Rapid Eye Movement Sleep and Dream Sleep

6

Birendra Nath Mallick

Abstract

Consciousness is an attribute of the brain, by the brain, and for the brain. Our understanding of neurophysiological mechanism of consciousness is rudimentary. The experimental scientists describe three states of consciousness as wakefulness, non-rapid eye movement sleep (NREMS), and rapid eye movement sleep (REMS); most dreams appear intermittently during REMS. As the dream (REMS) may apparently be compared with wake-like condition within sleep (NREMS), I proposed that understanding of this state would provide a better handle to explore the neuronal basis of consciousness. These states are reversible and contiguous and, while seamlessly transiting from one to the other state in health and diseased conditions, may overlap to various extent. In this chapter, I have combined some neurophysiological evidence with philosophical wisdom proposed by the philosophers and sages of ancient India in the *Upanishads*. In my view, an all-inclusive, background state, the *T-state* may explain the neurophysiological basis of consciousness and its proportional masking and unmasking are expressions of classical states.

Keywords

Cognitive states · Dream · EEG · Sleep · *Thuriya* · *T-state* · Upanishadic view · Wakefulness

B. N. Mallick (✉)
Amity Institute of Neuropsychology and Neurosciences, Amity University, Noida, Uttar Pradesh, India

R. C. Sobti, A. K. Ganju (eds.), *Biomedical Translational Research*,
https://doi.org/10.1007/978-981-16-8845-4_6

6.1 Rapid Eye Movement Sleep and Dream Sleep

Our healthy existence depends on how best we (our body) negotiate with our environment, living or non-living. By and large, such negotiations are dependent on our knowledge of understanding about the self and the surrounding. The acquisition of knowledge depends on how best we can extract the information due to interaction of self and surrounding. Our knowledge and understanding of this universe are done by the brain and ultimately depend on its (brain's) conscious state. Historically, in the absence of better defining characteristics, based on physical movement, the consciousness has been divided into wakefulness and sleep states, the latter has been further divided into sleep and dream states. The dream state is unique, involuntary state that behaviorally although one is deep asleep, as if consciously one appears to experience wakefulness-like condition, interestingly without any volitional control. Classically, the modern science grossly classifies consciousness into three states: wakefulness, sleep, and dream. Notwithstanding, in the ancient literature, the *Upanishads* (Mandukya Upanishad), based on their then contemporary wisdom, the philosophers and sages of ancient India have categorized the consciousness into four states and termed them as *Jagriti* (waking), S*ushupti* (sleep), *Swapna* (dream), and *Thuriya*. It is high time that the modern science should take note of these states and possibly using the modern sensitive gadgets try finding a meeting point while explaining the ancient philosophical and conceptual states. In attempting so, this author has explained the *Thuriya* state (and termed it as *T-state*) as all-pervasive background basal substrate state on which the rest of the three states get expressed (Mallick and Mukhopadhyay 2011). It has been proposed that inputs to the brain, globally or locally, reversibly and proportionately suppress (masking and unmasking) such background *T-state* causing expression of classical states in health and diseases. The modern experimental science does not recognize or conceptualize such basal background state on which the classical three states and their variations get expressed. In the absence of consideration of such state, the missing link of easy seamless transition and switching among various states and gradation within the same state during health and diseases would continue to remain a mystery.

Since our existence, historically, based on one's personal experience, the humans were aware of the three states, viz., awake, sleep, and dream. Although behaviorally one could grossly define awake and sleep states by the presence or absence of physical activity, inactivity does not necessarily define always either non-awake or asleep. Also, one finds it difficult to differentiate between rest, quiet-awake, awake but rest, asleep, and so on. Although behavioral studies on sleep and waking were conducted, inherently, it has limitations such as possible subjective biasness. As one would not be able to objectively define wakefulness and sleep states, critical scientific and experimental studies were limited until about the first quarter of the twentieth century. Thereafter, as recording of the electrical activities from the brain, the electroencephalogram (EEG), was possible, the sleep and waking states could be objectively defined and identified (Berger 1929; Rechtschaffen and Kales 1968); however, still one did not have any clue of objective identification of dream state. Subsequently, additional recording of eye movement and electrical activity from the

neck muscles, the electro-oculogram (EOG) and electromyogram (EMG), respectively, enabled us deciphering not only gradation of wakefulness and sleep but the dream state was also identified. A series of studies through the second-third of the twentieth century using those electrophysiological recordings not only had put the death nail on the passive theory of sleep but it gave birth to the concept that not only awake but also sleep is an active phenomenon [*reviewed in detail in* Moruzzi 1972]. The electrophysiological recordings of EEG, EOG, and EMG showed in animals as well as in humans that intermittently during sleep a paradoxical state appears when the brain becomes more active (apparently comparable to awake) and the eyes show significant activity/movement (increased EOG) while the antigravity muscles show almost no activity (atonia in the EMG). Therefore, this state was termed as rapid eye movement sleep (REMS) (Aserinsky and Kleitman 1953; Aserinsky 1999; Jouvet 1999) or paradoxical sleep (Jouvet and Michel 1958; Jouvet 1999). Subsequently, it was observed that usually this state is associated with vivid dreams. Hence, it has been termed as dream sleep as well, largely by the psychologists (Dement 1960); however, the term REMS has been most widely used and will be used in this piece. The vivid dreams appear intermittently during this state when otherwise one is fast asleep and one does not have a voluntary control over this state, while apparently, it provides intermittent manifestation of waking-like mental activity within the sleeping state (dreaming). Therefore, ***I thought a thorough exploration and understanding of neuronal regulation of this REMS state might offer us an objective as well as a better handle to experimentally study the neuronal basis as well as regulation of conscious states***.

6.2 Brainstem, REM-OFF, and REM-ON Neurons

Discovery of REMS as defined by the electrophysiological criteria (EEG, EOG, and EMG) in the mid-twentieth century invited leading researchers of the time to relook and reinterpret previous studies as well as explore further the brain regions and specific neurons responsible for its control (Aserinsky and Kleitman 1953; Moruzzi 1972; Jouvet 1999; Mallick et al. 2011). Experiments using localized lesion and transection of brain regions concluded that neurons at the core of the brainstem play a critical role in REMS regulation, which however are modulated by many other brain regions (Siegel 1989; Mallick and Inoue 1999; Steriade and McCarley 2005). The brainstem possesses, among many other types of neurons, the locus coeruleus (LC) as the primary source of noradrenaline (NA)-ergic neurons in the brain and somewhat extended more laterally placed laterodorsal and pedunculopontine tegmentum (LDT/PPT) possessing predominantly acetylcholine (ACh)-ergic neurons. Subsequent studies have shown that the LC and LDT/PPT possess GABA-ergic and glutamatergic neurons and terminals as well. The PPT ACh-ergic neurons are mostly active during REMS only or significantly increase activity during REMS and have been termed as REM-ON neurons (McCarley and Hobson 1971). In contrast, the LC-NA-ergic neurons behave in an opposite manner and are active during wake as well as non-REMS (NREMS) and become almost silent during REMS; they have

been termed as REM-OFF neurons (Hobson et al. 1975, 1983; Aston-Jones and Bloom 1981). Based on these independent, isolated studies and following the Lotka-Volterra model, it was proposed that the REM-ON and REM-OFF neurons reciprocally inhibit each other and form the basic scaffold for the regulation of REMS (McCarley and Hobson 1975; Sakai 1988); however, detailed mechanism was unknown.

6.3 Cessation of LC-REM-OFF Neuronal Activity Is a Prerequisite for REMS Generation

In previous studies the REM-OFF and REM-ON neuronal activities were recorded independently, in isolated experiments and in separate animals. For confirmation, ideally it was preferred to record them simultaneously in real time and in the same animal during normal behavioral sleep-waking-REMS as well as during REMS deprivation (REMSD). To my mind, it was necessary to understand if the cessation of REM-OFF neurons is a prerequisite or a coincidental occurrence associated with REMS. For that, we needed to know the mechanism of inhibition of the REM-OFF neurons, the execution of triggering of REM-ON neurons, and finally, the temporal relationship between the reciprocal activities between those two types of neurons. The reciprocal relationship between those two types of neurons was supported by their behavior during 96 h of continuous REMSD in freely moving normally behaving animals (Mallick et al. 1990). Incidentally, this is the only documented report where the effect of REMSD was studied on the activities of REM-ON and REM-OFF neurons although in separate cats.

In a series of studies, first we hypothesized that if cessation of REM-OFF neuronal activities was a necessity for the generation of REMS, continued activation of those REM-OFF neurons should prevent appearance of REMS. In behaving chronically prepared rats, we showed that if the LC neurons were kept continuously active for a long time, REMS was indeed prevented (Alam et al. 1993; Singh and Mallick 1996). To the best of my knowledge, this is the first documented study (in the literature) in behaving animals to chronically activate specific deep region of the brain with very small electrical current for a reasonably long duration to simulate an involuntary instinct behavior. Subsequently, we recorded electrophysiological sleep-wakefulness-REMS and the REM-ON and REM-OFF neuronal activities simultaneously in the same chronically prepared behaving animals and showed that temporally indeed they showed reciprocal relationship in their activities not only during spontaneous expression of REMS but also during brainstem reticular formation activation-induced waking (Mallick et al. 1998). Possibly this is still the only study where REM-ON and REM-OFF neurons have been recorded simultaneously (together) in the same animal, at the same time, during change of spontaneous conscious states as well as upon experimentally induced change of behavioral state. Consolidation of findings of these studies validated the reciprocal relationship between the REM-OFF and the REM-ON neurons. However, the mechanism of

activation and cessation of REM-ON and REM-OFF neurons in relation with REMS was not known.

6.4 Normally Why REMS Appears Only After a Period of NREMS and Does Not Appear During Waking

Although REMS is an instinct behavior, normally it appears only after a period of NREMS has been expressed. Also, it is not expressed during waking, apparently comparable expression e.g., hallucination has been reported during waking and during REMS-behavior disorder (Mahowald et al. 1998; Manni et al. 2002; Arnulf 2013). We proposed that the waking- and NREMS-inducing brain areas should have opposite effects on the REM-ON and REM-OFF neurons. Indeed, it was observed in chronically prepared behaving cats that the waking- and NREMS-inducing brain areas have inhibitory and excitatory effects, respectively, on the REM-ON and REM-OFF neurons (Thankachan et al. 2001). The stimulation of the NREMS area, although did not significantly affect the REM-OFF neurons, excited the REM-ON neurons (Mallick et al. 2004). These findings offered neuronal (cellular) mechanism of regulation of REMS; most importantly, they suggested that the REM-OFF neurons, which were active, must cease activity, while REM-ON neurons increase activity for the generation of REMS. The next issue for confirmation was to explore their neurochemical regulation that modulates REMS in health and diseases.

6.5 The Role of GABA on the Inhibition and Disinhibition of REM-OFF and REM-ON Neurons for the Regulation of REMS

We have seen above that ACh-ergic REM-ON and NA-ergic REM-OFF neurons are likely to be reciprocally connected, while the LC-REM-OFF neurons must cease activity for the generation and maintenance of REMS. In the late 1980s, it was a challenge to investigate the neurochemical basis of inhibition of those LC-REM-OFF neurons for the generation of REMS particularly in behaving animals. Notwithstanding, in a related in vitro slice preparation study, it was shown that ACh-ergic agonist, carbachol, depolarized the LC neurons suggesting that ACh directly would not inhibit the NA-ergic neurons (Egan and North 1985).

We proposed that ACh-ergic REM-ON projections would stimulate the GABA-ergic interneurons, which then would inhibit the NA-ergic REM-OFF neurons in the LC. Our contention was supported by the then reports that the LC possesses ACh-ergic projections as well as GABA-interneurons. The challenge to explore how ACh stimulated the GABA-ergic neurons in the LC was further compounded by the fact that the investigation needed to be conducted in chronically prepared behaving animals and the small size of the LC in the rats. We designed ***neuro-micro-anatomo-pharmaco-physio-behavioral study*** using a combination of serial sequential multiple microinjections of 200 nL of agonist and antagonist into the LC of

surgically prepared chronic rats. Microinjection of such extra-small quantity of chemical into the brain of freely moving living animals for behavioral study was among the early studies and was used for the first time from this lab in the 1990s. ACh-ergic and GABA-ergic agonist and antagonist individually or in a sequence were bilaterally microinjected locally deep into the LC in chronically prepared normally behaving freely moving animals and electrophysiological waking-sleep-REMS recorded continuously for long hours. The findings indeed confirmed that ACh-ergic inputs into the LC acted on the GABA-ergic neurons and initiated REMS, possibly by inhibiting the REM-OFF neurons and thus, supported our contention (Alam et al. 1993; Kaur et al. 1997; Mallick et al. 2001).

Combining findings of others along with that of ours, we proposed that activation of the REM-ON neurons released ACh, which stimulated the GABA-ergic neurons in the LC and the released GABA inhibited the REM-OFF neurons resulting in the generation and maintenance of REMS. However, it was not known how the REM-ON neurons remain inhibited and subsequently become active to initiate REMS. Earlier we have shown that the REM-OFF neurons receive excitatory and inhibitory inputs from the wake- and NREMS-active areas in the brainstem, while the REM-ON neurons receive opposite influence (Mallick et al. 2004). Integrating findings from other researchers (Williams and Reiner 1993; Inglis and Winn 1995) as well as that of ours (Pal and Mallick 2004, 2006), it was proposed that the NA from the REM-OFF neurons inhibits the REM-ON neurons preventing the appearance of REMS during waking. Subsequently, when some yet unidentified conditions are satisfied, GABA-ergic inputs from the substantia nigra (SN) act presynaptically on the NA-ergic inputs (terminals) coming from the LC REM-OFF neurons onto the PPT REM-ON neurons to withdraw the NA-ergic inhibition from the ACh-ergic REM-ON neurons and trigger them initiating REMS (Pal and Mallick 2009; Mallick et al. 2012).

6.6 Mathematical Modeling and Computational Simulation Studies (In Silico)

The REMS is a unique, instinct state, which under normal condition does not appear during waking but gets expressed only after the appearance of NREMS for some duration. Independently we have shown how waking and NREMS regulating areas in the brain modulate the REM-OFF and REM-ON neurons and their neuropharmacology for the generation of REMS. However, the facts are that under normal condition every NREMS is not followed by REMS, varied duration of NREMS appears before the expression of REMS, all REMS episodes do not continue for the same duration, and REMS may end up in NREMS or waking while, under abnormal conditions, REMS-like state (hallucination) appears during waking. Therefore, it was likely to be that there is complex interaction among various neural networks maintaining waking and NREMS for the regulation of REMS. The complexity gets further compounded by the fact that the synaptic strengths of the component neural networks and that of the networks at large are dynamic. As it is almost impossible to

modulate one or more of these networks simultaneously in vivo in behaving animals under controlled conditions, we reconstructed the neuronal connections as obtained from the animal studies (described above) into a mathematical model. In the said mathematical model, the input and output strengths of the networks could be modified individually or in combination. Such study revealed that as long as the inhibitory input from the brainstem waking area onto the REM-ON neurons remains active, despite the inputs from SN, REMS (as defined by the activity of the REM-ON neurons) does not appear (Kumar et al. 2012). The limitation of the said mathematical modeling simulation study is that it does not allow behavioral study; however, it provides in-depth understanding at the neuronal network level, which is not possible by the behavioral study; thus, they are complimentary. This finding is significant as it provides experimental evidence why REMS does not appear during waking and suggests possible mechanism of appearance of dream-like state (hallucination) during waking in diseased condition. The importance and power of this model is that it may be used to explore the possible neurophysiological and neuropharmacological deviations in association with REMS-associated changes in different species through evolution and possibly to predict the functional disorders in association with diseases.

6.7 Confirmation of the Neuro-Physio-Pharmacological Network with Support from REMS-Functional Correlates

Based on the findings from isolated independent studies, it was interpreted that GABA-induced inhibition of the LC-NA-ergic REM-OFF neurons is a necessity for the generation of REMS and non-cessation (continued activity) of the REM-OFF neurons prevents appearance of REMS. For confirmation of such neural network being responsible for maintenance of REMS, we hypothesized that if the LC-NA-ergic REM-OFF neurons were not allowed to cease activity, not only REMS should be reduced but there should be elevated level of NA in the brain and that should induce expression of otherwise REMS-loss associated changes (symptoms). Indeed, infusion of picrotoxin (Pic), a GABA-antagonist, into the LC prevented REMS and induced NA-induced increased Na-K ATPase activity (Kaur et al. 2004), and the latter was comparable to that observed otherwise due to REMSD (Gulyani and Mallick 1993, 1995; Mallick et al. 2000; Mallick and Singh 2011). Finally, to confirm if we downregulated the NA synthesis in the LC neurons using si-/sh-RNA, REMS was increased (Khanday et al. 2016). Additionally, if such rats with downregulated NA were deprived of REMS, the REMSD-associated NA-induced increased Na-K ATPase activity and neuronal apoptosis was prevented (Somarajan et al. 2016). These findings are proof-of-principle and perhaps fit case to extend the knowledge acquired in the laboratory (bench) from basic animal studies and take it to the bedside for human benefit. To prove, the knowledge may be translated (with or without modification) either by downregulating synthesis or release of NA or by preventing the action of NA in the brain to ameliorate REMS-loss-associated symptoms preferably in the humans.

6.8 Evolutionary Significance of REMS

As described above, the loss of REMS induces elevated level of NA in the brain and that causes many (if not all) of the associated acute and chronic symptoms (Mallick and Singh 2011). Interestingly, REMS is present in animals through evolution in different species and throughout life (ontogenically) in the same individual. The question is, if loss of REMS induces elevated NA and that adversely affects the brain, why in evolution has REMS come into existence and is being maintained (i.e., did not get lost) through generations and running millions of years through evolution? We have mentioned above that the NA-ergic REM-OFF neurons are continuously active through waking, slow down during NREMS, and cease activity during REMS. Therefore, it was likely that the level of NA must be highest during waking, reduced during NREMS, and very low during REMS. As a corollary, it was hypothesized that the NA level should be significantly reduced (i.e., the brain should be washed-off of excess NA) during REMS and it should be elevated during REMS-loss (REMSD). Indeed, we confirmed that NA level is least during REMS and it increases during REMSD (Mehta et al. 2017).

Further, we hypothesized that possibly low dose of NA is beneficial, while higher dose is damaging to the brain. We showed that lower dose of NA acts as an antioxidant that protects the brain (an antioxidant compromised organ) from oxidative insults and promotes neuronal growth as well as branching necessary for synaptogenesis (i.e., the plasticity), while higher dose increases their apoptosis, inhibits neuronal growth, and breaks down neuronal branches (Singh et al. 2019; Giri et al., *communicated after revision*). These findings offer cellular and molecular level explanation of REMS and its loss-associated functional gain or loss in terms of neuronal excitability and memory in health and diseases, respectively. Consolidation of these findings led to my hypothesis that ***through evolution, REMS has evolved to maintain the brain level of NA, which then maintains fundamental housekeeping process(es) of the brain*** (Mallick and Singh 2011; Singh et al. 2019).

6.9 Cognitive States, Dream, and REMS: Possible Neurophysiological Mechanism and Their Relationships

The REMS has been objectively identified by the presence of characteristic electrophysiological signals. The dreams appear intermittently during REMS, which has been sometimes termed as active REMS. However, objective criteria for unbiased identification of dream are missing, i.e., dreams can only be known if the dreamer chooses to convey the same and convey correctly to the observer (another person). Additionally, it depends if the dreamer remembers or how much one remembers correctly the dream content, its sequence of events, and so on. Thus, in the absence of defining objective characteristic, the dreams cannot be identified in animals, and humans may face language barrier to explain the dream content. Often the appearance of dream has been synonymously expressed with the expression of REMS; however, still we cannot comment on the content of the dreams. Notwithstanding,

based on personal experiences, it can be said that unlike NREMS and non-dream period of REMS, the dreams are characterized by cognitive expression, which may be an experience in the past (stored memory) or anew one (may be a creative one). Therefore, my hypothesis is that REMS and dreams are related but independent phenomena where the latter gets intermittently triggered and superimposed during REMS. As discussed above, consistent research has made significant progress in our understanding of the neuronal mechanism of regulation and functions of REMS; however, our knowledge about dream is at best, rudimentary. I proposed that during REMS, some REMS-related neurons intermittently become active and trigger some neurons in the brain areas involved with memory and thought processes so that dream is expressed superimposed on REMS. This proposition could be supported by the fact that there are phasic REM-ON neurons, which become intermittently active during REMS. Also, neurons from the brain area where phasic REM-ON neurons are located have been shown to project to several areas in the brain including the ventral tegmentum, amygdala, and SN, which are part of the limbic system and are (directly or indirectly) associated with memory (Genzel et al. 2015), cognitive processes (van der Helm and Walker 2011), and REMS (van der Helm et al. 2011; Yadav et al. 2019). Findings from our recent and ongoing studies show that presumably REM-ON ACh-ergic neurons modulate REMS by activating the SN (Yadav et al. 2019), amygdala (Yadav and Mallick 2022), and ventral tegmental area (under preparation), supporting our contention. These results would form the basis for future confirmatory studies ideally in humans.

6.10 Possible Existence of All-Pervasive, Overwhelming, Fundamental, Background State: The Consciousness

The modern experimental science (and scientists) recognizes three states of consciousness: wakefulness, NREMS, and REMS, and they may be objectively identified by the expression of characteristic electrophysiological signals. It is generally accepted that under normal, healthy conditions, though REMS follows NREMS and the latter follows wakefulness, these states may transit reversibly from one to the other state except wakefulness to REMS. There is no fixed or no proportionate length of time to be spent in a state before one may transit into the other state and the states may partially exist at the same time, i.e., there may be overlap among states. Also, in diseased condition, REMS may follow wakefulness, and proportion of simultaneous expression of more than one state may increase. I argued that perhaps the missing links in the modern classification of states are that although the consciousness has been classified into three distinct and discrete states, it has not conceived several factors including the following: (1) what the fundamental state is, which is partly or completely transformed into other states; (2) whether there is any background state on which these three states exist (get expressed); (3) where the two states would move when the third gets expressed, if these three states are discrete; (4) how these states are connected and communicate with each other to get expressed coherently and dynamically; and (5) if a state is transformed

from one to the other, whether each of the states would carry the same energy level or, if the energy levels are different, how and where the difference of energy between states get accommodated or accounted for (gained or lost). Further, because of the absence of a concept of such basal state, one finds it untenable to explain the overlapping and partial combination of existence of various states be it in health or in diseases. In principle, I argued that there is likely to exist a basal, all-pervasive, overwhelming, fundamental, background state (medium) on which the three classical states, viz., wakefulness, NREMS, and REMS, play around and get expressed. This concept at least helps explaining expression of common intermediary as well as various levels of transitory phases connecting the classical states. It also allows us to conceive how states can be of various combination, how they can overlap to different degrees, and how they can transit easily, completely or partially, in a reversible manner. Although apparently this concept may appear not to satisfy why normally REMS does not appear following waking, my argument against it is as follows: because grossly the EEG, EOG, and apparent cognitive experience (dreams and thoughts) in waking and REMS are comparable (except the voluntary physical acts), one may not be able to differentiate them, which needed subtler characteristic identifiable signals.

My concept of existence of such overwhelming, all-pervasive, basal, fundamental state satisfies the fundamental lacuna and discrepancy raised above. However, it needs to be explained, preferably in a demonstrable manner what the state could be and what should be its characteristic. I would explain with the following analogous conditions as examples and then offer neurophysiological explanation. In a fluid (liquid or gaseous) environment, e.g., pond, river, sea or, in the atmosphere for that matter, there are finer surface ripples of waves of various frequencies and intensities. Due to various quality and quantity (strengths), the inputs get either distributed or absorbed, i.e., indiscernible or aggregate at various location(s), and get expressed over the ripple on the relatively quieter fluidic surface. Such changes may get expressed as local wind, storm, gale, hurricane, etc. Those inputs could arise at various locations within the system or may be due to external influence modulating at different regions (even away from the expression) of the system. Another example could be if we mix up many waves of varying low intensity and frequencies (noise) generated from various generators, a network of frequencies can be created (e.g., a frequency shield). This mixture of networks may be influenced by various inputs from the said generators where some focal island of wave patterns may be created depending on the quality and quantity of inputs. These low, medium, or high energy containing waves (or wavelets) may be compared with the locality and non-locality concept of the quantum physics (details are not being discussed in this chapter). In the examples above, regarding recordable parameter of consciousness, the ripples are the EEG waves (may be the ultralow wave and frequency) due to local cortical neural networks at the cortical surfaces which are least influenced by far and near input(s), i.e., beyond the local basic network. These ripples are influenced by various levels of central and peripheral inputs, often involving the brainstem and thalamic reticular connections, which express synchronization and desynchronization of the

EEG. The local, sub-local, relatively wider, and global changes so generated give rise to wakefulness, NREMS, REMS, and their overlaps as well as variations.

6.11 Support from Ancient *Upanishadic* Literature to Explain Conscious State: The *T-State*

My views mentioned in the preceding paragraphs may be supported, at least conceptually and philosophically. I looked for if the ancient Indian philosophers and sages might have mentioned anything comparable out of their wisdom. The sixth chapter of *Mandukya Upanishad* refers to sleep-waking-dreaming, and in that segment, one finds a mention of a fourth state, called ***Thuriya-state***, which conceptually supports my explanation, although there is no experimental verification. In an attempt to assign an identity to the ripple explained above in my examples, I borrowed the concept of ***Thuriya state*** and termed it as ***T-state***, as the most fundamental, all-pervasive, background state primarily due to the waves created by the local neural networks, due to the local field potentials and for the sustainability of those networks. Various sensory-motor inputs from within and outside the networks give rise to potentials of various dimensions and phases, which are recorded as EEG associated with the three classical conscious states: the REMS and intermittent dreams (the interactions among the neurons in the core and primitive brain areas), the NREMS (the interaction of other neurons in the brain over and above those responsible for inducing REMS), and wakefulness (the strongest of the three apparently discrete states caused due to strong inputs from various parts of the body). Considering these, I have explained that quantitative and duration of masking and unmasking of part of the ***T-state*** describe various discrete or overlapping states during health and diseases (Mallick and Mukhopadhyay 2011); this is a testable hypothesis.

Acknowledgments To all my present students in the lab to go through and comment on an earlier version of this manuscript and helping me by arranging the references. Fundings from JC Bose fellowship and UGC-DRSII are gratefully acknowledged.

References

Alam MN, Kumari S, Mallick BN (1993) Role of GABA in acetylcholine induced locus coeruleus mediated increase in REM sleep. Sleep Res 22:541

Arnulf I (2013) Dream imagery, rapid eye movement sleep behavior disorder, and hallucinations. Sleep Biol Rhythms 11:15–20

Aserinsky E (1999) Eyelid condition at birth: relationship to adult mammalian sleep-waking patterns. In: Mallick BN, Inoue S (eds) Rapid eye movement sleep. Marcel Dekker, New York, pp 1–16

Aserinsky E, Kleitman N (1953) Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. Science 118:273–274

Aston-Jones G, Bloom FE (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1:876–886

Berger H (1929) Über das Elektrenkephalogramm des Menschen. Arch Psychiatr Nervenkr 87: 527–570
Dement W (1960) The effect of dream deprivation. Science 131:1705–1707
Egan TM, North RA (1985) Acetylcholine acts on m2-muscarinic receptors to excite rat locus coeruleus neurons. Br J Pharmacol 85:733–735
Genzel L, Spoormaker VI, Konrad BN, Dresler M (2015) The role of rapid eye movement sleep for amygdala-related memory processing. Neurobiol Learn Mem 122:110–121
Gulyani S, Mallick BN (1993) Effect of rapid eye movement sleep deprivation on rat brain Na-K ATPase activity. J Sleep Res 2:45–50
Gulyani S, Mallick BN (1995) Possible mechanism of rapid eye movement sleep deprivation induced increase in Na-K ATPase activity. Neuroscience 64:255–260
Hobson JA, McCarley RW, Wyzinski PW (1975) Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 189:55–58
Hobson JA, McCarley RW, Nelson JP (1983) Location and spike-train characteristics of cells in anterodorsal pons having selective decreases in firing rate during desynchronized sleep. J Neurophysiol 50:770–783
Inglis WL, Winn P (1995) The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation. Prog Neurobiol 47:1–29
Jouvet M (1999) Around the discovery of REM sleep in cats. In: Mallick BN, Inoue S (eds) Rapid eye movement sleep. Marcel Dekker, New York, pp v–ix
Jouvet M, Michel F (1958) [Study of the cerebral electrical activity during sleep]. C R Seances Soc Biol Fil 152:1167–1170
Kaur S, Saxena RN, Mallick BN (1997) GABA in locus coeruleus regulates spontaneous rapid eye movement sleep by acting on GABA-A receptors in freely moving rats. Neurosci Lett 223:105–108
Kaur S, Panchal M, Faisal M, Madan V, Nangia P, Mallick BN (2004) Long term blocking of GABA-A receptor in locus coeruleus by bilateral microinfusion of picrotoxin reduced rapid eye movement sleep and increased brain Na-K ATPase activity in freely moving normally behaving rats. Behav Brain Res 151:185–190
Khanday MA, Somarajan BI, Mehta R, Mallick BN (2016) Noradrenaline from locus coeruleus neurons acts on pedunculo-pontine neurons to prevent REM sleep and induces its loss-associated effects in rats. eNeuro 3(6):ENEURO.0108-16.2016
Kumar R, Bose A, Mallick BN (2012) A mathematical model towards understanding the mechanism of neuronal regulation of wake-NREMS-REMS states. PLoS One 7:e42059
Mahowald MW, Woods SR, Schenck CH (1998) Sleeping dreams, waking hallucinations, and the central nervous system. Dreaming 8:89–102
Mallick BN, Inoue S (eds) (1999) Rapid eye movement sleep. Marcel Dekker, New York, p 419
Mallick BN, Mukhopadhyay AK (2011) REM sleep and dream sleep: are they identical? Exploring the conceptual developments in the Upanishads and the present knowledge based on the neurobiology of sleep. In: Mallick BN et al (eds) Rapid eye movement sleep: regulation and function. Cambridge University Press, England, pp 21–30
Mallick BN, Singh A (2011) REM sleep loss increases brain excitability: role of noradrenaline and its mechanism of action. Sleep Med Rev 15:165–178
Mallick BN, Siegel JM, Fahringer H (1990) Changes in pontine unit activity with REM sleep deprivation. Brain Res 515:94–98
Mallick BN, Thankachan S, Islam F (1998) Differential responses of brain stem neurons during spontaneous and stimulation-induced desynchronization of the cortical EEG in freely moving cats. Sleep Res Online 1:132–146
Mallick BN, Adya HV, Faisal M (2000) Norepinephrine-stimulated increase in Na+, K+-ATPase activity in the rat brain is mediated through alpha1A-adrenoceptor possibly by dephosphorylation of the enzyme. J Neurochem 74:1574–1578

Mallick BN, Kaur S, Saxena RN (2001) Interactions between cholinergic and GABAergic neurotransmitters in and around the locus coeruleus for the induction and maintenance of rapid eye movement sleep in rats. Neuroscience 104:467–485

Mallick BN, Thankachan S, Islam F (2004) Influence of hypnogenic brain areas on wakefulness- and rapid-eye-movement sleep-related neurons in the brainstem of freely moving cats. J Neurosci Res 75:133–142

Mallick BN, Pandi-Perumal SR, McCarley RW, Morrison AR (eds) (2011) Rapid eye movement sleep: regulation and function. Cambridge University Press, London, p 478

Mallick BN, Singh A, Khanday MA (2012) Activation of inactivation process initiates rapid eye movement sleep. Prog Neurobiol 97:259–276

Manni R, Pacchetti C, Terzaghi M, Sartori I, Mancini F, Nappi G (2002) Hallucinations and sleep-wake cycle in PD. Neurology 59:1979

McCarley RW, Hobson JA (1971) Single neuron activity in cat gigantocellular tegmental field: selectivity of discharge in desynchronized sleep. Science 174:1250–1252

McCarley RW, Hobson JA (1975) Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. Science 189:58–60

Mehta R, Singh S, Khanday MA, Mallick BN (2017) Reciprocal changes in noradrenaline and GABA levels in discrete brain regions upon rapid eye movement sleep deprivation in rats. Neurochem Int 108:190–198

Moruzzi G (1972) The sleep-waking cycle. Ergeb Physiol 64:1–165

Pal D, Mallick BN (2004) GABA in pedunculo pontine tegmentum regulates spontaneous rapid eye movement sleep by acting on GABAA receptors in freely moving rats. Neurosci Lett 365:200–204

Pal D, Mallick BN (2006) Role of noradrenergic and GABA-ergic inputs in pedunculopontine tegmentum for regulation of rapid eye movement sleep in rats. Neuropharmacology 51:1–11

Pal D, Mallick BN (2009) GABA in pedunculopontine tegmentum increases rapid eye movement sleep in freely moving rats: possible role of GABA-ergic inputs from substantia nigra pars reticulata. Neuroscience 164:404–414

Rechtschaffen A, Kales A (eds) (1968) A manual for standardized terminology, techniques and scoring system for sleep stages of human subjects. Issue 204 of NIH Publication; U. S. National Institute of Neurological Diseases and Blindness, Neurological Information Network; UCLA, Brain Information Service, NINDB Neurological Information Network (U.S.)

Sakai K (1988) Executive mechanism of paradoxical sleep. Arch Ital Biol 126:239–257

Siegel J (1989) Brainstem mechanisms generating REM sleep. In: Kryger M et al (eds) Principles and practice of sleep medicine. Saunders, Philadelphia, pp 104–120

Singh S, Mallick BN (1996) Mild electrical stimulation of pontine tegmentum around locus coeruleus reduces rapid eye movement sleep in rats. Neurosci Res 24:227–235

Singh A, Das G, Kaur M, Mallick BN (2019) Noradrenaline acting on alpha1 adrenoceptor as well as by chelating iron reduces oxidative burden on the brain: implications with rapid eye movement sleep. Front Mol Neurosci 12:7. https://doi.org/10.3389/fnmol.2019.00007

Somarajan BI, Khanday MA, Mallick BN (2016) Rapid eye movement sleep deprivation induces neuronal apoptosis by noradrenaline acting on alpha1 adrenoceptor and by triggering mitochondrial intrinsic pathway. Front Neurol 7:25. https://doi.org/10.3389/fneur.2016.00025

Steriade M, McCarley RW (eds) (2005) Brain control of wakefulness and sleep. Kluwer Academic/Plenum, New York

Thankachan S, Islam F, Mallick BN (2001) Role of wake inducing brain stem area on rapid eye movement sleep regulation in freely moving cats. Brain Res Bull 55:43–49

van der Helm E, Walker MP (2011) Sleep and emotional memory processing. Sleep Med Clin 6:31–43

van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP (2011) REM sleep depotentiates amygdala activity to previous emotional experiences. Curr Biol 21:2029–2032

Williams JA, Reiner PB (1993) Noradrenaline hyperpolarizes identified rat mesopontine cholinergic neurons in vitro. J Neurosci 13:3878–3883

Yadav, R. K. and Mallick, B. N., Dopaminergic- and cholinergic-inputs from substantia nigra and pedunculo-pontine tegmentum, respectively, converge in amygdala to modulate rapid eye movement sleep in rats, Neuropharmacology, 2022 (in press). https://doi.org/10.1016/j.neuropharm.2021.108607

Yadav RK, Khanday MA, Mallick BN (2019) Interplay of dopamine and GABA in substantia nigra for the regulation of rapid eye movement sleep in rats. Behav Brain Res 376:112169. https://doi.org/10.1016/j.bbr.2019