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Jouvet M. The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle. *Ergeb. Physiol. Bioi Chem. Exp. Pharmakol.* 64:166-307, 1972.
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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 *SCI*® indicates that this paper has been cited in more than 730 publications.]

From Amines to Sleep

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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 serotoninergic (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 (putativeiy 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 cholinoceptive 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.

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