Neurobiology of Sleep-Wakefulness Cycle 2(1): 21-26, 2002

SLEEP: WHAT IT IS? (ON DEFINITION OF THE NOTION)

V.I. MALOLETNEV
Department of Human Psychophysiology, I.S. Beritashvili Institute of Physiology, Georgian Academy of Sciences, Tbilisi

Accepted in revised form 5 March 2002; recieved 9 January 2002.

Summary

It is assumed that the biological function of sleep is to compensate the limitation imposed by internal properties underlying the principle of chemical synaptic transmission (as high sensitivity to changes of ionic gradients, limited supplies of the mediator accessible to discharge, tendency toward synaptic depression etc.) and provide the reliability of the synaptic apparatus of CNS neural networks. This function is performed by slow wave fraction of sleep which, depending on conditions, can be triggered by switch-on the internal (microsleep or essential sleep) or external (normal physiological or preventive sleep) contours of the CNS mechanisms of self-regulation.

Key Words: slow wave sleep, biological function, synaptic transmission, self-regulation.

About 15 years ago I have received from Dr. U.J. Jovanovic the letter containing two questions:

1. What is your definition of wakefulness (or waking)?
2. What is your definition of sleep (or sleeping)?

Up to now I have not the satisfactory responses on these questions and I have not found such responses in the literature. Obviously, the correct scientific definition of any phenomenon must include the notions about its mechanisms and function - otherwise the definition will be not more then description. So, it is to be supposed that one of the main reason of absence of adequate definition of sleep is due to the lack of clear understanding of its function (but can I say the same about the function of wakefulness?).

Making an attempt to define the sleep function (see Maloletnev 1988, 1993) I was guided by two undiscutable facts:

1. The sleep can not be substituted by tranquil enfeeble wakefulness with closed eyes in outward appearance indiscernible from sleep (remember the insomnia);
2. The main acknowledged objective indication of sleeping state is special pattern of electroencephalogram and correspondingly the characteristic pattern of neuronal activity.

These facts allowed to suppose that sleep is the special state of the brain and is necessary first of all for the maintains of brain's homeostasis. But such a supposition remain unanswered the main question: how did the sleep do it?

The study of the relationship between sleep and the homeostatic status of the organisms (see Maloletnev 1988, 1993 for references) showed that:

1. Sleep characteristics reveal a marked dependence on the fluctuations of homeostasis;
2. The general somatic homeostatic shifts are responsible for changes in sleep characteristics (mainly its slow wave fraction - SWS) only in that they affect the parameters of cerebral metabolism;

Correspondence: Maloletnev Victor, Prof., Department of Human Psychophysiology,
I.S. Beritashvili Institute of Physiology, Georgian Academy of Sciences,
14, L. Gotua str., Tbilisi, 380060, Georgia.
E-mail: physiology@posta.ge

3. The restorative properties of sleep are most clearly manifested in the improvement of performance quality of complicated motor skills which require an extremely high level of motor coordination. Such complicated motor actions are feasible only with the integration of a whole range of the "neural centers" involved into a single functional system. Presumably the efficiency of such a system largely depends on the precision of intercentral relations, - i.e. in the final analysis it is dependent upon the characteristics of the synaptic transmission processes in the neuronal networks of the CNS. Therefore, correlation between SWS and the performance was considered as a proof for a putative relationship between sleep and the processes affecting the functional state of central synapses.

Let's consider the basis of this assumption.

As is known, the afferent activation of central structures is always accompanied by changes in the ionic composition of the pericellular environment and primarily by changes in the kinetics of K^+ and Ca^{2+} ions. It must be accentuated that particularly pronounced changes was observed in the cerebral cortex during EEG activation evoked by direct electrical stimulation of the mesencephalic ascending activating system (MAAS).

In accordance with the available theoretical knowledge, changes of the ionic constants and membrane transport processes should be most clearly reflected on the functional state of those elements of neuronal network which are characterized by a high surface-to-volume ratio (Weight 1974). Consequently, the greatest sensitivity to the shifts resulting in the CNS from the afferent activation should be revealed by its synaptic apparatus. Specifically the changes of ionic gradients plays a dominant role in the development of the depression of synaptic transmission.

In this context it is essential to note that the peculiarities of the morphological and functional organization of the MAAS, that play the crucial role in the genesis of sleep, should be contributive to its particular sensitivity to factors causing synaptic depression. These peculiarities include the thin diameter of presynaptic terminals, lack of the myelin sheath over a considerable part of the presynaptic segment, the high ratio of presynaptic button volume to its surface.

The every reason to believe that a marked tendency toward synaptic depression is generally characteristic for MAAS gives the experiments showing that the reaction of EEG activation to a direct electrical stimulation of the mesencephalic reticular formation (MRF) rapidly became extinguished and that the number of habituating neurons in this region is greater than in other compartments of the CNS.

Correlation of the data presented allows to conclude that there exists a high probability of a direct interconnection between sleep and the depression of synaptic transmission. In order to test the hypothesis to the effect that sleep in its turn can affect the processes of synaptic transmission, we investigated the influence of sleep on habituation, or to be more precise, on synaptic depression underlying it (Maloletnev 1993). The obtained results have suggested that during sleep the functional state is normalized in those of the CNS synapses which during wakefulness develop shifts towards synaptic depression.

When exam the putative specific relationship between sleep and the regulation of the functional state of central synapses one should take into account that a temporal switch-off of a corresponding afferent channel is a principal consideration in liquidating the synaptic depression (Kandel 1980). Thereby our attention was drawn to the above mentioned fact: when passing from wakefulness to sleep there occurs a change in the activity pattern of the majority of neurons (see Steriade and Hobson 1976).

A great body of information has been accumulated to data, attesting that central to this phenomenon is the reorganization of intercentral relations and, consequently, the repatterning of interneuronal relations. It has been shown, in particular, that occurrence in the EEG of slow waves and the so-called sleep spindles reflect the changed interrelations between structures of the reticular-thalamic-cortical system and the reorganized interactions in the neuronal modules of the MRF (Satoh et al. 1979; Rocha 1980; Eguchi and Satoh 1982), thalamus (Purpura 1974; Hirsch et al. 1983) and cortical hemispheres (Steriade 1978; Inubushi et al. 1978a; b).

From the neurophysiological point of view such a repatterning presupposes that during the EEG synchronization and, consequently, at falling asleep, the synaptic inputs determining the impulsation pattern of a given neuron during wakefulness yield their dominant role to the synapses whose activity before the functional reorganization attending the onset of sleep was either completely blocked, or masked by the prevailing afferent inputs.

The foregoing would seem to suggest that the reorganization of the input influences in the process of falling asleep sets up conditions for a temporary decline of activity or even for a complete switch-off of the synapses that are most active during wakefulness, and, consequently, this might contribute to the restoration of the functional state of those synapses.

Besides, the restorative effect of sleep can be realized via the influence of other factors. Thus, in the context of an increased proportion of the periods of inhibition the spontaneous activity of the central neurons, observed during SWS, special interest attaches to the data indicating that the process of postsynaptic inhibition is attended by an increased accumulation of intramitochondrial glycogen (Schabadasch 1972). This means that the intensification of inhibitory processes during SWS might contribute to the normalization of the energetic metabolism of neural elements. On the other hand, it should be noted that the increased concentration of extracellular K, recorded during EEG activation in the hemispheric cortex with the onset of synchronization tends towards normalization (Astrup and Nornerg 1976) - i.e. sleep might favour the correction of ionic shifts, leading to the depression of synaptic transmission.

Proceeding from the foregoing facts reported in this paper and from theoretical postulates the following conclusion may be drawn:

By its neurophysiological nature, transition from wakefulness to sleep is a process of functional reorganization of the CNS internal structure, setting up conditions for the normalization the functional state of its synapses, i.e. of those elements of the neuronal network which account for a major workload.

Such a conclusion allows to suggest a new approach in the treatment of some well-established facts and to put forth a number of considerations concerning the biological implications of sleep. In particular this concerns the sleep deprivation experiments.

Deprivation, i.e. suppression of sleep, is the principal method used in studying the functions of sleep. Deprivation experiments made it possible to reveal one regularity which merits special attention. It turned out that fits of drowsiness in the process of deprivation occur as episodes of the so-called micro-sleep, which are short of time during which the EEG shows bursts of high-amplitude slow waves, K-complexes, and sleep spindles (Dement and Mitler 1974; Naitoh 1976). Unless this takes place one can observe "lapses of consciousness" (Johnson and Naitoh 1974; Polzella 1975) and disturbances of perception, owing to which the contact with the ambient environment is impaired and subjects begin to act erratically.

The results obtained by method of sleep deprivation are unambiguously interpreted as a direct outcome of "elimination" or "extraction" of sleep. In the analysis of the results of the sleep deprivation experiments an all-important circumstance is ignored, viz that for deprivation it is essential to apply awakening stimuli, which counteract falling asleep. From the neurophysiological point of view, this presumably means that sleep deprivation per se is a stimulation of the activating system of the brain for the purpose of evoking the arousal reaction rather than sleep "extirpation". In other words, sleep deprivation might be viewed as the process of a prolonged stimulation of the activating system, the EEG desynchronization reaction being considered as response of this system.

If the activation reaction characteristics during deprivation are analysed from this standpoint, one can identify a number of indicators which, according to the common accepted criteria (Thompson and Spencer 1966), are typical for habituation (i.e. synaptic depression). Not out of place to mention here that the experiments on cats showed the rapid extinction of the reaction of EEG activation to a direct MRF stimulation and it is precisely habituation that underlies such an extinction (Oniani et al. 1976).

Thus, the foregoing allows to conclude that the direct and, presumably, the basic reason for the occurrence of microsleep fits under conditions of deprivation is the depression of impulsation conduction in the synaptic apparatus of the brain activating system.

In the light of the considered data the neurophysiological processes, resulting in falling asleep in response to monotonous stimulation and in the onset of microsleep under conditions of deprivation seem identical: in both situations the direct, and, presumably, the basic reason for the onset of sleep is the homosynaptic depression - or similar to it phenomenon - arising in synaptic apparatus of the activating system of the brain. Proceeding from the functional peculiarities of this type of sleep, we propose to define it as the "pure sleep", sleep per se or "essential sleep" (ES). The ES switch-on mechanism might be conceptualized as follows.

Under conditions of prolonged exposure to factors stimulating the organism to wakefulness, prerequisites are created in the synaptic apparatus of the activating system for the development of synaptic transmission depression. As a consequence, the transmission of impulsation decreases in the input, output and/or intrareticular synapses, which results in the decline of the activating effect of afferent impulsation on MRF, and, consequently, in the decrease of the share of tonic impulsation set to the rostral compartments of the brain. As a result there occurs a reorganization of the interneuronal relations owing to a release of the inhibitory thalamic and cortical elements from the suppressing reticular control (Mancia et al. 1974; Singer 1979). This results in the repatterning of the activity of the reticular-thalamic-cortical networks, expressed in the EEG synchronization and in the switch-on of the mechanisms of sleep spindles generation.

In terms of biology, ES presumably represents one of the versions of the "escape" phenomenon - in this case the CNS escape from the excessive extracerebral stimulation. Its functional implication is determined by the fact that at this moment conditions are set up for the restoration of negative shifts in those of the central synapses which account for the greatest load during wakefulness, i.e. in the synapses of the activating system. The repatterning of the activated synapses of the given neuron due to the reorganization of intraneuronal interactions is the chief factor favouring restoration. On account of the fact that the EEG synchronization, attending ES, entails an intensification of inhibitory processes and a decreased concentration of extracellular K, the possibility cannot be ruled out that this type of sleep can be conductive to the normalization of the energetic metabolism and the restoration of ionic constants.

In the context of the concepts under discussion ES is considered as a manifestation of the action of the fundamental and, probably, phylogenetically old mechanisms of the CNS functional state self-regulation.

Normal physiological sleep, occurring at regular intervals under normal conditions, differs from ES both in its genesis and the function performed. Thus, proceeding from ethological observations it may be assumed that there are two basic factors involved in the sleep onset: a) the attainment by the organism of a certain homeostatic state following the satisfaction of basic vital needs (see Sterman and Wyrviecka 1967; Soulairac et al. 1972) and b) the activation of the mechanisms which regulate the circadian periodicity of biological processes. The above considerations give every reason to suggest that the shifts of the ionic constants in the brain intercellular environment over a certain admissible limit might serve as another endogenic signal for the switch-on of physiological sleep.

Proceeding from the present knowledge, the neurophysiological switch-on mechanism of physiological sleep can be presented in the following way.

Depending upon the existing conditions the triggering signals from external timers and/or interoceptors activate the system of the so-called prosencephalic hypnogenic complex, involving the prefrontal cortex and suprachiasmal nucleus, viewed presently as the principal regulator of the circadian periodicity of bodily biological functions, and the preoptic area of the anterior hypothalamus (see Rusak and Zucker 1979). Abundant neural ties, and especially neurohumoral influences enable this complex to control and modulate the activity of many CNS compartments (see Oniani 1980). However, with respect to the question under discussion, of prime importance is the dominant role of the complex in triggering the going-to-sleep behavior (Sterman and Clement 1974) which, under normal conditions, necessarily preceeds falling asleep. Such a behavior consists of: a search for a place meeting safety, temperature comfort, etc. requirements; taking the most convenient posture for the relaxation of the postural musculature; closing the eyes.

From the neurophysiological point of view, the realization of the going-to-sleep behavior will directly result in the reduction of the CNS afferent flow, primarily due to the decrease of impulsation coming from muscular proprioceptors. As is known, a considerable number of afferent impulses in MRF come directly via these channels, while the activity level of another essential part of the activating system - the posterior lateral hypothalamus - displays a critical dependence upon the flow of proprioceptive impulsation (Gellhorn 1961). In other words, the realization of the going-to-sleep behavior necessarily leads to a decrease in the tone of the activating system, and, - given the proper conditions, - to falling asleep. This assumption is favoured by numerous experimental results, and clinical observations, demonstrating the somnogenic effect of muscular relaxation.

In the final analysis, the described sequence of events leads, presumably, to a reorganization of interneuronal relationship and, correspondingly, to a repatterning of functioning synapses, which is expressed in the change of the activity mode of central neurons - i.e. there occurs a functional reorganization of the CNS neuronal networks. In our view, this reorganization determines the basic difference between wakefulness and sleep.

As was noted above, the repatterning of interneuronal relations might favour the elimination of a tendency to shifts towards the depression of impulsation transmission in the synapses, tonically activated during wakefulness.

Summing up the concepts developed, one might conclude:

a. From the neurophysiological point of view the main event during transition from wakefulness to sleep is a process of functional reorganization of the CNS internal structure, consisting in the fact that the synaptic inputs determining the activity pattern of a given neuron during wakefulness yield their dominant role to the synapses whose activity during the wakefulness was less intensive. This reorganization set up the condition for the normalization of the functional state of the synapses which account for a maximal work load during wakefulness - primarily the synapses of MAAS;
b. In the extremal conditions this process of functional reorganization become apparent as a "microsleep" episodes which we define as the "essential" form of sleep and which in the context of the concepts under discussion is considered as a

manifestation of the fundamental and, probably, phylogenetically oldest mechanisms of the CNS functional state self-regulation;

c. The basic biological function of normal physiological sleep consists in preventing the CNS from such a mode of activity that creates the danger of a sudden switch-on to ES episodes, for at these moments the control is lost over the external events and the organism becomes readily exposed to potentially dangerous factors, which, obviously, is incompatible with survival under the serve conditions of natural selection.

In general it is assumed that the biological function of sleep is to compensate the limitations imposed by internal properties underlying the principle of chemical synaptic transmission (as high sensitivity to changes of ionic gradients, limited supplies of the mediator accessible to discharge etc.) and to provide the reliability of the synaptic apparatus of CNS neuronal networks. This function is performed by SWS which, depending on conditions, can be triggered by switch-on of the internal (essential sleep) or external (normal physiological or preventive sleep) countours of self-regulation.

As for functional role of the rapid eye movement (REM), or paradoxical phase of sleep it seems more plausible to assume that biological implication of this phase is rather determined by its place in the basic system, regulating the temporal organization of physiological processes, then by the function of sleep per se. In the context of the developed concepts the REM sleep is considered to be reflection of the endogenic oscillator functioning, determining the average level of activity in the biorythm of the sleep-wakefulness cycle (see Maloletnev, 1988, 1993).

References

Astrup, J., Norberg, K. Potassium activity in cerebral cortex in rats during progressive severe hypoglycemia. *Brain Res.*, 1976, 103: 418-423.

Dement, W., Mitlew, M.M. An introduction to sleep. In: O. Petre-Quadens and J.D. Schlag (Eds.), *Basic Sleep Mechanisms*. Acad. Press, N.Y., London, 1974: 271-296.

Eguchi, K., Satoh, T. Cross-correlation analysis of midbrain reticular pairs during sleep-wakefulness cycle of the cat. *Brain Res.*, 1982, 245, 2: 259-266.

Gellhorn, E. Some fundamental characteristics of autonomic physiology and their implications for the higher functions of the brain. In: *1st International Conf. Mental Retardation*, USA, 1961: 83-97.

Hirsch, J.C., Fourment, A., Marc, M.E. Sleep-related variations of membrane potential in the lateral geniculate body relay neurons of the cat. *Brain Res.*, 1983, 259, 2: 308-312.

Johnson, L., Naitoh, P. The operational consequences of sleep deprivation and sleep deficit. *AGRD-AG, NATO*, 1974, 193: 43.

Inubushi, S., Kobayashi, T., Oshima, T., Torii, S. Intracellular recordings from the motor cortex during EEG arousal in unanaesthetized brain preparations of the cat. *Jap. J. Physiol.*, 1978a, 28: 669-688.

Inubushi, S., Kobayashi, T., Oshima, T., Torii, S. An intracellular analysis of EEG arousal in cat motor cortex. *Jap. J. Physiol.*, 1978b, 28: 689-708.

Kandel, E.R. *Cellular Basis of Behavior*. Mir, Moscow, 1980, (Russian translation).

Maloletnev, V.I. On the biological function of sleep. In: T. Oniani (Ed.), *Neurobiology of Sleep-Wakefulness Cycle*, Metsniereba, Tbilisi, 1988: 255-286.

Maloletnev, V.I. *Biological Function of Sleep*. (Monograph. Russian, English resume), Metsniereba, Tbilisi, 1993.

Mancia, M., Margnelli, M., Mariotti, M., Spreafico, R., Broggi, G. Brain-stem-thalamus reciprocal influences in the cat. *Brain Res.*, 1974, 69, 2: 297-314.

Naitoh, P. Sleep deprivation in human subjects: a reappraisal. *Waking and Sleeping*, 1976, 1: 51-60.

Oniani, T.N. *Integrative Function of the Limbic System. Metsniereba*, Tbilisi, 1980, (in Russ.).

Oniani, T.N., Koridze, M.G., Kavkasidze M.G., Gvetadze, L.B. The effect of electrical stimulation of mid- and inter- brain structures on the dynamics of different phases of sleep and their correlation. In: T. Oniani (Ed.), *The Neurophysiology of Emotions and Sleep-Wake Cycle, Metsniereba, Tbilisi*, 1976: 28-62, (in Russ.).

Polzello, D.J. Effects of sleep deprivation on short-term recognition memory. J. *Experimental Physiol.*, 1976, 104: 193-200.

Purpura, D.P. Intercellular studies of Thalamic Synaptic mechanisms in evoked synchronization and desynchronization of electrocortical activity. In: O. Petre-Quadens and J.D. Schlag (Eds.), *Basic Sleep Mechanisms*. Acad. Press, N.Y., London, 1974: 99.

Rocha, A.F. Temporal influence of the reticular formation on sensory processing. In: J.A. Hobson and N. Brazier (Eds.), *The Reticular Formation Revisited*. Raven Press, N.Y., 1980: 105-115.

Rusak, B., Zucker, J. Neural regulation of circadian rhythms. *Physiol. Rev.*, 1979, 59, 3: 449-526.

Satoh, T., Eguchi, K., Watabe, K. Functional relationship between cat brainstem neurons during sleep and wakefulness. *Physiol. Behav.*, 1979, 22, 4: 741-745.

Shabadash, A.L. Intramitochondrial glycogen and its experimental changes in neurocytes. In: *Mitochondria. Molecular Mechanisms of Enzymic Reactions*. Nauka, Moscow, 1972: 52-56, (in Russ.).

Singer, W. Central core control of visual cortex functions. In: F.O. Schmitt and F.G. Worden (Eds.), *The Neurosciences, IV-th Study Program,* MIT Press, Cambridge, London, 1979: 1093-1110.

Soulairac, A., Tangapregassom, M.J., Tangapregassom, A.M. Analyse electroencephalographique souscorticale des etats de soif et de satiete chez le rat. *CR Acad. Sci.*, 1972, 265: 97-99.

Steriade, M. Cortical long-axoned cells and putative interneurons during the sleep-waking cycle. *Behavioral and Brain Sci.*, 1978, 3: 465-514.

Steriade, M., Hobson, J.A. Neuronal activity during the sleep-waking cycle. *Progress in Neurobiology*, 1976, 6: 155-376.

Sterman, M.B., Clemente, C.D. Forebrain mechanisms for the onset of sleep. In: O. Petre-Quadens and J.D. Schlag (Eds.), *Basic Sleep Mechanisms*. Acad. Press, N.Y., London, 1974: 83-97.

Sterman, M.B., Wirwicka, W. EEG correlates of sleep: evidence for separate forebrain substrates. *Brain Res.*, 1967, 6, 1: 143-163.

Thompson, R.F., Spencer, W.A. Habituation: A model phenomenon for the study of neuronal substrates of behavior. *Psychol. Rev.*, 1966, 73, 1: 16-43.

Weight, F.F. Physiological mechanisms of synaptic modulation. In F.O. Schmid (Ed.), *The Neurosciences. Third Study Program.* MIT Press, 1974: 929-942.