

Jouvet M. The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle. *Ergeb. Physiol. Biol. Chem. Exp. Pharmacol.* 64:166-307, 1972.

[Department of Experimental Medicine, Claude Bernard University, Lyon, France]

This review summarizes the anatomical, physiological, and pharmacological evidence that brain stem catecholaminergic and cholinergic systems are involved in the executive mechanisms of waking and paradoxical sleep whereas serotonergic neurons of the raphe system would appear to be responsible for slow wave sleep. [The SC® indicates that this paper has been cited in more than 750 publications.]

From Amines to Sleep

Michel Jouvet

Department of Experimental Medicine
Claude Bernard University
8, avenue Rockefeller
69008 Lyon
France

In 1970, the late R. Jung, who was a coeditor of *Ergebnisse der Physiologie* invited me to write a review related with the role of monoaminergic and cholinergic neurons in the sleep-waking cycle. At the same time, G. Moruzzi (from Pisa) was also invited to summarize the "classical" neurophysiology of sleep and waking. This led to numerous letters between Moruzzi and myself in which we tried to delimit our respective fields. These letters are precious to me because they express the physiological thoughts of a great scientist who died in 1986. I concluded my review, which included 700 references, with the hypothesis that the serotonergic (5HT) system (mostly the rostral raphe) plays a "determinant" role in slow wave sleep while both norepinephrine (NE) and dopamine (DA) subsystems located in the area of the locus coeruleus and substantia nigra seem to be involved in the control of EEG and behavioral waking, together with a putative cholinergic ascending system. Both NE-containing neurons of the locus coeruleus and ACH systems (putatively located in this area) were thought to play a

determinant role in the executive mechanisms of paradoxical sleep (PS). The theory that each neurotransmitter might be involved with a specific function could explain most of the experiments performed before 1972. At that time, "wet neurophysiology" was a new and promising field in the exploration of the sleep-waking cycle. It is probably because I reviewed new material which could be summarized in a simple and rather heuristic theory that this paper is so frequently cited, as is an earlier and shorter version of the theory.¹

This monoaminergic theory lived about six years.² It has been invalidated, at least for the role of indolamine, by new findings concerning the unitary activity of 5HT neurons.³ On the one hand, the discovery of ACH-containing perikarya intermingled with NE-containing neurons in the locus coeruleus area in the cat have validated the hypothesis of cholinceptive and/or cholinergic PS executive mechanisms.⁴ On the other hand, the discovery of new waking systems (like the histamine-containing neurons located in the posterior hypothalamus) has given rise to new candidates for waking.⁵ The explosive discovery of numerous peptidergic systems in the brain (sometimes located in the monoaminergic or cholinergic system) has made it totally impossible to have a clear picture of the functional anatomy of the sleep-waking cycle.⁶

During these last 20 years, we have learned again that physiology was not only animated anatomy (as was thought after Haller and clearly criticized by Cl. Bernard). Moreover, it is probably hopeless to search for a necessary and sufficient cause (as some mythical hypnogenic peptides) for sleep or waking since such a concept cannot apply in complex systems. New light may come from new techniques that will make it possible to assess, in vivo, the delicate balance of the energetics of glucose consumption—aerobic or anaerobic of the various systems which control sleep-waking. This will permit us to discover the hierarchy of the conditions that are sufficient for waking or sleep.

1. Jouvet M. Biogenic amines and the states of sleep. *Science* 163:32-41, 1969. (Cited 910 times.) [See also: Jouvet M. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology*-Philadelphia: ISI Press, 1986. p. 304]
2. Morgane P J & Stem W C. Serotonin in the regulation of sleep. (Essman W, ed.) *Serotonin in health and disease. Volume II*. New York: Spectrum Press, 1978. p. 205-45.
3. Jacobs B L & Jones B E. The role of central monoamine and acetylcholine system in sleep wakefulness states: mediation or modulation? (Butcher L L, ed.) *Cholinergic-monoaminergic interactions in the brain*. New York: Academic Press, 1978. p. 271-90.
4. Sakai K. Executive mechanisms of paradoxical sleep. *Arch. Ital. Biol.* 126:239-57, 1988.
5. Lin J S, Sakai K & Jouvet M. Evidence for histaminergic arousal mechanisms in the hypothalamus of cat. *Neuropharmacology* 27:111-22, 1988.
6. Borbely A A & Tobler I. Endogenous sleep-promoting substances and sleep regulation. *Physiol. Rev.* 69:605-70, 1989.

Received April 17, 1991