Experientia 38 (1982), Birkhäuser Verlag, CH-4010 Basel/Switzerland

Regulation of physiological functions during sleep in mammals

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One of the last articles by W. R. Hess is entitled 'Sleep as a Phenomenon of the Integral Organism'[8]. It seems worth quoting from this article the following passage, which characterizes well the attitude toward experimental research of a successful pioneer in many fields of physiology.

'Once individual experiments have been concluded, it is essential that the data are interrelated and woven into a theoretical fabric. In this process of general theoretical integration I have repeatedly gained new insight particularly in respect to the organization of the diencephalon. Coordination of the findings is also necessary, if the true significance of the data is to be ascertained; this is especially true in biology... scepticism toward a synthetizing approach to biology means neither more nor less than giving up hope ever to understand the integration of life functions - the alpha and omega of the unity of the individual organism.'

Hess's words apply particularly to studies on the somatic and vegetative (autonomic) phenomenology of sleep. In fact, behavioral events are the result of a functional organization that can often be directly envisaged by the observer. Moreover, sleep phenomenology is instrumental in the process of decoding into operational propositions the related patterns of electrical and chemical activity of neural structures. There is no doubt that an effort to achieve a theoretical integration of such propositions ought to be carried out under the guidance of the unifying concept of *regulation.*

Following this line of thinking, this article in honor of W. R. Hess approaches from a theoretical point of view the problem of physiological regulations during sleep in mammals.

I. Changes in regulation during sleep

The study of the homeostatic regulation[4] of physiological functions is a basic line of research whose development has revealed, however, that also non-homeostatic operations do occur. In particular, voluntary and instinctive activities during wakefulness (W) may impose a load on or interfere with homeostatic control mechanisms at central and/or effector levels, so as to overwhelm their regulatory power. Deviations of fundamental biological variables from control ranges are, nevertheless, limited, since homeostatic mechanisms during W are capable of re-establishing a functional equilibrium. In contrast, the study of the somatic and vegetative phenomenology of sleep has shown a basic functional dichotomy. In fact, homeostatic regulation appears to be a discontinuous process, being present during synchronized sleep (SS) and absent during desynchronized sleep (DS).

The experimental evidence for a dichotomy in the functional organization of SS and DS stages concerns, in particular, temperature[6,15,17], cardiovascular[13] and breathing[16,21,26] regulations. Available findings suggest that such a dichotomy depends basically on a change in the functional relationships between diencephalic (mainly hypothalamic) and rhombencephalic structures. In other words, during DS, brain stem reflex and control mechanisms are released from hypothalamic regulatory influences which are active during W and SS[14,16-18].

Therefore, during DS, many biological variables are less precisely regulated and free to drift out of the normal range of homeostatic regulation. This does not always happen because of the short duration of DS episodes. At any rate, DS can be considered as a poikilostatic condition. From the regulatory point of view, the central fact is that external and internal stimuli calling for specific regulations during W and SS are less effective or even ineffective during DS. Yet, the loss of specificity of stimuli during DS is not associated to a loss of their non-specific arousing influences. The arousing effect, however, requires much higher stimulus intensities as compared to those which normally elicit the specific regulatory response. Moreover, such stereotyped behavioral responses to different stimuli clearly represent a regression in terms of the phylogenesis of regulatory mechanisms.

The suspension of homeostatic regulation during DS is more evident in those functions which, like thermoregulation, depend on control mechanisms located prevalently in the hypothalamus. In functions characterized by widely distributed control mechanisms, like respiration and circulation, this functional condition may be partially masked by the persistence of peripheral autoregulation or single reflex regulation. Nevertheless, also striking changes in reflex activity do occur during DS[13,21,26]. Such changes are different in the different functions, depending on the degree of their normal subordination to higher levels of integration. In other words, the functional condition of DS reveals phylogenetically determined levels of functional autonomy, as a result of the temporary regression from the normal degree of diencephalization. Thus, differences in DS phenomenology among species are accounted for by inborn patterns of morphofunctional organization and autonomy of brain stem and spinal operative levels.

The inactivation of hypothalamic homeostatic regulation during DS may be seen as a result of ascending influences of brain stem mechanisms effecting DS phenomenology. In this connection studies on hypothalamic units in waking and sleeping cats[20] are worth mentioning. In general, differences in firing rates of hypothalamic units between quiet W and SS are statistically not significant. These data are consistent with the patterns of somato-visceral activity that, throughout quiet W and SS, strictly meet the criteria of homeostatic regulation.

In contrast, the firing rates of almost all hypothalamic units during DS differ significantly from those of quiet W and SS. Two different populations of hypothalamic units were observed, one increasing, the other decreasing the firing rate during DS. The splitting of hypothalamic units into two functionally different populations may be considered as indicative of a loss of balance in the activity of inhibitory and excitatory neurons. This pattern of activity is consistent with the suspension of hypothalamic homeostatic regulation during DS.

The concise analysis of the phenomenal evolution of sleep in the next section may help to clarify the functional organization underlying the different stages of sleep. For a detailed description of the somatic and vegetative phenomenology of sleep in mammals the reader is referred to recent reviews[2,18].

II. Functional significance of the phenomenal evolution of sleep

In the phenomenal evolution of sleep the onset is followed by two contrasting sets of events, namely SS and DS, occurring with ultradian rhythm.

The behavioral repertory of the onset of sleep (OS) consists of the search for a safe ecological niche and the preparation of the body for the natural sleep posture. The somatic motor and postural repertories of OS are obviously related to changes in vegetative functions supporting muscular activity, which, however, are not specific to sleep. The complexity and variety of such performances in different species imply the integrated activity of the whole encephalon. On this basis, the stage of OS can be considered as an expression of the end result of phylogenetic evolution of the mammalian encephalon. Moreover, according to a hierarchical criterion, the leading neural structures in this stage of sleep, as far as behavioral phenomenology is concerned, are the same as in W, that is telencephalic[14].

SS is characterized by cessation of goal-directed motor activity, resulting in the suspension of the active contact of the organism with the environment. The concomitant decrease in postural activity depends on a specific regulation of muscle innervation rather than on a generalized tendency to hypotonia. This protective resting posture, varying among species, minimizes energy expenditure. In this respect the influence of hypothalamic thermoregulatory structures acquires a remarkable significance in so far as sleep posture is an aspect of behavioral thermoregulation. The vegetative phenomenology of SS is indicative of closed-loop operations, maintaining homeostasis at a lower level of energy expenditure with respect to W. This functional condition, characterized by a tonic increase in the parasympathetic outflow combined with a slight attenuation in sympathetic activity, was defined as 'trophotropic endophylactic' by Hess[7]. The somatic and vegetative phenomenology of SS is elicited by a regulatory system that has shifted from the control of activity to that of rest without changing its operative logic. The leading neural structures in this stage of sleep are, evidently, diencephalic[14].

During DS, postural and goal-directed motor activities are suppressed. The generalized muscle atonia depends on tonic brain stem inhibitory influences on spinal motoneurons[22]. The somatic phenomenology of DS is not the expression of a continuous process of sleep deepening beyond SS, but rather the sign of a functional dichotomy in the sleep cycle. Postural atonia and myoclonic twitches both depend on an open-loop mode of operation at spinal and higher levels. The basic vegetative event is a tonic decrease in sympathetic activity associated with random bursts of sympathetic outflow and phasic decreases in parasympathetic outflow. The vegetative changes with respect to SS also appear to be the result of an open-loop mode of operation which contradicts the logic of neural control of homeostasis. The leading neural structures in this stage of sleep are rhombencephalic[9].

In conclusion, the evolution of sleep in mammals implies a stepwise functional regression, which, in a reverse fashion, attains the successive functional levels of the phylogenetic development of the encephalon. In other words, sleep stages appear as functional landmarks of the discontinuous development of the mammalian encephalon through successive superimposition of increasingly complex hierarchical levels[12].

III. Phylogenetic basis of the phenomenal organization of sleep

The concept that sleep represents a sort of revisitation of neural phylogenesis deserves some more comments. Experimental evidence concerning the ontogenesis of the sleep cycle[24,25,28] and some studies of sleep phenomenology in inframammalian classes[27] support the view that the mechanisms of DS should be more ancient than those of SS. Moreover, the appearance of fully developed SS in relation to homeothermy[1] and, conversely, the suspension of temperature regulation during DS in homeotherms[6,15,17] are consistent with the inference that DS is a sleep stage depending on mechanisms which developed at a primitive level of neural organization. In this respect, the lack of evidence, in many inframammalian species, of DS according to criteria based on mammalian phenomenology may be scarcely relevant. As a matter of fact, such a lack may be due to many reasons, ranging from inadequate experimental conditions to improper observational criteria. Concerning the latter, it is reasonable to suspect that DS phenomenology may be rather different in inframammalian classes with respect to mammals as a result of morphofunctional differences[3]. Moreover, as far as neurovegetative control mechanisms are concerned, inframammalian species cannot display the SS-DS functional dichotomy occurring in mammals[18].

Another problem may be raised, namely, the persistence of DS in adult mammals after the ontogenetic development and the precise control of the circadian duration of DS[5,19]. It may be inferred that the functional state of DS, although characterized by a functional regression to a more primitive regulatory mode, is necessary also in species showing a high degree of tele-diencephalization. In view of similarities in the somatic and vegetative phenomenology of sleep and sleep-like states throughout the vertebrate phylum[11], the hypothesis can be advanced that the development of mechanisms of tonic inhibition and of centrally driven phasic activity (open-loop) such as those underlying DS in mammals, may have played an important role in the process of tele-diencephalization. In other words, the simple morphofunctional pattern of reflex activity may have evolved into more complex internuncial circuits as a result of the possibility to attain increasingly effective sensory-motor uncoupling.

The rhombencephalon bears a special significance in the phylogenetic development of sensory-motor uncoupling as a structure still underlying such uncoupling during DS in mammals[23]. Therefore, its ancient power of morphofunctional induction may still be effective particularly as far as monoaminergic mechanisms of sleep processes are concerned[10]. In particular, the activity of the rhombencephalon during DS may be related to maturation and operative efficiency of tele-diencephalic circuits in the newborn and the adult mammals, respectively.

IV. Conclusion

The previous considerations can be summarized by a simple diagram showing the rank of functional dominance attained by the telencephalon (T), the diencephalon (D), and the rhombencephalon (R) in the different sleep stages (fig.). The array of structures in each sleep stage has been inferred from the behavioral and bioelectrical phenomenology of sleep. The diagram shows that the transition between consecutive sleep stages and between sleep and wakefulness is always characterized by the ascent of two structures to the contiguous superior ranks and by the descent of the first rank structure to the lowest rank. Such a regular change in the pattern of functional organization is by no means incidental, but indicates that the phylogenetic development underlies the phenomenal evolution of the sleep-wakefulness cycle. In fact, out of 6 theoretically possible permutations (T-D-R, D-R-T, R-T-D, T-R-D, D-T-R, R-D-T) in the pattern of functional organization, only the 3 meeting an imperative phylogenetic criterion do occur, namely, T-D-R in W and OS, D-R-T in SS, and R-T-D in DS. The limiting criterion is the stability of the hierarchical organization of the D-R functional relationship, which is also revealed by the structural continuity of D and R cores. Two of the actual permutations (in W-OS and SS) show the normal D-R hierarchical relationship (-D-R and D-R-) characterized by homeostatic regulation of physiological functions. In contrast, hierarchical inversion (-R-D and R-D-) or hierarchical split (D-T-R) of such a relationship is obviously impossible. Only D-R split with hierarchical inversion (R-T-D) is possible (in DS). In this case, however, the descent of D to the lowest hierarchical rank is clearly instrumental in bringing about such a functional organization, which is necessarily characterized by a loss of homeostatic regulation.

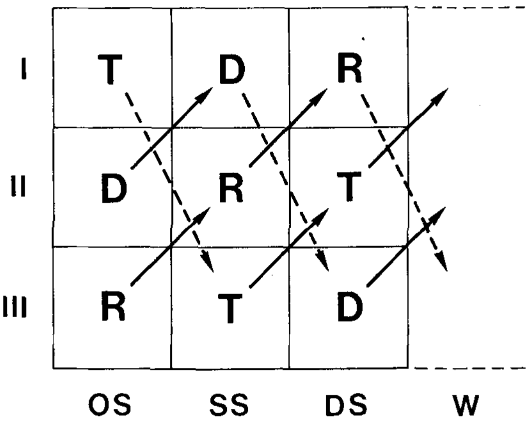

Diagram showing the rank of functional dominance attained by the telencephalon (T), the diencephalon (D) and the rhombencephalon (R) in the different sleep stages (OS: onset of sleep; SS: synchronized sleep; DS: desynchronized sleep). The array of structures in each sleep stage has been inferred from the behavioral and bioelectrical phenomenology of sleep. Permutations in the pattern of functional organization occur in an orderly way, as indicated by arrows.

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Dynamic changes of membrane structure in chemically and electrotonically transmitting synapses[1]

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Introduction

One of Walter Rudolf Hess' pioneering contributions to Neurobiology[2] was his well known method by which point-by-point electrical stimulation of deep brain structures could be achieved in the freely moving animal (Hess[15]). This procedure combined with a painstaking histological localization of the stimulation sites opened the way for the mapping of the waking brain. Behavioral effects such as sleeping, drinking, eating, orienting, locomotion, grooming, flight, defence and attack could be elicited in a manner unknown to previous investigators who had performed their experiments on animals kept in the deeply anesthetized state.

Twenty years ago when we began to explore the fine structure of synaptic membranes in the central nervous system, we were facing a similar situation. Thus, the commonly accepted technique of preparing the specimens was primarily aimed at an optimal preservation of cells and tissues, and little attention was paid to the functional state of the neurons immediately preceeding death. The best fixation of the tissue was achieved when the animals were kept under deep nembutal anesthesia, while their vascular system was perfused with carefully buffered Ringer followed by aldehyde solutions. Every laboratory at that time developed its own ritualized procedure in order to compete for the best results in tissue preservation.