Published in final edited form as:

Sleep Med. 2018 September ; 49: 14–19. doi:10.1016/j.sleep.2018.05.030.

The mysteries of sleep and waking unveiled by Michel Jouvet

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Abstract

A great pioneer in sleep research, Michel Jouvet applied rigorous scientific methods to the study of sleep-wake states and associated changes in consciousness which, with his vivid imagination and creative mind, he unveiled as the mysteries of sleep and waking such as to inspire a generation of researchers in the field. His initial discovery of a third state distinguished from waking (W) and slow wave sleep (SWS) by the paradoxical association of W-like cortical activity with sleep-like behavior and muscle atonia that he accordingly called “paradoxical sleep” (PS) began his investigation over some 50 years of the mechanisms of these three sleep-wake states. Using primarily lesion and pharmacological manipulations, he sought the systems which are necessary and sufficient, and he thereby provided an early blueprint of how the neuromodulatory systems could determine the sleep-wake states. With the application of increasingly more selective lesion and other advanced techniques including, importantly, single unit recording combined with histochemical identification of recorded units, the monoamines and acetylcholine, together with peptidergic systems have been revealed to play modulatory, yet not essential, roles acting upon other intermingled glutamatergic and GABAergic neurons that are the effector neurons of the sleep-wake states and their cortical and behavioral correlates.

Keywords

Gamma; Paradoxical sleep; REM sleep; Slow Wave Sleep

1. Scientific approach to the mysteries of sleep and waking

Brought up in the tradition of Claude Bernard, Jouvet insisted upon a rigorous experimental approach to medical and scientific problems; but he presented those problems in an engrossing manner as though unveiling great mysteries, the mysteries of sleep and waking. He began his research career in Neurology and Neurosurgery examining the loss of consciousness in comatose patients and establishing for the first time the subcortical

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Conflict of interest

The author declares no conflict of interest.

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electrophysiological criteria for brain death [1]. Following early studies with Magoun in California, he pursued an experimental approach in animals to determine the brain regions which were necessary for consciousness, and the mechanisms by which consciousness was altered naturally during sleep. In his laboratory in Lyon, he first utilized complete transections in cats to establish which part, the telencephalon or rhombencephalon, of the brain was necessary for the waking state characterized by cortical fast activity with behavioral arousal, and which was necessary for sleep, characterized by cortical slow wave activity with behavioral quiescence (Fig. 1).

With these studies, he discovered, as he describes, by “serendipity”, a third state which he then called “rhombencephalic sleep”, according to its presence and apparent origin in the brainstem, that was distinct from slow wave sleep (SWS) or what he called “telencephalic sleep”, according to its presence and origin in the telencephalon [3]. He went on to reveal that this third state was distinct, since it was characterized by waking-like fast cortical activity accompanied by sleep-like behavior, and most notably as he discovered, by postural muscle atonia, leading him in 1959 to call it “paradoxical sleep” (PS) [4, 5]. With this terminology, Jouvet captured the essence of the state most commonly now referred to as rapid eye movement (REM) sleep, as identified and so-called by Aserinsky and Kleitman in humans in 1953 [6] and by Dement in cats in 1958 [7].

Indeed, PS then represented and still represents the greatest mystery of the organism since, in contrast to SWS, the brain is not at rest, and in contrast to waking (W) the body cannot move, except as Jouvet discovered following lesions in the pontine tegmentum that resulted in cats ‘acting out their dreams’ during PS without atonia. Jouvet also described phasic activity occurring in association with REMs during PS, which originated in the pons and traveled to the geniculate and occipital cortex as “ponto-geniculo-occipital (PGO) spikes” [8], an activity which he portrayed as a code that served to program the central nervous system during PS with the genetic information that is particular to the individual. These theories remain today as hypotheses or even mysteries.

Jouvet developed multiple approaches in his laboratory to examine the phylogenetic, ontogenetic, as well as phenomenological, but most particularly the mechanistic aspects of sleep and waking. He continued his study of the structures and later the chemicals in the brain that would be responsible for the different sleep-wake states (Fig. 1). As he portrayed in his usual humorous manner, he applied an approach of “search and destroy” to discover the systems which were “necessary and sufficient” for the generation of each state and its component parameters. Following the histochemical revelations of the monoamines (MA) by the Swedes in the 1960’s, Jouvet launched an integrated program that included histochemical mapping combined with electrolytic lesions of the MA-containing neurons or their pathways and pharmacological depletion of the MA, an approach in which I was to participate as a graduate student in his lab [9, 10]. From these early studies, Jouvet provided seemingly incontrovertible evidence that serotonin (Ser) neurons of the raphe nuclei not only promoted SWS but were moreover necessary for SWS. Based upon lesions, he concluded that noradrenaline (NA) neurons of the locus coeruleus (LC) were critically involved in the generation of PS. However later he found that pharmacological studies did not confirm this role of NA in PS, but suggested that other neurons in the area of the LC must be involved.

From pharmacological studies, he brought out the importance of acetylcholine (ACh) neurons in the pontine tegmentum for PS. Lastly, the importance of the catecholamines (CA) in stimulating and maintaining W was demonstrated by severe deficits in cortical activation following lesions of the ascending NA pathways and in behavioral arousal following lesions of the dopamine (DA) neurons in the substantia nigra (SN) and ventral tegmental area (VTA) [11].

2. Single unit recording reveals the particular roles of sleep-wake neuromodulatory systems

In contrast to Steriade and Hobson [12], Jouvet did not believe that single unit recording would provide an understanding of the mechanisms of sleep-wake states. As he claimed, not totally inappropriately, in any one region one third of the neurons increases, one third decreases, and one third does not change their discharge rate during any one state. However, in the first recordings of presumed Ser neurons in the dorsal raphe (DR) of cats, all were found to decrease firing during SWS and remain silent during PS, in such a manner that they could not possibly generate SWS [13]. In fact, the Ser neurons showed a similar profile of discharge across the sleep-wake cycle, as the NA LC neurons, which fired maximally during behaviorally aroused waking and decreased firing during SWS to become silent during PS in rats [14]. These single unit recording studies thus represented the major challenge to the theory that Ser neurons generated SWS. They also for the first time provided a profile of how these neuromodulatory neurons, including NA and Ser, of the arousal systems with diffuse projections through the central nervous system (CNS) [15], would discharge to promote both the behavioral arousal and cortical activation of waking, and also how they would be silenced during SWS such as to permit the appearance of PS (Fig. 1).

From pharmacological and other studies in Jouvet's and others' laboratories, ACh neurons were believed to play an important role in both W and PS [16]. However, their role was difficult to confirm since single unit recording was problematic, because the ACh neurons in the pontomesencephalic (PMT) and basal forebrain (BF) were found to be intermingled with other equivalent numbers of GABA and glutamate (Glu) neurons, which comprise the major population of neurons through the reticular core extending from the reticular formation (RF) through the hypothalamus and into the BF and can also give rise to long projections throughout the brain [17–20]. By application of juxtacellular recording and labeling combined with histochemical staining of the recorded/labeled neuron in rats, it became possible to characterize the discharge properties and profile of the ACh neurons across sleep-wake states in both the BF and the PMT [21–23] (Fig. 1). In both regions, the ACh neurons, which have widespread projections like neurons of the RF, though not diffuse projections like the MA neurons [24], discharge in association with fast, gamma (>30 Hz) cortical activity during both W and PS and thus would stimulate cortical activation, but could also promote muscle atonia during PS, when the MA neurons are silent, as early pharmacological studies had suggested.

3. Investigating the role of neuropeptides reveals other important neuromodulatory substances for sleep-wake states

Following the revelation of neuropeptides in the brain by Guillemin in the 1960's and 70's, Jouvet launched an investigation for the study of their role in sleep-wake states. As for the MA, he proceeded by mapping of the neurons containing different pituitary hormonal releasing factors (adrenocorticotropin hormone, ACTH; corticotropin-like intermediate lobe peptide, CLIP; Corticotropin Releasing Factor, CRF; growth hormone releasing hormone, GHRH; luteinizing hormone releasing hormone, LHRH) and other peptides (oxytocin; prolactin; vasopressin; vasoactive intestinal peptide, VIP), which were largely concentrated in the hypothalamus and then by injecting these factors into the cerebrospinal fluid. He also proposed that some long lasting and long acting neuropeptides could play a critical role in SWS and/or PS and that perhaps the release of Ser during W would be involved in stimulating the synthesis of a sleep-promoting peptide and thus explain the ostensibly important role of Ser in the sleep cycle [25]. With the subsequent discoveries of the endorphins (or enkephalins) and other peptides in the brain in the 1970's, Jouvet proceeded to examine their potential roles in the sleep-wake cycle, convinced of their potential importance, though finally not finding any particular peptide which was necessary or sufficient for any one sleep-wake state.

It was the discovery in the 1990's of orexin (Orx or hypocretin) and its receptor that for the first time indicated that a peptide could play an essential role in the maintenance of a state, in this case in the maintenance of behavioral waking, since in its absence, narcolepsy with cataplexy occurs [26] [27]. Like NA neurons, the Orx neurons were found to have very diffuse projections throughout the central nervous system. But here again, single unit recording from the neurons containing Orx was important in order to determine their profile of discharge across the sleep-wake cycle, and thus the way in which they could maintain waking by their diffuse projections. By using juxtacellular recording and labeling in head-fixed rats [28], it was determined that Orx neurons discharge selectively during W, whereas they are silent during SWS and PS, as W-active neurons (Fig. 1). Moreover, they appeared to discharge most robustly during aroused waking and in association with positive reward, which might explain why narcoleptic patients, who lack Orx neurons, experience cataplectic attacks in situations of strong emotions and oftentimes of laughter [29].

With the subsequent discovery of another peptide, melanin concentrating hormone (MCH) in the hypothalamus, it was learned that neurons containing this peptide appeared to play an opposite role from those containing Orx [30, 31]. Indeed, juxtacellular recording and labeling of MCH neurons revealed that they discharge in a reciprocal manner to the Orx neurons, being silent during W, then discharging during sleep and maximally during PS, as sleep-active neurons [32] (Fig. 1).

4. Single unit recording reveals the full complexity of sleep-wake effector systems

Despite his skeptical view of the possible insights into sleep-wake mechanisms through single unit recording, Jouvet welcomed into his laboratory in the 1970's Kazuo Sakai from Japan, who specialized in this approach. In fact, although Sakai was not able to identify definitively the neurotransmitter of the neurons from which he recorded, he very carefully examined, by electrophysiological and pharmacological techniques, their properties, projections and most probable neurotransmitter identity. In early studies, he identified neurons in the region of the LC, which did not appear to be noradrenergic and which projected to the medullary RF, that discharged specifically in association with the muscle atonia of PS. He therefore proposed that these neurons were the effector neurons of the muscle atonia and PS, whereas the NA along with Ser neurons were permissive neurons since their silence was a necessary prerequisite for PS occurrence [33]. He also recorded neurons more rostrally in the region of the laterodorsal and pedunculopontine tegmental nuclei (LDT and PPT), which discharged in association with PGO spiking during PS. Later, he proposed that such PGO-on and PS-on neurons were ACh neurons [34–36]. Recording in the posterior hypothalamus (PH) of mice, he was later able to employ juxtacellular recording and labeling to demonstrate that histamine (HA) neurons discharged during W and so comprised another component of central arousal systems [37] (Fig. 1).

Jouvet was not entirely incorrect when he claimed that some neurons increase while others decrease or do not change their discharge in association with any one state in any one region. However, the Ser, NA, ACh, Orx, and MCH neurons appear to be state selective in their discharge and therefore their role in sleep-wake states. On the other hand, GABA and Glu neurons, which are codistributed with the ACh neurons in the BF and PMT and with the Orx and MCH neurons in the hypothalamus, are heterogeneous in their profiles of discharge and include wake- and sleep-active neurons [22, 23, 38] (Fig. 1). Indeed, regions which have been characterized as sleep centers, including the preoptic area (POA) and ventrolateral preoptic area (VLPO) include wake-active neurons in addition to SWS- and PS-active neurons [39, 40]. Reciprocally, regions which have been characterized as wake centers, including the PH, include sleep-active neurons in addition to wake-active neurons [41]. Indeed, sleep- and wake-active neurons are distributed through the reticular core of the brain, which includes the brainstem RF, extending into the hypothalamus and up into the BF and POA. Moreover, in contrast to our sometimes simplistic ideas, not all sleep-active neurons are GABA neurons in these regions, but include both GABA and Glu neurons, since they likely work together while differentially affecting their different target neurons in other regions. Their different functional profiles would appear to be regulated by their different receptors to the different neuromodulatory transmitters. Accordingly, the early idea that sleep and waking centers were present in the brain is too simplistic. On the other hand there are different concentrations of functionally different cell types with different projections that may provide a certain dominance of their roles in regulating sleep-wake states from different regions through the reticular core of the brain [42].

5. Can stimulation unmask sleep-wake systems?

Jouvet was highly skeptical of the value of electrical stimulation for localizing or identifying sleep-wake systems, as was pioneered by Hess in the 1940's and 50's [43]. As Jouvet commented, the effect of the stimulation depended upon its frequency, eliciting waking with high frequencies and SWS with low frequencies from most areas of the brain. Yet, it was learned from single unit recording that the neurons in the cortex and thalamus actually discharged at different frequencies during waking and sleep and most particularly fired in different patterns during waking and sleep [12]. Thus under the influence of neuromodulatory systems, the same neurons could fire fast in a tonic mode during waking and PS, but fire slowly in a bursting mode during SWS [44]. Within the thalamo-cortical-thalamic circuit, the GABA neurons of the thalamic reticular nucleus (Rt) were shown to play an important role in driving spindles through low threshold bursting at 10–14 Hz during the onset of SWS [45], but also to potentially play an important role in pacing gamma activity during waking when they discharge tonically at high gamma frequencies [46] (Fig. 1). So, the same neurons can fire at different frequencies and drive different rhythms in the telencephalon, including fast gamma activity, spindles and slow oscillations, thereby showing that the early results indicating that different cortical activities could be driven by different frequencies from the same system were not totally misleading.

One of the problems with electrical stimulation overlapped with that of recording from particular neurons in any region in which different cell types are intermingled and all cell types would be stimulated in that region at the same time. In subcortical regions, where the neuromodulatory systems, which have distinct discharge profiles and apparent roles but are intermingled with other GABA or Glu neurons with different profiles, the results of such stimulation would indeed be misleading or uninterpretable, as Jouvet claimed. However now, with the development of optogenetics and chemogenetics which allow stimulation of specific cell types, this problem has been overcome for the neuromodulatory systems. Thus, it has now been shown with optogenetic stimulation of NA in the pons and Orx neurons in the PH that waking is evoked [47, 48]. Optogenetic stimulation of ACh neurons in the BF or PMT elicits cortical activation with waking or PS [49–51]. On the other hand, applying these techniques to the stimulation of GABA or Glu neurons does not provide any specificity with regard to functional subtypes of these neurons, since in any one region wake-active, SWS-active and PS-active GABA and Glu neurons can be intermingled [42] (Fig. 1). Nonetheless, as more specific genetic constructs are developed for specific GABA or Glu neurons which have particular receptors for the neuromodulatory transmitters, such stimulation can likely soon be restricted to functionally distinct cell types as well.

6. Research as a process driven by new techniques

Full of imagination along with insight and creativity, Jouvet was a pioneer in applying scientific method to understanding the mechanisms of sleep and waking. First, he revealed the phenomena of sleep and waking along with the correlates in consciousness of those states, including dreams. He presented these with the greatest intrigue and inspiration as mysteries to be solved through the experimental approach. As a neurologist and neurosurgeon, he sought the structural basis in the brain of the generation of sleep-wake

states and their correlates in consciousness as affected by central lesions of the brain. Utilizing the scientific tools of the day, he began in animals using total brain transections which yielded through his prepared mind the serendipitous discovery of the state of PS along with clues as to the rhombencephalic location of the neural systems crucially involved in its generation. He proceeded with electrolytic lesions of histochemically identified MA neurons and correlated these effects with pharmacological depletion or enhancement of the important neuromodulatory systems. But with newer techniques, certain theories which were so cherished had to be modified, most notably that involving Ser, a process which he described with his wonderful humor as the “encounter, the honeymoon, the divorce and the reconciliation”. Indeed, his original tenet that only by identifying those systems which were both “necessary and sufficient” subsequently proved too simple, as he also realized when using specific neurotoxins to find, as he and others later did, that no one neuromodulatory system is essential for waking or sleep nor would any one all by itself be sufficient [52, 53].

In fact, it has become evident that, although the neuromodulatory systems play very important roles in regulating sleep-wake states, the GABA and Glu neurons, which make up the vast population of functionally diverse neurons in the telencephalon and rhombencephalon, including the RF, hypothalamus and BF, comprise the effector neurons of the activating and de-activating systems within the reticular core [42] (Fig. 1). Moreover, many of the neurons in the telencephalon, particularly the thalamo-cortical systems, do not discharge selectively during one state or produce one state, but produce all three states along with their associated unique states of consciousness, by different patterns of discharge across the sleep-wake cycle. These revelations have come to the fore by application of multiple techniques, including very importantly single unit recording, which Jouvet brought into his laboratory to great effect, despite his skepticism.

As a great pioneer, Jouvet revealed the mysteries of sleep and waking which to his own disappointment, he was not able to solve, yet was able to unveil in a manner to inspire a generation of researchers to apply yet other new techniques to try to solve. In this process of research, he, like we all should do, remained true to the basic principles of experimental medicine laid down by Claude Bernard. He formulated many imaginative and daring, sometimes simple hypotheses, which he submitted to rigorous testing by multiple experimental approaches and for which he accepted the verdict of the experimental results, albeit supporting or nullifying his hypotheses. He was driven by genuine curiosity to reveal and understand the mysteries of sleep and waking.

These mysteries included very significantly dreaming, dreaming in cats, his subject of choice, but also in man and most notably in himself. From >5000 personal dreams he recorded, as we learn in his “Memoires d’un Onirologue” [54] and can also appreciate from the fictional 18th century scientific hero, Le Conte Hugues la Scève, in his novel “Le Chateau des Songes” [55, 56], Jouvet recounts the bizarre incorporation of his life’s experiences with researchers and cats alike in many different places of the world and periods of his life; dreams which he interprets as a scientist who attempts to extract the encoding of his individuality across diverse spatial and temporal domains. Yet, he has also represented these dreams in many fantastical drawings in which his unique consciousness emerges (unpublished). In this manner, Jouvet applies the principles of reductionism in science, but

also goes beyond to bring out the full richness of the brain and also his unique mind in its varied states of consciousness through waking and sleep.

Acknowledgments

I thank all the students, fellows, research associates and technicians who contributed to the research reviewed from my laboratory. The author's research was supported by grants from the Canadian Institutes of Health Research (CIHR MOP-13458, 82762 and 130502) and USA National Institutes of Health (MH 60119).

Abbreviations in text

ACh	acetylcholine
BF	basal forebrain
Glu	glutamate
LC	locus coeruleus
MA	monoamines
MCH	melanin concentrating hormone
NA	noradrenaline
Orx	orexin
PGO	ponto-geniculo-occipital
PMT	pontomesencephalic tegmentum
PS	paradoxical sleep
RF	reticular formation
Ser	serotonin
SWS	slow wave sleep
W	waking

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Fig. 1.

Sleep-wake state neural systems. Sagittal schematic view of the rat brain depicting neurons with their chemical neurotransmitters, pathways and discharge profiles by which they influence cortical activity or behavior across the sleep/wake cycle. Waking (W) is characterized by fast (gamma, >30 Hz) activity on the cortical EEG (upper left) and high postural muscle tone on the neck EMG (lower right); slow wave sleep (SWS) by slow EEG (delta, < 4 Hz) and low tone on the EMG; and paradoxical sleep (PS) by fast EEG and atonia on the EMG. The dashed line represents the transection between the telencephalon and the rhombencephalon or brainstem following which SWS persists in the telencephalon and PS in the rhombencephalon in addition to W. Neurons that are active during W (red symbols) include cells with ascending projections toward the cortex, which stimulate fast cortical activity (filled symbols), and cells with descending projections toward the spinal cord, which stimulate motor activity with postural muscle tone typical of behavioral W (open symbols). Those with predominantly ascending projections discharge in association with fast EEG activity (gamma+) and cease firing with delta activity (delta-) to be active during both W and PS (W/PS-max active, filled red symbols). They include cholinergic (ACh), GABAergic (GABA) and glutamatergic (Glu) neurons. Those with more diffuse or descending projections discharge in association with behavioral arousal and EMG activity (EMG+) and cease firing with muscle atonia to be active during W and silent during PS (EMG+, W active, open red symbols); they include noradrenergic (NA), serotonergic (Ser), histaminergic (HA), orexinergic (Orx), glutamatergic (Glu) and some GABAergic neurons. Neurons that are active during sleep include cells with ascending projections toward the cortex, which discharge maximally with slow wave activity during SWS (gamma-, delta+, SWS-max active, blue symbols) and those with descending projections toward the hypothalamus, brainstem or spinal cord, which discharge maximally with muscle atonia during PS (EMG-, PS-max active, aqua symbols). They include MCH neurons, GABA (with some glycine, Gly) and some Glu neurons. Abbreviations: 7g, genu 7th nerve; ac, anterior commissure; ACh, acetylcholine; BF, basal forebrain; CPu, caudate putamen; Cx, cortex;

DR, dorsal raphe; EEG, electroencephalogram; EMG, electromyogram; GiA, gigantocellular, alpha part RF; Gi RF, gigantocellular RF; GiV, gigantocellular, ventral part RF; Glu, glutamate; Gly, glycine; GP, globus pallidus; HA, histamine; Hi, hippocampus; ic, internal capsule; LC, locus coeruleus nucleus; LDT, laterodorsal tegmental nucleus; MCH, melanin concentrating hormone; Mes RF, mesencephalic RF; NA, noradrenaline; opt, optic tract; Orx, orexin; PH, posterior hypothalamus; PnC, pontine, caudal part RF; PnO, pontine, oral part RF; POA, preoptic area; PPT, pedunculopontine tegmental nucleus; PS, paradoxical sleep; RF, reticular formation; Rt, reticularis nucleus of the thalamus; s, solitary tract; scp, superior cerebellar peduncle; Ser, serotonin; SN, substantia nigra; Sol, solitary tract nucleus; SWS, slow wave sleep; Th, thalamus; VTA, ventral tegmental area; W, wake. Modified from [2].