crucial role in stabilizing sleep." *Proc. Natl. Acad. Sci. U.S.A.* 102 (2005): 1743–1748.
- Alam, M. N., S. Kumar, S. Rai, M. Methippara, R. Szymusiak, and D. McGinty. "Role of Adenosine a(1) Receptor in the Perifornical-Lateral Hypothalamic Area in Sleep-Wake Regulation in Rats." *Brain Res* (2009).
- Benarroch, E. E. "Suprachiasmatic Nucleus and Melatonin: Reciprocal Interactions and Clinical Correlations." *Neurology* 71, no. 8 (2008): 594-8.
- Brazier, M. A. "The History of the Electrical Activity of the Brain as a Method for Localizing Sensory Function." *Med Hist* 7 (1963): 199-211.
- Chemelli, R. M., J. T. Willie, C. M. Sinton, J. K. Elmquist, T. Scammell, C. Lee, J. A. Richardson, S. C. Williams, Y. Xiong, Y. Kisanuki, T. E. Fitch, M. Nakazato, R. E. Hammer, C. B. Saper, and M. Yanagisawa. "Narcolepsy in Orexin Knockout Mice: Molecular Genetics of Sleep Regulation." *Cell* 98, no. 4 (1999): 437-51.
- Crunelli, V., D. W. Cope, and S. W. Hughes. "Thalamic T-Type Ca<sup>2+</sup> Channels and Nrem Sleep." *Cell Calcium* 40, no. 2 (2006): 175-90.
- Dourmashkin, R. R. "What Caused the 1918-30 Epidemic of Encephalitis Lethargica?" *J R Soc Med* 90, no. 9 (1997): 515-20.
- Fort, P., C. L. Bassetti, and P. H. Luppi. "Alternating Vigilance States: New Insights Regarding Neuronal Networks and Mechanisms." *Eur J Neurosci* 29, no. 9 (2009): 1741-53.
- Fredholm, B. B., K. Battig, J. Holmen, A. Nehlig, and E. E. Zvartau. "Actions of Caffeine in the Brain with Special Reference to Factors That Contribute to Its Widespread Use." *Pharmacol Rev* 51, no. 1 (1999): 83-133.
- Gallopín, T., P. H. Luppi, B. Cauli, Y. Urade, J. Rossier, O. Hayaishi, B. Lambolez, and P. Fort. "The Endogenous Somnogen Adenosine Excites a Subset of Sleep-Promoting Neurons Via A2a Receptors in the Ventrolateral Preoptic Nucleus." *Neuroscience* 134, no. 4 (2005): 1377-90.
- Gong, H., D. McGinty, R. Guzman-Marin, K. T. Chew, D. Stewart, and R. Szymusiak. "Activation of C-Fos in Gabaergic Neurons in the Preoptic Area During Sleep and in Response to Sleep Deprivation." *J Physiol* 556, no. Pt 3 (2004): 935-46.
- Gong, H., R. Szymusiak, J. King, T. Steininger, and D. McGinty. "Sleep-Related C-Fos Protein Expression in the Preoptic Hypothalamus: Effects of Ambient Warming." *Am J Physiol Regul Integr Comp Physiol* 279, no. 6 (2000): R2079-88.
- Hassani, O. K., M. G. Lee, and B. E. Jones. "Melanin-Concentrating Hormone Neurons Discharge in a Reciprocal Manner to Orexin Neurons across the Sleep-Wake Cycle." *Proc Natl Acad Sci U S A* 106, no. 7 (2009): 2418-22.
- Livingstone MS, Hubel DH. "Effects of sleep and arousal on the processing of visual information in the cat." *Nature* 291 (1981): 554–61.
- McGinty, D., H. Gong, N. Suntsova, M. N. Alam, M. Methippara, R. Guzman-Marin, and R. Szymusiak. "Sleep-Promoting Functions of the Hypothalamic Median Preoptic Nucleus: Inhibition of Arousal Systems." *Arch Ital Biol* 142, no. 4 (2004): 501-9.
- Moruzzi, G., and H. W. Magoun. "Brain Stem Reticular Formation and Activation of the EEG. 1949." *J Neuropsychiatry Clin Neurosci* 7, no. 2 (1995): 251-67.

- Niedermeyer, Ernst, F. H. Lopes da Silva, and Ovid Technologies Inc. "Electroencephalography Basic Principles, Clinical Applications, and Related Fields." Philadelphia: Lippincott Williams & Wilkins, 2005.
- Sadun, A. A., J. D. Schaechter, and L. E. Smith. "A Retinohypothalamic Pathway in Man: Light Mediation of Circadian Rhythms." *Brain Res* 302, no. 2 (1984): 371-7.
- Saper, C. B., T. E. Scammell, and J. Lu. "Hypothalamic Regulation of Sleep and Circadian Rhythms." *Nature* 437, no. 7063 (2005): 1257-63.
- Sherin, J. E., P. J. Shiromani, R. W. McCarley, and C. B. Saper. "Activation of Ventrolateral Preoptic Neurons During Sleep." *Science* 271, no. 5246 (1996): 216-9.
- Siegel, Jerome H. *The Neural Control of Sleep and Waking*. New York: Springer, 2002.
- Steriade, M., D. A. McCormick, and T. J. Sejnowski. "Thalamocortical Oscillations in the Sleeping and Aroused Brain." *Science* 262, no. 5134 (1993): 679-85.
- Thakkar, M. M., S. C. Engemann, K. M. Walsh, and P. K. Sahota. "Adenosine and the Homeostatic Control of Sleep: Effects of A1 Receptor Blockade in the Perifornical Lateral Hypothalamus on Sleep-Wakefulness." *Neuroscience* 153, no. 4 (2008): 875-80.
- Vetrivelan, R., P. M. Fuller, Q. Tong, and J. Lu. "Medullary Circuitry Regulating Rapid Eye Movement Sleep and Motor Atonia." *J Neurosci* 29, no. 29 (2009): 9361-9.

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