reversal of the waking and total sleep duration in dogs occurs only in the diurnal 12-h part of the circadian cycle. Many previous interpretations of the comparative data on sleep should be reconsidered according to the new technical requisites (telemetry) and to the concept of an integral waking-sleep function, influenced by the circadian biorhythm.

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7. Neural regulation of sleep

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One cannot understand and discuss the neural mechanisms underlying sleep without taking into account the mechanisms responsible for the physiologically opposite state of wakefulness. As we shall see below, both states depend on the functional interplay of 2 antagonistic cerebral neuronal systems. Obviously, under physiological conditions, the whole cerebrum participates in the sleep-wakefulness cycle. However, certain parts of it appear to be of paramount importance, so that the concept of an arousing (or activating) and of a hypnogenic (or deactivating) system is to a great extent justified. The 2 systems seem to be topographically concentrated in the brain stem with a rostral extension into the posterior diencephalon.

The neurophysiological research aimed at understanding the neuronal regulation of sleep and wakefulness was mainly based on the analysis of the effects of cerebral lesions and cerebral electrical stimulation. In both approaches neurophysiologists studied whether, and in which way, experimental manipulation of the brain affected the sleep and wakefulness behavior in animals. Or whether it affected somatic and visceral epiphenomena of the 2 states, or the cerebral electrical activity which, as is now well known, shows characteristic patterns for each physiological condition between the extremes of alertness and deep sleep.

Modern sleep neurophysiology was heralded by the classical experiments of W.R. Hess (1927)[1] and Frederic Bremer (1935)[2]. Hess showed beautifully that protracted low rate electrical stimulation of the midline thalamus in the cat is followed by behavioral sleep; and Bremer demonstrated, also in the cat, that the transection of the neuraxis at midbrain level ('cerveau isolé' preparation) is followed by EEG patterns of sleep.

It was Bremer's experiment which, although later than that of Hess, prompted most of the experimental work on the sleep-wakefulness physiology during the following years. The sleep-like EEG patterns of the 'cerveau isolé' animal were ascribed to the suppression of an ascending influence with the function of keeping the cerebrum awake. In 1949, Moruzzi and Magoun[3] started a long series of experiments (see Rossi and Zanchetti[4] for references of the early work, and Moruzzi[5] for an excellent and exhaustive review) which showed that this ascending influence originates from the reticular formation of the rostral part of the pons and of the midbrain. Selective destruction of these brain stem regions is followed by a behavioral state of hypersomnia and by sleep-like EEG patterns, whereas their electrical stimulation at high frequency in the sleeping animal produces immediate arousal. This led to the hypothesis of the 'reticular activating system', i.e. of a cerebral neuronal system or circuitry responsible for the maintenance of the waking state. However, further experiments showed that if the 'cerveau isolé'[6–9] or the precollicularly decerebrated

animals[10] are kept alive for a long time ('chronic' preparations), after a certain period of hypersomnia, they again show behavioral and EEG patterns of wakefulness. This led to the suggestion that neuronal circuits contributing to the maintaining of wakefulness are also located rostral to the brain stem reticular structures. This hypothesis was analysed and discussed at length by Moruzzi[5], who concluded that there is enough experimental evidence to identify the site of these circuits in the posterior hypothalamus. It should be mentioned that, as far as can be inferred by anatomical clinical studies, this rostral extension of the activating system seems particularly important in the human being[11-13].

On the basis of the findings, summarized above, which lead to the recognition of an activating reticular influence, for some years during the fifties sleep was regarded as a 'passive' phenomenon, i.e. as the consequence of the decrease in activity of the activating system. However, a consistent series of experimental findings proved that this was only part the reason for sleep and an actively sleep-inducing cerebral neuronal mechanism had also to be taken into consideration.

The first line of evidence of an active hypnogenic influence stemmed from experiments of cerebral stimulation, the first one of which was that of Hess, mentioned above, i.e. sleep induction by electrical stimulation of midline thalamic nuclei. Later experiments showed that EEG and behavioral signs of sleep could also be elicited by the stimulation of other brain sites, such as certain brain stem areas[12,14-16] and the basal forebrain[17,18] (for complete bibliography, see Moruzzi[5]).

The second line of evidence was drawn from experiments of cerebral lesion. They can be subdivided into 2 main groups. a) Experiments pointing to the existence of sleep-inducing neuronal circuits, located in the lower brain stem and responsible for both NREM and REM phases of sleep. The first data were provided by Batini et al.[19] in 1958: in the cat, they obtained the suppression or marked reduction of EEG and ocular patterns of NREM sleep by completely transecting the brain stem just in front of the trigeminal main sensory nucleus ('pretrigeminal' preparation). Subsequently, arousal from sleep was produced by functional inactivation of the lower brain stem, due to selective administration of barbiturates[20] or cooling[21]. Finally, destruction of the ponto-bulbar raphe system was shown by the Jouvet group[22,23] to prevent the occurrence of REM sleep. b) Experiments indicating the involvement of the anterior hypothalamus in sleep maintainance. A dramatic insomnia was provoked in the rat by Nauta[24] by transverse section in the rostral half of the hypothalamus. The finding was confirmed by McGinty and Sterman[25] in the cat and more recently by Bremer[26,27].

To recapitulate, the results of a number of experiments, started by Hess and Bremer a long time ago, have contributed to the modern view that the neural regulation of sleep and wakefulness is dependent on the activity of neuronal circuits having their principal spatial location in the brain stem and diencephalon. The arousing or activating system finds its structural substrate in the reticular structures of the rostral brain stem and in the posterior hypothalamus. The hypnogenic or deactivating system appears to be made by neurons of the lower brain stem, by the raphe nuclear complex and by the anterior hypothalamus; the midline thalamic nuclei certainly contribute to the hypnogenic function (Koella[28]), although their precise role is still to be elucitated. Obviously, the 2 systems are closely interrelated not only anatomically, but also functionally. Generally speaking, they can be regarded as antagonistic systems. Both of them are under the influence of neuronal influences of central as well as of peripheral origin (Rossi and Zanchetti[4], Rossi[13], Moruzzi[5]). One should also be reminded of the quite interesting work of Jouvet[23] leading to a peculiar neurochemical characterization of the neuronal circuits subserving sleep and wakefulness.

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