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Mammalian NREM and REM sleep: Why, when and how

Rubén V. Rial [a,b,c,*], Mourad Akaârir [a,b,c], Francesca Canellas [a,b,c,d], Pere Barceló [a,b,c], José A. Rubiño [a,b,c,d], Aida Martín-Reina [a,b,c], Antoni Gamundí [a,b,c], M. Cristina Nicolau [a,b,c]

[a] Laboratori de Fisiologia del son i els ritmes biologics. Universitat de les Illes Balears, Ctra. Valldemossa Km 7.5, 07122 Palma de Mallorca (España)
[b] IDISBA. Institut d'Investigació Sanitaria de les Illes Balears
[c] IUNICS Institut Universitari d'Investigació en Ciències de la Salut
[d] Hospital Son Espases, 07120, Palma de Mallorca (España)

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ABSTRACT

This report proposes that fish use the spinal-rhombencephalic regions of their brain to support their activities while awake. Instead, the brainstem-diencephalic regions support the wakefulness in amphibians and reptiles. Lastly, mammals developed the telencephalic cortex to attain the highest degree of wakefulness, the cortical wakefulness. However, a paralyzed form of spinal-rhombencephalic wakefulness remains in mammals in the form of REMS, whose phasic signs are highly efficient in promoting maternal care to mammalian litter. Therefore, the phasic REMS is highly adaptive. However, their importance is low for singletons, in which it is a neutral trait, devoid of adaptive value for adults, and is mal-adaptive for marine mammals. Therefore, they lost it. The spinal-rhombencephalic and cortical wakeful states disregard the homeostasis: animals only attend their most immediate needs: foraging defense and reproduction. However, these activities generate allostatic loads that must be recovered during NREMS, that is a paralyzed form of the amphibian-reptilian subcortical wakefulness. Regarding the regulation of tonic REMS, it depends on a hypothalamic switch. Instead, the phasic REMS depends on an independent proportional pontine control.

1. Introduction

Although most researchers believe that sleep is universal in animals, the present review will defend that true sleep only can be found in mammals. Therefore, our main goal will consist in analyzing only the mammalian sleep. Nevertheless, when needed, a few mentions will be made to non-mammalian sleep.

In behavioral terms, sleep is currently diagnosed attending to eight signs: 1) quiescence, 2) easy reversibility, 3) preferred sleeping places, 4) stereotyped body positions, 5) raised sensory thresholds, 6) circadian organization and 7) homeostatic regulation and 8) it is a pleasing state (Piéron, 1912; Flanigan et al., 1973; Durie, 1981; Borbély, 1982; Rial et al., 2018).

Sleep also may be diagnosed by recording the electrophysiological variables of sleeping mammals and birds. In this case, the record receives the name of polysomnography (PSG), and includes brain (EEG), muscular (EMG) activities, together with eye movements (EOG) and, eventually, other signs: heart rate, respiration, Body Temperature (BT) (central and peripheral) etc. The polygraphic sleep, only defined in homeothermic vertebrates, revealed the existence of two sleep states: non-REM sleep (NREMS) and REM sleep (REMS) (Aserinsky and Kleitman, 1953).

The neuroanatomical and functional difference between NREMS and REMS is so important that many authors believe that the two types of sleep are independent states of conscience. The duality of sleep contributes to its mysterious nature: why two sleep states must exist? Attempting to explain this mystery, our group proposed, that the evolution of the reptilian waking gave origin to the mammalian sleep, including the cycles of NREMS and REMS (Rial et al., 1993, 2007; Nicolau et al., 2000). Briefly, reptiles spend their waking time in two main states: 1) basking-tigmothermic thermoregulatory behavior - in the following, "Basking Behavior" (BB) - and 2) a set of foraging, reproductive, defensive, and agonistic behaviors (in the following, "Goal Directed Behaviors", (GDB). According to our proposal, BB and GDB

* Corresponding author at: Laboratori de Fisiologia del son i els ritmes biologics. Universitat de les Illes Balears, Ctra. Valldemossa Km 7.5, 07122 Palma de Mallorca (España).

E-mail addresses: rvrial@uib.es (R.V. Rial), mourad.akaarir@uib.es (M. Akaârir), francesca.canellas@ssib.es (F. Canellas), pbarcelocaldentey@gmail.com (P. Barceló), josepsico78@hotmail.com (J.A. Rubiño), aida.martin.reina@gmail.com (A. Martín-Reina), antoni.gamundi@uib.es (A. Gamundí), cristina.nicolau@uib.es (M.C. Nicolau).

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were the direct antecessors of NREMS and REMS, respectively. Importantly, both BB and GDB are compulsory. The first one is needed to raise the reptilian BT to attain full physiological efficiency, while the GDB is needed for performing most life sustaining activities (Rose, 1981; Huey, 1982; Karasov and Anderson, 1984; Pietruszka, 1986; Mukherjee et al., 2018).

2. The birth of the mammalian sleep

At the Cretaceous-Paleogene boundary - about 250 million years ago - some individuals of the primitive reptilian stock increased their energetic metabolism and developed incipient endothermy. In this way, they were able to extend their activity, first to twilight hours and, after successive metabolic developments, to the entire nighttime. However, attempting to attain the maximal visual sensitivity needed for life in the dark, they abandoned the ocular filters present in the eyes and retina of their reptilian ancestors, who used them to avoid the dangerous highly energetic short-wave contents of the diurnal light. The described processes are known as the Nocturnal Evolutionary Bottleneck (NEB) (Walls, 1942) and is currently considered responsible of the evolution, from reptiles to the first mammals, that began being nocturnal and continue being so in most extant species, (Gerkema et al., 2013; Heesy and Hall, 2010; Wu et al., 2017).

The abandon of the visual filters increased the risk of blindness consequent to the casual exposure to the highly energetic components of diurnal light. To minimize such risk, pre-mammals remained immobile in lightproof burrows with closed eyes during light time. So, their chronotype was inverted, from the strict diurnal one of their reptilian ancestors, to strict nocturnal chronotype, a trait that is still dominant in most mammals. Another factor that forced the nocturnal chronotype was the competence with big sized diurnal dinosaurs. So, those first mammals were forced to remain paralyzed in their burrows during light time during ~180 million years, until the Cretaceous-Paleogene extinction event that leaved the light time free from dangerous competitors. One would ask, what should do those primitive mammals during a so immense span of time? The answer: they invented sleep (Rial et al., 2022). Then after the K-PG extinction event, they became free to diverge, occupying, not only the nighttime, but also the daylight period. This was how the well-known variation of mammalian sleeping modes and chronotypes appeared.

2.1. The circadian regulation of sleep in the transition reptiles-mammals

Reptiles possess a Zeitgeber regulating the circadian cycles of rest-activity, mostly according to the environmental warm/cool diurnal cycles (Ellis et al., 2009: Dayananda et al., 2020). However, after developing homeothermy, the constancy in the BT of those pre-mammals would easily fool the hypothalamic control of their circadian cycles, making possible a permanent activity, increasing, therefore, the risk of accidental exposure to daylight and the consequent blindness and extinction. To avoid such risk, early mammals suffered a high evolutionary pressure to substitute the original warm/cool basic reptilian Zeitgeber by that of modern mammals, mostly sensitive to light/dark daily oscillations (Aschoff, 1965; Czeisler et al., 1981). Most likely, the changes crystalized when the original hypothalamic warm/cool reptilian switch controlling the alternation between activity and rest was transformed into the mammalian wake-sleep Flip-Flop (Saper et al., 2001), with independent sleep-promoting and wake-promoting neuronal ensembles interconnected by mutually inhibitory fibers (Bringmann, 2018). In this way, the sleep-wake Flip-Flop probably served as a fail-safe mechanism guaranteeing the stability of the cycles and avoiding the accidental abandon of shelters at inappropriate times. Although these processes explain the origin of the mammalian sleep (Rial et al., 2022), they leave unexplained why sleep shows two sub-states.

The present report will provide with reasonable evidence supporting the hypotheses described in previous paragraphs. But our main goal aims at explaining the origin and the persistence of NREMS as well as the tonic and phasic traits of REMS. We will see that the two stages were an unavoidable result of the interaction between the anatomic and functional properties of different brain regions.

To make a detailed description of the facts described in previous paragraphs, we will use, as a departure point, the words of Crick and Mitchison (1983): *'Any purely psychological theory is hard pressed to explain the large amount of REM in the womb and any purely developmental theory must account for the quite appreciable amount of sleep in adult life'*.

3. The definition of wakefulness

Wakefulness can be defined as a behavioral state with capability for perceiving environmental stimuli and elaborating adaptive responses. We will apply this definition to affirm the existence of several types of wakefulness that successively appeared in function of the ontogenetic and phylogenetic development of the brain. We propose, first, the existence of a primary spinal-rhombencephalic wakefulness that can be found in early vertebrate embryos, in fish and, in a paralyzed form, during mammalian REMS. To our knowledge, the existence of such state was first proposed by Corner and Schenk, (2015). However, we will expand their proposal by adding a second wakefulness, the brainstem-diencephalic one. It can be found in active poikilothermic vertebrates but also, during NREM sleep, in paralyzed mammals. We will add a third state, the cortical wakefulness, only present in mammals. The existence of three types of wakefulness along the vertebrate's phylogeny and ontogeny will help us to understand the first part of Crick and Mitchison's observation, namely, why REMS is so abundant in newborns.

3.1. The ontogenetic development of wakefulness

The embryological development of the brain begins with the formation of the spinal cord. This is followed by the successive development of medulla, pons, midbrain, diencephalon, to end with the full development of the telencephalic cortex (Joseph, 2000; Prayer et al., 2006; Yigiter, and Kavak, 2006). Obviously, the functional maturation of the brain follows the same caudo-rostral order (Kadić and Predojević, 2012) and the same stages of brain development can be found in vertebrate's phylogenesis. For instance, the telencephalic development is practically zero in prochordates (Lacalli, 2001) but successively increases in size and complexity in fish, amphibians, reptiles, and mammals (Butler and Hodos, 2005; Butler et al., 2011).

3.2. Spinal wakefulness

The experimentally isolated spinal preparations of fish can produce rhythmic swimming movements and escape responses to dangerous stimuli that are identical to those of intact animals, with good intersegmental coordination (Cohen and Wallén, 1980; Sigvardt, 1989; Grillner and Wallen, 2002; Cangiano and Grillner, 2003). Similar observations have been reported in tadpoles (Corner, 1964; Corner and Crain, 1965; Stehouwer and Fare1, 1980, 1981), in reptiles (Kusuma, Ten Donkelaar, 1980; Srivastava, 1992) and even in experimentally decorticated adult mammals (Sherrington, 1910 - cited by Hart, 1971 - Handa et al., 1986; Sigvardt, 1989).

In ontogenetic terms, the spinally controlled jerks are the earliest signs of spontaneous activity observable in mammalian embryos. They appear as a consequence of the random firing of spinal motoneurons (Blumberg and Lucas, 1994; Corner and Schenck, 2015) but are rapidly transformed into sensory evoked reflexes, that is, in signs of spinal wakefulness, with capability for elaborating complex motor responses well-adapted to the causal stimuli (Humphrey, 1964; De Vries et al., 1985; Corner, 1985; Saint-Amant and Drapeau, 1998; Suzue and Shinoda, 1999; Oberlander et al., 2002; Tadros et al., 2015; Fitzgerald, 2005). We see, therefore, that in absence of the anterior parts of the

brain, be it due to low development, or to experimental procedures, the spinal cord is capable of elaborating adaptive responses, i.e., of wakefulness.

3.3. Rhombencephalic wakefulness

The brainstem, together with medullar and spinal regions, is responsible of basic life sustaining functions, including respiratory control (Chatonnet et al., 2002; Alheid et al., 2004), cardio-circulatory activity (Hoffmann and de Souza, 1982; Sévoz-Couche et al., 2003), digestive reflexes (mastication, swallowing, retching) (Amri and Car, 1988; Lu et al., 1997; Turman et al., 2001) and even facial expressions (Auclair et al., 1996; Huang et al., 2009), including ocular movements, for instance, the gaze following behavior (Cohen, 1974; Verzijl et al., 2003; Dos Santos et al., 2006) as well as many other sensory-motor responses. For example, it has been found that, after categorizing the significance (positive or negative) of a given visual stimulus, the motor responses of larval zebrafish are activated through contralateral or ipsilateral tecto-bulbar tracts, respectively, coordinating so the visual tracking and the mobility towards, or away, the stimulus (Helmbrecht et al., 2018).

Therefore, the rhombencephalon of primitive vertebrates, but also of undeveloped mammalian embryos is capable, by itself, of actively controlling alternative periods of muscular atonia (quiescence) (Valatx et al., 1964; Corner, 1977; Hobson, 2009) interspersed with episodes of waking that, in their most primitive form, were identified as startles and escape behaviors, i.e., the basic components of the fight-fright-flight behavioral pattern (Bolles, 1970; Bullock, 1984; Corner and Schenck, 2015).

Concluding, convincing evidence exists showing that primitive vertebrates and mammalian embryos possess a kind of simplified spinal-rhombencephalic wakefulness. After an almost complete block of the motor output, this form of waking was transformed into the REMS of adult mammals. Most likely, the neural control of the spinal-rhombencephalic wakefulness is fully coincident with that of the rhombencephalic sleep, (REM sleep) minus the atonia of REMS, i.e., the main difference between the rhombencephalic waking - as defined in previous paragraphs – and REM sleep. In fact, when the neural mechanisms responsible of the atonia fail, the result is the REM sleep without atonia (RSWA) or the REM behavioral disorder (RBD). Several authors recognized the presence of rhombencephalic behavioral patterns in mammalian embryos, calling them “Motor Primitives” (Dominici et al., 2011) and “Rapid Body Movements (Corner and Schenck, 2015). In the following, and to recognize the relation between REM sleep and the rhombencephalic waking - as defined in previous paragraphs - we will call it as REM wakefulness (REMW). Of course, the motor activity of both REM sleep and REMW involves not only ocular movements, but also muscular activity in many other body regions. However, we will conserve the reference to ocular movements, to remember the close parallel between REM Sleep and REM wakefulness. Therefore, we will use the acronyms REMS and REMW for the rhombencephalic sleep and the rhombencephalic wakefulness.

3.3.1. The adaptive significance of the phasic signs of REMS

The REMS shows two main substages: phasic REM and tonic REM (Moruzzi, 1963). Many authors recognized that the muscular twitches and jerks observed during phasic REM sleep are the remainder of a partial suppression of startles and orienting reflexes (Emde and Metcalf, 1968; Wu et al., 1989; Wu and Siegel, 1990; Blumberg and Lucas, 1994; Blumberg and Stolba, 1996; Morrison, 2005; Jha et al., 2005). i.e., the result of an incomplete obliteration of GDB. In rat pups, the twitches and jerks are astoundingly frequent, with an estimated frequency of tens of thousands per day (Blumberg and Seelke, 2010; Blumberg et al., 2013). Therefore, an important question is: why animals developed a highly efficient system to inhibit skeletal motor neurons during REMS and, almost simultaneously, why the system drains high amounts of incomplete movement patterns in newborns that, with lower intensity, continue existing in the REMS of adult mammals (Roffwarg et al., 1966).

The tonic immobility of REMS depends on GABAergic and glycinergic medullar neurons that inhibit the spinal motoneurons, (Soja et al., 1987; Morales et al., 2006; Vetrivelan et al., 2009). However, the inhibitory drive progressively fades along every REMS episode because of the progressive activity of excitatory glutamatergic neurons located in the medial medulla. These neurons disinhibit the motoneuronal output and allows the expression of the phasic signs of REMS, i.e., the eye movements, vocalizations, muscular twitches, and jerks. In consequence, the phasic signs of REMS should never be considered random byproducts of the state, but the result of a well-regulated balance between the GABAergic-glycinergic inhibition of skeletal motoneurons and their glutamatergic stimulation (Brooks and Peever, 2016).

The production of such enormous amounts of activity should be rather costly and only can be understood if newborns obtain some compensatory advantage. It is currently believed that they serve for sensorimotor maturation (Roffwarg et al., 1966; Mirmiran et al., 2003; Petersson et al., 2003; Khazipov et al., 2004; Dattilo et al., 2012; Blumberg et al., 2013; Tiriac et al., 2015; Corner and Schenck, 2015). This belief is mostly based on two facts: 1) an inverse correlation between the total number of twitches and jerks of REMS and the maturation of the brain and 2) because it has been found that the experimental suppression of REMS in newborn animals provoke deficits in brain maturation. In our opinion, these arguments are weak: 1) because correlations should never be used for supporting categorical affirmations of causal relationships, 2) because the correlation may be more parsimoniously explained as a mere epiphenomenon of the general brain development, and 3) because suppressing REMS in infant animals is only one among the immense number of ways to interfere with the delicate machinery of brain development. Thus, it is no wonder if suppressing the infantile REMS cause additional derangements (Gamundí et al., 2005).

We do not completely reject the idea that the REMS phasic activities may contribute to the progressive development of the brain sensory-motor capabilities. But we will remember an advantage that was first proposed by Allin and Banks (1972) suggesting that the twitches and jerks are adaptive by themselves. Isolated sleeping rat pups exposed to low temperatures respond first, by increasing the Brown Adipose thermogenesis but, after further temperature descents, the production of metabolic heat may be insufficient and the pups risk becoming cool. The easiest way to avoid hypothermia lies in obtaining heat from the dam. It has been found that, apart from the twitches and jerks, cooled rat pups also emit 22 kHz ultrasonic vocalizations that induce maternal retrieval (Noirot, 1972; Allin and Banks, 1972; Curry et al., 2013; Harshaw, and Alberts, 2012; Verjat et al., 2019).

The relation between the decrease in BT and the calls of isolated rat pups has been disputed by affirming that the calls are an acoustic by-product of laryngeal braking, a respiratory maneuver that premature infants use for improving the pulmonary gas exchange (Blumberg, & Alberts, 1990; Blumberg, 2001). But this might be dubious. First, this alternative only refers to the calls, but leaves unexplained the association of calls with jerks and twitches that altogether depend on the activity of the peduncular-pontine tegmental nucleus (PPT), a structure that plays an essential role in the production of the phasic components of REMS (Shouse and Siegel, 1992; Mccauley and Elwood, 1984; Kreider, and Blumberg, 2000; Karlsson et al., 2005; Savoy, 2005). Second, more recent reports make explicit mention to the calls in cats and rats as indicative of negative emotional states, and remarks its dependence on the PPT (Brudzynski et al., 2011; Brudzynski, 2013a; Brudzynski, 2013b). But more important, the described alternative leaves unexplained the responses of the dams. Indeed, the pup calls, irrespective of the mode of production, induce dams to leave the nest for searching the calling pup. However, the search only appears in lactating females but neither in males nor in virgin females (Allin and Banks, 1972). The result is that the mother finds her pup and returns it to the nest, so joining it with their siblings. Then, the ventral stimulation, received from

twitching or sucking pups, elicits immobility in the mother (Stern and Johnson, 1990; Stern et al., 1992; Pedersen, 1997; Morgan et al., 1992; Lonstein et al., 1998). Nevertheless, dams cease responding when pups are inactive, incapable of latching to the nipple and suckling. In other words, dams readily respond to the calls emitted by isolated, cooled and/or hungry pups – most likely in poikilostatic REMS - but are less interested in warm, well-fed, and quietly sleeping pups - probably in NREMS - with a well-controlled BT. Moreover, inter-pup competition has been observed in many altricial species. Frequently, the huddling pups fight for the nipples (Gilbert, 1995; Coureaud et al., 2000; Drummond et al., 2000; Bautista et al., 2003, 2008; Madden et al., 2009) and shuttle between the border and the core of the huddle (Bautista et al., 2003; Alberts, 2007; Gilbert et al., 2010), so optimizing the rise of their BT by tigmothermic procedures, i.e., gaining heat from the warm skin of mother and siblings, avoiding hypothermia and so minimizing the metabolic expenditures (Alberts, 1978, 2007). To our knowledge the neural source of the fights between siblings remains unknown. But given the reduced development of the pups' brain, we can postulate that they stay in REMW. Obviously, the phasic activity of REM sleeping pups is adaptive.

To conclude, the phasic traits of REMS of infants serve for communicating negative emotional states to the mother, demanding contact, defense, heat and/or milk (Brudzynski, 2007, 2013a, 2013b; Wöhr et al., 2010; Schwarting and Wöhr, 2018). Furtherly, it can be postulated that the frequency of twitches, jerks and ultrasonic calls must be proportional to the degree of cooling/hunger/danger, which should progressively increase in proportion to the duration of the REMS episode of the isolated pups and the consequent time-dependent drop in temperature, (or increased hunger, or any other type of discomfort). These changes coincide with the progressive regulatory mechanisms described by Brooks and Peever (2016) for the phasic sigs of REMS. In summary, these signs are *regulated* responses to negative emotional states dependent of the same spinal-rhombencephalic neuronal networks controlling the phasic signs of REMS.

Altogether, the full set of calls, muscular twitches, and jerks, is a paradigmatic example of evolutionary exaptation (Gould and Vrba, 1982). The fight, fright, and flight reflexes appeared, in primitive vertebrates, as defensive responses for escaping from unexpected and/or dangerous environmental stimuli, but finished as calls demanding help to the mother. But most important is that the myoclonic twitches, jerks, and calls may have an immense and immediate survival value for immature pups, much higher than a complete atonia and perhaps even higher than the presumed advantages of the eventual REMS-dependent improvements in sensorimotor development.

Notably, similar calls, jerks and twitches have been observed in many other rodent species (Noirot, 1972). Furthermore, similar haptic and vocal activities have been reported for mother-infant "in ovo" communication in reptiles (Herzog and Burghardt, 1977; Vergne and Mathevon, 2008; Vergne et al., 2009, 2012; Sicuro et al., 2013; Ferrara et al., 2013), birds (Brua et al., 1996; Evans, 1990; Evans et al., 1994; Gräns and Altimiras, 2007; Nichelmann and Tzschentke, 1997; Rumpf and Tzschentke, 2010) and "in utero", in pre-term mammalian fetus, including humans (Stern, 1997; Hofer, 2002; Swain et al., 2007), i.e., in species showing maternal care. In every case, the mother readily responds to the calls by retrieving and covering the eggs - or pups - and protecting them from predation, hunger, or cooling. The wide distribution of these activities suggests an old phylogenetic origin and confirm their high adaptive significance (Bass and Chagnaud, 2012).

3.4. Brainstem-diencephalic wakefulness

The thermoregulatory behavior is an evident - but not unique - example of a second type of wakefulness, the diencephalic wakefulness. For example, the hypothalamic controlled capacity for behavioral selection of the preferred environmental temperature is widespread in vertebrates (Crawshaw et al., 1981), having been observed in fish (Reynolds et al., 1976; Nelson and Prosser, 1979; Beitinger and Magnuson, 1979; Reynolds and Casterlin, 1979; Matern et al., 2000; Newell and Quinn, 2005; Golovanov, 2006), amphibians (Corner, 1964; Casterlin and Reynolds, 1977), reptiles (Kluger et al., 1973; Berk and Heath, 1976; Nelson et al., 1984) and is conserved in mammals (Schradin et al., 2007; Terrien et al., 2011), including wakeful human adults (Shim and Jeong, 2011). Indeed, when possible, we largely prefer to rely to behavioral thermoregulation more than on metabolic thermogenesis (Parmeggiani, 2011, pp 43).

Importantly, the behavioral thermoregulation occurs under the diencephalic wakefulness, of fish and reptiles, but also during the diencephalic mammalian sleep (NREM). However, the behavioral thermoregulation is the single possibility for body warming in poikilothermic animals. Therefore, its importance is maximal in them.

We are aware of some reports affirming the existence of NREMS and even REMS during nighttime in supposedly sleeping lizards (Shein-Idelson et al., 2016; Libourel et al., 2018). However, we should remark, first, that the presence of REMS was doubted in a posterior report of the same authors (Libourel and Barrillot, 2020). But we should add that even the existence of true sleep must be definitively discarded in poikilothermic vertebrates after understanding that the so-called reptilian nocturnal sleep is a passive hypothermic state that appears when the experimental animals are kept under inadequate housing conditions (Rial et al., 2022). Indeed, mammalian sleep – what we will dare to qualify as "true sleep" - is the result of complex and active processes, and the old belief that sleep results from reduced sensory input and/or low brain activity, has been discarded since long (Dement, 2017).

The mammalian brainstem is not only capable of exerting complex behavioral patterns to control BT, but also of many other activities needed for homeostatic control that can be even observed in experimentally decorticated mammals. They can show well-coordinated postural and locomotor capacities, normal grooming, and complete defensive responses. (Woods, 1964; Lovick, 1973; Berntson and Micco, 1976; Humphries et al., 2005; Blumberg and Plumeau, 2016). Furthermore, in late gestational ages, when the mammalian cortex is still presumably undeveloped (Yigiter, and Kavak, 2006; Prayer et al., 2006) human fetuses respond to stimuli perceived through the abdominal wall of the mother. They can even discriminate between the mother's voice and other sounds, showing variable responses to acoustic stimuli, meaning that the lower part of their auditory system, i.e., mesencephalic posterior colliculi, isthmus and rhombencephalic cochlear nuclei, are already functional (Lecanuet and Schaal, 1996; Kisilevsky et al., 1998; Grimwade et al., 1970; Sohmer and Freeman, 1995). Moreover, many sensory and motor manifestations that are active in premature and at term human newborns, disappear after a few weeks, to return after a while (Strauss and Stavy, 1982; Muir, and Hains, 2004). In every case, these "U" shaped developmental processes have been satisfactorily explained as being dependent, first from spinal, medullar-brainstem activities and, after further maturation – the second branch of the "U" process - from higher brain structures (Jane et al., 1972; Berntson and Micco, 1976; Atkinson, 1984; Morton and Johnson, 1991; Muir and Hains, 2004; Field et al., 1980; Johnson, 2001; Richards, 2001; Dubowitz et al., 1986; Khodadadifar, 2015).

The existence of brainstem-diencephalic wakefulness receives a strong additional support from the behavior of anencephalic human newborns. They show, on many cases, normal sleep-wake cycles and, while awake, can perform elaborate behavioral patterns, including responses to noxious stimuli, feeding and respiratory reflexes and even social interactions, involving eye movements and facial expressions (Francis et al., 1984). The complexity of their behavior arrived up to the point that, on occasions, parents often mistakenly believed that their child was normal during the first or second month of life (Halsey J.H.H. et al., 1968; Hoffman and Liss, 1969; Shewmon, 1988; Pant et al., 2010).

Altogether, the described facts show that sub-mammalian vertebrates and immature mammals possess, not only the already described

spinal-rhombencephalic waking, but also the brainstem-diencephalic waking.

3.5. Cortical wakefulness

The cortical control of the sensory-motor systems of wakeful mammals is evident and undisputed. The critical steps for developing the cortical wakefulness were 1) the development of spinal-thalamocortical sensory fibers, 2) the extensive production of telencephalic neurons, 3) the development of cortico-cortical association connections, and 4) the development of direct cortico-spinal motor fibers (Butler and Hodos, 2005; Butler et al., 2011). These newly developed sensory-motor systems allowed the production of the complex behavioral patterns of wakeful mammals. A complete description of the control and the main traits of the cortical wakefulness lies beyond the scope of the present review and has been recognized in many reports, (Schwartz and Roth, 2008; Berridge et al., 2012; Wright et al., 2012; Cirelli and Tononi, 2015; Brown and McKenna, 2015).

3.5.1. Intersegmental interactions within the wakefulness of the vertebrate brain

Table 1 shows the three main stages of anatomical and functional development of waking behavior in vertebrates: A) Cortical-diencephalic behavior, B) Brainstem behavior and C) Rhombencephalic-spinal behavior. In addition, A1, A2, A3, A4, and A5 are substages, with examples, of the cortical-diencephalic behavior, B1, B2, B3 and B4 substages and examples of the Brainstem behavior, and, finally, C1 and C2 are the substages and examples of Rhombencephalic-spinal behavior.

Table 1
Neuroanatomical brain regions (in red), main behavioral states (in blue) and the corresponding functions, with examples in black. A) Main state: Wakeful sensory-motor cortical activity (only possible in mammals). A1) Voluntary behavioral output. Example: learned motor activity. A2) Diencephalic voluntary homeostasis. Example: Satisfaction of hunger; A3) Diencephalic unconscious homeostasis. Example: Sweating/vasomotor responses; A4) intrusion of Rhombencephalic waking: Example: alarm reactions (fight-flight-fright responses). B) Main state: Mammalian NREM sleep; example: B1) Reptilian Slow Wave Wakefulness. B2) Example: voluntary reptilian behavioral output; B3) Voluntary (Tectal) eye movements B4) and involuntary (rhombencephalic) cardio-respiratory reflexes (present in all vertebrates, mammals, reptiles, and fish). C) Main state: mammalian REM sleep (paralyzed rhombencephalic-spinal waking); C1) automatic rhombencephalic waking (REMW). Example: flight-fright-flight reflexes (present in all vertebrates); C2) (Unconscious spinal reflexes. Example: the flexion reflex in response to painful stimuli (present in all vertebrates).

A) Cortical-diencephalic Behavior
A1) Cortical Mammalian Conscious Waking
A2) Voluntary cortical sensory-motor output
A3) Voluntary diencephalic homeostasis
A4) Automatic (reflex) diencephalic homeostasis
A5) RhW Automatic (reflex) rhombencephalic Behavior
B) Brainstem Behavior
B1) Mammalian NREM sleep
B2) Voluntary Reptilian sensory-motor output
B3) Voluntary reptilian Tectal vision and audition
B4) Automatic hindbrain and spinal reflexes
C) Rhombencephalic-Spinal Cord Behavior
REM sleep
C1) RhW Automatic reflexes
C2) Automatic Spinal Reflexes

The main purpose of Table 1 lies in showing that the signs of the three main stages and substages are successively nested within each other. Indeed, the included examples show that the cortical-diencephalic behavior may enclose many signs originated in lower brain regions. Likewise, the brainstem can nest abundant functional signs of rhombencephalic and spinal behaviors. In other words, the examples provided in Table 1 show that the most modern brain regions often use important functional properties of lower and older brain regions. Interestingly, the traits of lower brain regions also can invade more modern, upper brain regions. For example, the rhombencephalic-spinal regions can invade the cortical EEG, during REM sleep, with the low voltage-mixed frequency waves typical of mammalian wakefulness. However, the cases of retrograde invasion - from lower to higher brain regions - are scarce.

It seems, therefore, that the cortical-diencephalic wakefulness may use many functional capabilities of lower regions. This might be due to the urgency needed for responding to dangerous situations. For example, alarming stimuli demands a rapid response, with quick access to spinal motoneurons, the final common pathway. Therefore, the alarm reaction must use the shortest and quickest connections for a rapid and efficient behavioral output. On the contrary, the elaboration of non-so urgent responses may take profit of the superior analytical and functional capacities of cortical regions, accepting the cost of a reduced speed.

As a final note, we should remark that the different types of behavioral output depend, not only on the simple activation or inhibition of motoneurons, but also on the capability for elaborating, or not, voluntary responses. Indeed, the entire behavioral repertoire of fish is always constituted by a set of automatic reflexes. Instead, the cortical wakefulness may determine the production of voluntary activities, but also permits the irruption of subcortical responses. For example, the diencephalic thermoregulatory control is voluntary and fully conscious when we decide to use clothing to minimize the heat loss, but the skin vasoconstriction, serving for the same purpose, is always an involuntary diencephalic reflex.

3.6. Motor quiescence and sleep

When we described the eight traits defining sleep we put the quiescence in the first place. In fact, there is a unanimous agreement in recognizing that quiescence is the most significant trait of sleep: when an animal rests, it might be quietly awake but it also may be asleep. But, if it is moving, it is not sleeping. Moreover, quiescence is always a pre-sleep routine, up to the point that we proposed that sleep is an upgrade of quiescence (Rial et al., 2022) agreeing with many previous reports affirming that sleep serves for guaranteeing quiescence (Webb, 1974; Meddis, 1983; Rial et al., 1997, 2007, 2010; Siegel, 2009, 2011).

Animals possess many active neural mechanisms to block the behavioral output: entopeduncular nuclei, medullary and pontine reticular zones, parabrachial region, pedunculopontine nuclei and nearby areas, substantia nigra, subthalamic nucleus, ventromedial thalamic nucleus, zona incerta, etc. (Klemm, 2001). But passive quiescence also appears in hypothermic cool-blooded animals. Now, we would like to analyze the mechanisms that mammals use to enter in sleep. It seems evident that most authors assumed – implicitly - that the descent in BT is the primary cause of the reptilian pre-sleep quiescence. We arrive at this conclusion after observing that all reports dealing with the evolutionary origin of sleep searched it in the reptilian nocturnal quiescence and we know that reptiles are thermo-conformers during nighttime, i.e., they show hypothermia when they rest. Of course, reptiles possess many other neuronal mechanisms to block the behavioral output. But they always use hypothermia to enter in their nocturnal "sleep-like" state.

On the other hand, it is known since long that the reptilian telencephalic cortex possess a single cellular layer (Johnston, 1915) in stark contrast with the six layered mammalian cortex (Cajal, 1909–, 1911). These facts explain the huge difference in the behavioral feats of wakeful reptiles and wakeful mammals. Surprisingly, all reports dealing with the evolutionary origin of wakefulness, automatically assumed not only that the mammalian pre-sleep quiescence evolved for the reptilian nocturnal rest, but also that the mammalian wakefulness evolved from the reptilian one.

The truth is that reptiles and mammals differ, not only in the absence of true sleep, but also in their wakefulness. Indeed, the reticulospinal fibers constitute the most primitive descending system involved in the motor control of sub-mammalian vertebrates (Ten Donkelaar, 1982; Roh et al., 2011) while the descending corticospinal – pyramidal - tract only exists in mammals. Regarding the sensory control, two main nuclear groups can be found in the dorsal thalamus: lemnothalamic and collothalamic. The first one receives lemniscal input direct from the retina and other sensory systems. It projects to primary cortical neurons and is dominant in mammals. Furtherly, most mammalian sensory systems – excepting the auditory system - show no synaptic relay in the midbrain. The second neuronal thalamic group, the collotalamic one, is predominant in diapsid reptiles and birds and receives visual, auditory, somatosensory and multisensory input from the mesencephalic colliculi (optic tectum and torus semicircularis) and primarily project to striatal and ventrolateral pallial regions (Butler and Hodos, 2005; Butler, 2008; Roh et al., 2011). In summary, mammals and reptiles show different mechanisms for controlling the motor output and the sensory input, with mesencephalic dominance in reptiles and telencephalic dominance in mammals. So, we must conclude that the reptilian wakefulness is subcortical, while the mammalian one is cortical, and consequently, we will need to explain, not only the origin of the mammalian sleep but also the origin of the cortical wakefulness.

After having settled the problem, we would like to return to our question: which is the origin of the pre-sleep rest behavior of mammals? We have two options: a) mammals began sleeping after becoming passive thermo-conformers, as we know reptiles do before entering in their nocturnal rest; or b) mammals use, some active mechanism to suppress the behavioral output as a compulsory pre-sleep state. It is unnecessary to remember that sleep is an active process. Therefore, the option "a" must be rejected. The following lines will put particular emphasis in the substantia nigra, pars reticulata (SNr).

All vertebrates, from cyclostomes to mammals and birds, possess a well-developed SNr, (Stephenson-Jones et al., 2011, 2012, 2013; Ericsson et al., 2013; Juvin et al., 2016; Grillner & Robertson, 2015, 2016) and the organization of the basal ganglia – responsible of controlling the motor output - has been highly conserved (Medina and Smeets, 1991; Reiner et al., 1998; Grillner and Robertson, 2015). In fact, the SNr blocks the production of unwanted movements in all vertebrates, from lampreys to mammals and birds. (Grillner and Robertson, 2016).

The neurons of the basal ganglia receive input from two sources: excitatory Glutamatergic (GAD2 receptors) and inhibitory parvalbumin-GABAergic. The first one is the so-called direct pathway and plays a role in promoting motor activity. The second group – the indirect pathway - enhances the inhibitory output of the Globus pallidus interna and the SNr (Freeze et al., 2013). It has been found in mice that the optogenetic activation of the SNr neurons of the indirect pathway successively suppress locomotion (LM), non-locomotor movements (MV), including eating, grooming, and postural adjustments, to end in the quiet wakefulness (QW) of pre-sleep behavior (Liu et al., 2020). However, a direct succession from locomotion (or movement) to sleep was never observed. Indeed, the consequences of successive optogenetic stimulations always follows the natural sequence: LM→MV →QW →Sleep, i.e., transitions toward reduced arousal and motor activity. Instead, transitions in the opposite direction are strongly suppressed (Liu et al., 2020). In summary, the direct pathway disinhibits the motor responses, while the indirect one strengthens the inhibition and blocks the unwanted movements, promoting therefore the Quiet Wakefulness necessary as a pre-sleep behavior (Hikosaka, 2008; Liu, and Dan, 2019; Liu et al., 2020; Lai et al., 2021).

On the other hand, we proposed, in several previous reports, that the mammalian sleep evolved from the reptilian wakefulness. At a first sight, this proposal may seem preposterous and demanding a too complex evolutionary process. But, in fact, it only requires an extremely simple and pre-existent modification: blocking the ongoing behavior, i.e., exerting the main function of the SNr (Liu et al., 2020). Therefore, the conversion, from the reptilian subcortical waking to the resting pre-sleep of mammals, was already available in the first vertebrates and sleep should have evolved, not from a dubious reptilian sleep, but as the result of the activity of the SNr suppressing the behavioral output of the subcortical vertebrate wakefulness. Such suppression has been always an absolute need to stop unwanted movements, but it was not less important as a pre-sleep mechanism. Indeed, the coexistence between subcortical and cortical wakefulness would be catastrophic, as it is evident after observing the pathological consequences of REM sleep without atonia, of the REM behavioral disorder, of the somnambulism, of the periodic leg movements, etc. Undoubtedly, the entire set of motor disorders associated to sleep are intrusions of subcortical wakefulness and it is evident that Mother Nature, by using the SNr took extreme care to block all possibilities of the behavioral irruption of subcortical wakefulness during sleep.

3.7. *Interim summary*

The previous paragraphs showed that the ontogenesis of behavioral states repeats the phylogenetic sequence: mammalian embryos and newborns show cycles of spinal-rhombencephalic wake, with phasic signs that mostly serve as communication links between mother and embryo. These embryonic cycles appear in adult mammals as the cycles of phasic tonic REMS. In successive developmental stages, the brainstem-diencephalic wakefulness is the main state providing homeostatic and behavioral control in poikilothermic vertebrates. But it also appears in mature mammals during NREMS. The series ends with the mammalian cortical wake, in which rhombencephalic, brainstem-diencephalic and cortical wake are fused (Table 1). When, because of the low development, the cortical waking is impossible - for example in immature altricial species, these animals show a combination of spinal/rhombencephalic/brainstem/diencephalic waking when they are awake (Soussignan, 2003), a combination that also occurs during the NREMS-REMS cycles (i.e., during the rhombencephalic and diencephalic sleep, respectively) (Parmeggiani, 2011). During NREMS, the motor output is suspended because of the inhibitory command of the substantia nigra, pars reticulata (Lai et al., 2020), or because of the glycinergic-GABAergic inhibition of motor neurons during REMS. In next paragraphs we will refer to the independence of the two mechanisms blocking the motor output of NREMS and REMS. Indeed, the existence of two separate systems to block the behavioral output adds strength to the independent origin and the successive expression of rhombencephalic and brainstem types of waking. As an interim conclusion, we will remark first, that the spinal-rhombencephalic and brainstem-diencephalic stages of wakefulness are unavoidable and, without exception, never fail to appear in all vertebrates. All must surpass them in successive embryonary stages, all continue exerting vital functions in adults, to control, as described, different behavioral and homeostatic controls, and all - excepting the cortical wakefulness - can be included within the concept of primitive wakefulness.

4. EEG and behavioral states in vertebrates

While the EEG is the most important sign to define the electrographic wakefulness and sleep in mammals and birds, it has been much less studied in sub-mammals. As a result, some EEG traits of sleep remain

poorly understood in cool blooded animals.

The main EEG signatures used to define the electrographic states are amplitude, frequency, temporal characteristics, and several isolated graphisms. The alpha, beta, delta, theta, and gamma frequency bands of the EEG have been widely used to study the human wake-sleep states and, by extension, the mammalian states. In addition, the sigma spindles, PGO potentials, K complexes and high voltage isolated spikes are frequently used graphisms for further state differentiation. The following paragraphs will analyze the relationships between EEG and behavioral states in the whole vertebrate class.

The delta EEG, also called Slow Wave EEG (SWEEG), with high amplitude, low frequency waves is an essential, *but not exclusive* sign of NREMS. Indeed, SWEEG has been mostly described in NREM sleeping mammals, but also in wakeful newborns (Emde and Metcalf, 1968; Vecchierini et al., 2007; André et al., 2010), in the REMS of primitive mammals, e.g., platypus (Siegel et al., 1998) and even in some brain regions during human REMS (Bernardi et al., 2019). Furthermore, high power SWEEG has been recorded after the administration of scopolamine, an anticholinergic drug that permits the expression of wakeful-like behavior in subjects that, seemingly, are in a dissociated state of subcortical-cortical wakefulness. The scopolamine drugged subjects seem to be completely awake and respond to verbal orders but, after elapsing the effects of the drug, retain no memory of their acts (Wikler, 1952; Ostfeld et al., 1960; Schallert et al., 1980; Vanderwolf, 1988; Dringenberg and Vanderwolf, 1997; Castro-Zaballa et al., 2019). We should thus conclude that the presence of delta EEG cannot be used to automatically presume NREMS. Indeed, what characterizes the state of an animal is their behavior and not an EEG pattern. The scopolamine drugged subjects are awake, undoubtedly, but their waking is not the complete cortical wakefulness of non-drugged individuals. Most likely, it is a dissociated state showing a mixture of rhombencephalic, diencephalic and cortical wakefulness, as described in Table 1.

Delta EEG also has been recorded in reptiles - not in presumedly sleeping reptiles, as it was searched by many authors - but during their subcortical wakefulness (Bullock and Basar, 1988; Gaztelu et al., 1991; De Vera et al., 1994; González et al., 1999; Knyazev, 2012; Halász and Bódizs, 2013; Piercy et al., 2015) always heralding the low activity of their reduced pallium that, even in mammals, become blocked when the basic homeostatic functions require the activity of diencephalic regions. In these cases, the anti-homeostatic pallial interferences must be blocked (see § 3.6). In fact, the mammalian delta EEG is a sign of partial or total functional decortication (Massimini et al., 2005; Patron et al., 2019; Walter et al., 2019). Therefore, the basic meaning of the SWEEG waves is the same in mammals and in poikilothermic animals: blocking the anti-homeostatic telencephalic activity and freeing subcortical regions to perform essential life-sustaining activities (Rial et al., 2010).

The presence of rapid EEG – beta and gamma EEG - with low amplitude, high frequency waves - is the basic sign of the mammalian waking, but it also appears during REMS (Aserinsky and Kleitman, 1953; Maloney et al., 1997; Vyazovskiy et al., 2009). However, the beta EEG recorded in REM sleeping subjects is always accompanied by muscular atonia, which means that the beta EEG of REMS heralds a partial form of cortical wake devoid of motor output. Indeed, it has been repeatedly recognized that the rhombencephalon is necessary and sufficient for generating REMS (Siegel et al., 2011; Luppi et al., 2012; Weber et al., 2015) and the REMS of primitive mammals, probably with low cortical development, is limited to rhombencephalon that may, or may not, be accompanied by beta EEG, for example, in platypus (Siegel et al., 1999).

These facts prompted the affirmation that the forebrain aspects of REMS, including the dreams and the fast EEG, are a relatively recent evolutionary acquisition (Siegel, 1995; Siegel et al., 1998, 1999; Siegel, 2004; Solms, 2000) and, since they lack salient phenotypic traits – other than the EEG - may have non-adaptive significance. Indeed, the ability for animals to survive, depends on their capacity to show well-adapted behavioral patterns, but not because of showing a certain EEG pattern or experiencing certain dreams.

Summarizing, the EEG is not a reliable indicator of behavioral state in animals other than adult metatherian (marsupials) and eutherian (placental) mammals. When awake, modern mammals consistently show fast, small amplitude, mixed frequency EEG because of the excitatory activity of cholinergic and serotonergic neurons of the basal telencephalon and rafe, respectively (Dringenberg and Vanderwolf, 1997, 1998; Szymusiak et al., 2000). In the words of Steriade, and McCarley (2013) the beta and gamma EEG herald the fine sculpturing of activation-inhibition of different cortical areas necessary to perform the multisensory analysis of the environment, that is, to attain a full cortical wakefulness. However, in primitive mammals (platypus) the beta EEG may or may not be observed during REMS.

4.1. *The phylogenetic development of NREMS and REMS: divergence or convergence?*

A surprising EEG disparity was observed after comparing the polygraphic sleep of monotremes (platypus) and cats, as representative of primitive and modern mammals, respectively. Two types of REMS were recorded in the platypus, one with moderate EEG amplitude, and another one with high voltage EEG. But the firing activity of pontine neurons was found to be similar in sleeping cats and echidnas (Siegel et al., 1996). However, since unequivocal signs of NREMS and REMS seems to be inexistent in reptiles, it was concluded that the two states were the result of the divergent differentiation of a primitive sleep state with mixed NREM-REMS characteristics. i.e., the SWEEG of NREMS, together with the fast EEG of REMS. So, the platypus seemed to be the intermediate step between the REMS of echidnas, that show SWEEG - but seems to be devoid of REMS - and the REMS of modern mammals, with low amplitude, mixed frequencies EEG (Siegel et al., 1999).

It is evident that, if confirmed, the hypothesis of divergence would invalidate the main tenet of the present report; indeed, we are defending the existence of several and independent types of wakefulness that gave origin to the two sleep states, independently of each other. Instead, the platypus seems to show a mixture of NREM/SREM. Therefore, we will need to ascertain which one of the two alternatives, convergence, or divergence, was the one selected by Mother Nature.

The polygraphic sleep was also studied in a primitive bird, the ostrich (*Strutio camelis*). The results seemed to add evidence to the mixed NREMS/REMS hypothesis, because the forebrain EEG of NREM sleeping ostriches oscillated between high frequency, low voltage EEG and SWEEG (Lesku et al., 2011). Therefore, mammals and birds seemed to have followed a parallel evolution. Both began showing a primitive sleep, with mixed NREMS/REMS traits that in modern mammals and birds diverged to end as the well-differentiated EEG of NREMS and REMS.

However, the length of the REMS episodes and the total amount of REM sleeping time of adult ostriches was found to be longer than that of any other bird (Rattenborg et al., 2009). Therefore, an even larger proportion of REMS was expected in ostrich chicks, as it is always observed in immature mammals. However, a recent study reported substantially smaller amounts of REM in ostrich chicks than in adults, with no significant changes in NREMS. Therefore, the ontogenesis of REMS in ostriches seemed to be remarkably different from that observed in mammals (Lyamin et al., 2021).

The conundrum continued after finding that the sleep of another primitive bird, the tinamou (*Eudromia elegans*), showed the typical, well-differentiated EEG of NREMS and REMS of modern birds (Tisdale et al., 2017). The authors concluded that, although the tinamou data does not rule out the possibility that the ancestor of extant birds would exhibit a mixed ostrich-like/platypus-like sleep state, it does complicate the initial interpretation.

But the complexity increased after analyzing the sleep in Budgerigars (Canavan and Margoliash, 2020). These authors observed that the use of incorrect illumination during the experimental analysis was responsible of many of the differences currently alleged between mammalian and

avian sleep.

However, the problem is, in fact, inexistent. Obviously, the presence of mixed NREM-REM traits cannot be used as a signpost to infer the direction of the evolutionary arrow (see Fig. 1) Indeed, the evolution may have occurred towards divergence, as currently interpreted, but also in the opposite direction. That is, instead of marking the transition from a mixture of pre-REMS-REMS to independent NREMS and REMS (A1 to C1, Fig. 1), it can also be interpreted as signaling towards convergence, from REMS and NREMS (A2 to C2, Fig. 1) to mere sleep, a possibility also suggested by Corner and Schenk (2015). So, the results obtained in monotremes and ostriches should not be used to consider the existence of a conflict between convergence and divergence.

On the other hand, we should remember that the main data used to affirm the existence of a primitive state with mixed NREM-REM traits was the presence of SWEEG both in platypus (Siegel et al., 1999) and in ostriches (Rattenborg et al., 2009) and we may remember the low value of the SWEEG for the differential diagnosis of sleep stages in animals other than metatherian and eutherian mammals (see § 4).

In our opinion, the hypothesis of divergence is a jump to the void: no explanation has been elaborated for when and how such jump occurred and much less why. Indeed, nobody developed a credible hypothesis to explain the advantages or disadvantages of showing one or two sleep states. Instead, the proposal defended in the present report does not consider neither advantages, nor disadvantages; it simply explains a set of facts that cannot be ignored: primitive, low brained vertebrates, had no option other than using the activity of their spinal cord/hindbrain to be awake and survive. In a next evolutionary stage, they used the brainstem-diencephalon to control the bodily homeostasis and, both the spinal-rhombencephalon and the brainstem-diencephalon were used for controlling REMS and NREMS, independently of each other, but also irrespective of their function.

Pursuing a reasonable answer, we will search the behavioral differences between NREMS and REMS. It is evident that the eight traits we used to define the behavioral sleep (§ 1) may apply to both states, with only minute differences: both show quiescence, reversibility, specific body positions, use the same sleeping places, show raised sensory thresholds, circadian organization, homeostatic regulation, and both are pleasing states. In sum, it seems that Mother Nature did big efforts to hide the huge neuroanatomical and functional difference between states. Furthermore, Aserinsky and Kleitman (1953), and all following researchers, needed a sophisticated set of electronic equipment to distinguish NREMS and REMS. It is thus evident that the existence of two sleeping states has been invisible during hundreds of years. In other words, both states merely converged into a single behavioral state: sleep.

To conclude, we can maintain our proposal. The evolutionary pathway for the development of NREMS and REMS began with the development of a primary spinal-rhombencephalic waking. It was followed by the brainstem waking and both were enclosed within the cortical waking but upsurged again during sleep in the form of REMS and NREMS respectively. Therefore, the possibility of a common primitive origin and modern divergence should be discarded. In fact, both names “NREM” and “REM” are always appended with the word “sleep”.

5. The paradoxical homeostasis of wakefulness

Along this report, we made several allusions to the anti-homeostatic nature of the wakefulness, be it rhombencephalic or cortical. Undoubtedly, the homeostatic physiological regulation is deeply disturbed during REMS (Parmeggiani, 2011). However, continuous homeostatic disturbances occur during cortical wakefulness. For instance, a wakeful grazing lamb may keep active its entire homeostasis but, on perceiving a wolf, the homeostatic stability disappears. Among many other disturbances, the heartbeat frequency, respiration, arterial pressure, blood glycemia, etc., abandon the previous stability. In consequence, wakefulness may be considered as a state exposed to continuous anti-homeostatic disturbances. Indeed, the homeostasis aims at maintaining a physiological steady state (Cannon, 1929), but, in dangerous situations, the wakefulness permits temporal, but serious alterations in the physiological constants with the purpose of increasing the survival chances (Laborit, 1976). These facts gave origin to the concepts of *Rheostasis*, the homeostasis of change (Mrosovsky, 1990) and *Allostasis*, the process by which the internal equilibrium of an organism is maintained by responding to environmental stressors (McEwen, 2002; McEwen and Wingfield, 2003). We already described that in neurological terms, the delta EEG heralds the need of recovery from the homeostatic perturbations suffered during wakefulness. Indeed, animals showing cortical wakefulness and those showing REMW, must make continuous efforts for searching food, finding reproductive partners, escaping dangers, predators, etc. These activities represent disruptions in the immediate homeostatic regulations while attempting to maintain nutritional stability, physical integrity, reproductive efficiency, etc. These facts can be summarized affirming that the active wakefulness continuously generates allostatic loads that must be compensated with subsequent periods of rest, whose epiphenomenon, the Delta EEG power (i.e., NREMS) heralds the work of subcortical regions for recovering the homeostatic balance (Knyazev, 2012; Halász and Bódizs, 2013).

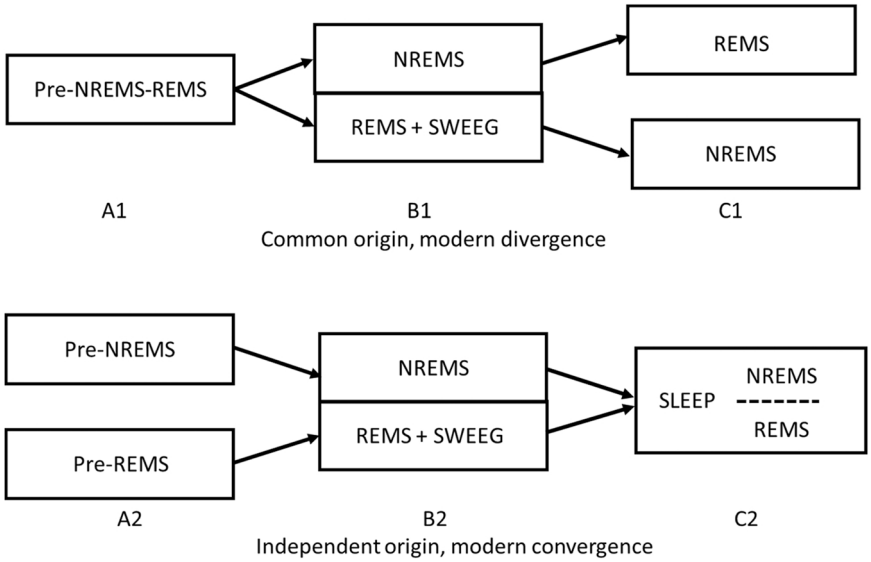

Fig. 1. Two alternatives to explain the origin of NREMS and REMS.

6. The ultra-paradoxical homeostasis of REMS

Many authors recognized the existence of homeostatic regulation for REMS (Dement, 1960; Agnew et al., 1967; Morden et al., 1967; Beersma et al., 1990; Benington and Heller, 1994; Wurts and Edgar, 2000; McCarthy et al., 2016; Weber et al., 2018; Park and Weber, 2020). Indeed, when the expression of REMS is experimentally suppressed, the REMS propensity increases, as shown by repeated attempts to re-enter in REMS and by the progressive increase in the number of phasic REMS signs (Vogel, 1975; Shea et al., 2008).

We would like to remark here the dissonance between the most salient signs of REMS and the concept of homeostasis. Indeed, the thermal poikilostasis and cardiorespiratory irregularities of REMS are a set of factors that could be rightly considered as indicative of homeostatic abandon, in an evident conflict with the well demonstrated homeostasis of REMS. In an extreme antithetic contrast, the word "poikilostasis" (Parmeggiani, 2011), represents, precisely, the demolition of the physiological homeostasis caused by the high sympathetic activity accompanying REMS (Somers et al., 1993). Indeed, the sympathetic system is responsible of the physiological lability in thermoregulatory (Parmeggiani and Rabini, 1970; Parmeggiani, 1977, 2011) cardio circulatory (Mancia and Zanchetti, 1980) and respiratory (Phillipson, 1978; Sullivan, 1980) activities. Under this viewpoint, the existence of homeostasis in REMS involves a new paradox superimposed to the old, well recognized paradoxical nature of REMS that determined naming the REMS as paradoxical sleep - the EEG signature of waking, associated with the behavioral signs of deep sleep - (as described by Aserinsky and Kleitman, 1953; Jouvet et al., 1959). We are now referring to what we would name the "ultra-paradoxical" aspect of REMS, that may be responsible of our current ignorance on the nature of the REMS homeostatically regulated variable. Indeed, conciliating the general homeostatic regulation with the thermal, respiratory, and cardio circulatory poikilostasis, i.e., what we would call "the homeostatic regulation of the REMS physiological dysregulation", seems to be impossible.

Nevertheless, we can remember here that the positive value of the phasic signs observed in the REMS of newborns largely outweighs the subsequent negative thermal and cardio-respiratory irregularities of the REMS observed in infant and adult mammals. Moreover, most terrestrial mammals sleep in comfortable and thermally isolated nests or burrows, i.e., in microenvironments in which the environmental challenges are dampened, and the importance of the eventual physiological dysregulations of REMS is small. The situation changes in adult marine mammals, in which the thermal constraints of aquatic life - high thermal conductivity and high specific heat - largely outweigh the importance of the phasic signs of the adult's REMS. Indeed, it is known that the total duration of REMS episodes oscillates between maximal levels, in thermoneutral environments (Szymusiak and Satinoff, 1981), intermediate levels in mildly cool environments (Satoh, 1968; Kovalzon, 1973; Alfoldi et al., 1990; Almirall et al., 1997) and zero in marine mammals (Madan, and Jha, 2012; Lyamin et al., 2018). These facts are the expression of the allostatic thermal load attained in different environments, a load that must be dissipated - when possible - by entering in NREMS, to recover full homeostatic control or, alternatively, must disappear when impossible, for example in marine mammals, because of the thermal properties of water.

Considering these facts, we propose that the homeostatic regulation of the mammalian REMS depends on two mechanisms: first, a permissive flip-flop (Lu et al., 2006; Fuller et al., 2007; Chen et al., 2018) controlling the NREMS-REMS transitions by switching the direction of the interchange of heat between periphery and core (Charles et al., 1980; Whitten et al., 2009). Indeed, the cephalic temperature increases during REMS in opposition to the peripheral temperature, a difference that is reversed during NREMS (Deboer et al., 1994, 2008; Harding et al., 2019). These changes might constitute a defensive mechanism to guarantee a minimal brain temperature when the peripheral losses of heat begin to be excessive. In fact, it has been found that the skin thermoreceptors drive the changes of state, from NREMS to REMS and vice versa (Szymusiak et al., 1980; Whitten et al., 2009) compensating so the allostatic load acquired during the poikilostatic REMS, REMW and cortical wakefulness.

Apart from the described permissive, on-off flip flop, we propose that a second, independent proportional system regulates the production of the phasic signs of REMS. Indeed, we already described that the number and the intensity of calls, jerks and twitches of immature animals increase in proportion to the degree of cooling, hunger and any other risk compromising the life of newborn animals (Brooks and Peever, 2016) but lack importance within the well-isolated sleeping nests of adults. In this way, the advantages of the communication mother-infant greatly outweigh the disadvantages of the poikilostatic REMS, REMW and cortical waking. Therefore, the ultra-paradoxical nature of REMS can be explained: REMS may be a state with highly disturbed homeostasis, but the disturbances – jerks, twitches, calls, thermoregulatory and cardiorespiratory irregularities – provide with a highly adaptive value that outweighs the REMS hindrances. The existence of two modes of regulation for REMS suggests that REMS is, in fact, a combination of two different states: REMS tonic and REMS phasic (Simor et al., 2020). The state of rat pups quietly sleeping in tonic REMS is truly different, in anatomical and physiological terms, from that of cooled, isolated and/or hungry rats calling help to the dam. The first ones, are undoubtedly, sleeping. But the immature brain of the last ones is, undoubtedly, in REMW. They can perceive environmental stimuli and can elaborate adaptive responses. We thus conclude that the phasic REMS is a wakeful rhombencephalic state.

7. The second part of the Crick & Mitchison dilemma

The results and hypotheses described so far refer basically to developmental processes. Therefore, the search for an answer to the first part of the Crick and Mitchison observations may have been accomplished. Now, we should find a response to the second part: "*any purely developmental theory must account for the quite appreciable amount of sleep along adult life*".

7.1. The adults' REMS is a neutral trait

It is well-known that 1) people taking monoamine oxidase inhibitors show long term reductions in REMS, or no REMS at all, but show no compensatory rebounds (McCarthy et al., 2016), 2) the reductions in REMS cause no cognitive impairments (Flood and Cherkin, 1987; Marwari and Dawe, 2018; Gazea et al., 2019) and even may cause discrete improvements in memory retrieval (Flood and Cherkin, 1987; Rasch et al., 2009), 3) traumatic hindbrain lesions in humans cause a persistent suppression of REMS with no observable derangements (Osorio and Daroff, 1980; Lavie et al., 1984; Magidov et al., 2018), 4) cetaceans entirely lack REMS, (Lyamin et al., 2008) and 5) fur seals show no REMS when in the sea, but show normal amounts in land, without subsequent rebounds (Lyamin et al., 2018). We can summarize these facts affirming that REMS may disappear in adults without consequences.

Thus, we feel forced to propose that REMS persists because it provides, in most adult mammals, with neither advantages, nor disadvantages. In other words, the presence of REMS is essential in newborns, but in adults *it is a neutral trait, devoid of adaptive significance*.

We would like to remember that in the paragraphs 2.1 and 3.7 we remarked that the spinal-rhombencephalic and brainstem-diencephalic stage of wakefulness i.e., the REMW, are unavoidable and, without exception, never fail to appear *in all vertebrates, including marine mammals*. We may add now that, undoubtedly, cetaceans show REMW during an unspecified developmental phase of their brain, - possibly in utero - but the function of neural structures controlling such state were suppressed upon reaching adulthood immersed in cool water.

7.2. Neoteny

Some seemingly inexplicable traits observed in adults may simply be remnants of embryonary or infantile traits that persist despite their loss - or change - in adaptive significance. Such processes receive the generic name of Neotenies (Foxon, 1933).

Many examples of neotenic organs have been described in the human body. The bellybutton is a scar from the placenta, a structure of vital importance in the embryo but is functionless in adults. Similar examples have been described in many other animals. It must be noted, however, that the persistence of neotenic traits in adults is not compulsory. Two examples of lost embryonic traits are the *foramen ovale* communicating the two atria of the human fetus hearth, and the *ductus arteriosus*, an artery connecting the aorta and the pulmonary artery. Both communications are compulsory in embryos to avoid the detour of blood to the functionless lungs before birth. Every mammalian fetuses possess a *foramen ovalis* and a *ductus arteriosus*. But, although in most cases they disappear shortly after birth, they may persist in some adults.

Likewise, the phasic traits of REMS may have been highly adaptive for infants but, in adulthood may be neutral, with no known advantage, and, possibly, may have disappeared when they were mal-adaptive. This may have occurred in marine mammals in which the insupportable REMS poikilothermy forced the abandon of REM sleep. Summarizing, the persistence of REMS in adult terrestrial mammals seems to be a paradigmatic example of a functionless neotenic trait that was lost in adult marine mammals.

7.3. Sleep, science and epistemology

The epistemological rules may provide additional food for thought. First, it is well established that "*adaptation is an onerous concept that should be invoked only when necessary to explain the facts*" (Williams, 1966/, 2018). It is in fact too easy to find ad hoc explanations for everything, and even to imagine adaptive - and unfalsable - explanations for both the presence and absence of a given trait. In such cases, if one adaptive explanation fails, it is simply replaced by another. But sufficient ingenuity enables affirming many successive adaptive explanations. Therefore, given that the presumption of adaptation is more expensive that its negation, the principle of parsimony compels the negation of adaptation.

A corollary of the Williams' statement is that the burden of the proof must be charged to the defenders of any eventual adaptation. All sleep researchers are aware of the inexistence of solid proofs for the dozens of hypotheses developed to explain the existence of two sleep states and the adaptiveness of REMS. Therefore, these hypotheses should be in principle rejected. Either an undisputable, solid proof is provided, or the null hypothesis must prevail.

Still in epistemic terms, science should adopt a methodology based on falsifiability, because no number of positive experiments can ever prove a theory. On the contrary, a single experiment is enough for falsifying it (Popper, 1934/, 1959). In relation to REMS, the existence of a single adult surviving without REMS and with no discernible health or cognitive dysfunctions is enough to dismantle the adaptiveness of REMS (Siegel, 2021).

Two schools of evolutionary thinking have been defined: adaptationism (also called Panglossianism) and neutralism (Gould and Vrba, 1982). Panglosians naively believe that every anatomical or physiological trait stabilized in a living species must be adaptive. Otherwise, the trait would never have appeared, or would never be maintained. Possibly, pure Panglossian scientists are, at present, inexistent. Conversely, neutralists believe in the existence of neutral traits in populations. The best-known example of neutral mutations are the synonymous mutations in the ADN that, most likely, cause neither advantages nor disadvantages for the survival of individuals (Kimura, 1977).

7.4. Population genetics

In addition, the Selection Coefficient of a given gen is an index of the strength of selection for, or against to, genotypes possessing such gen (Bulmer, 1971; Herron and Freeman, 2014). In practical terms, the Selection Coefficient would be + 1 for traits that would be extended to a complete population in a single generation – for instance, the immunity to an otherwise mortal pest, and − 1 for those that would cause immediate death with zero descendants because of a high sensitivity for the same pest. In the middle, genes with indexes comprised between + 1 and − 1 would show increases or decreases, respectively, in the survival probability after a finite number of generations, while those with a zero index would represent an absolute neutrality. It is evident that, discarding spontaneous random mutations or genetic drift, those traits with selection coefficients approaching zero would need a high number of generations and an extreme environmental constancy to become established - or discarded - in the entire population. Regarding REMS, we assume that the possession of genes to show phasic signs of REMS in newborns may have a high positive value, but the index may turn negative for marine mammals. Likewise, the index would be zero, i.e., neutral, in animals that sleep in thermoneutral environments, that is, in well isolated nests or burrows. This is the case of most adult mammals - including humans - that despite supporting significant episodes of poikilothermic REMS, show no significant disturbances in BT.

On the other hand, we may analyze the interspecific, interindividual and intraindividual variations in total REMS time. Such variability provides with a measure of the selection coefficients of different species, of different individuals in a single species, and within a single individual. There is overwhelming evidence showing 1) an immense variation exists in the traits defining NREMS and REMS; 2) that such variations depend on multiple factors: body size, predation, alimentation, age, circadian time, mode of life, health and reproductive status, gender… The high number of factors modifying the traits are indicative of low power of the selective forces for or against REMS. In other words, REMS is immensely flexible, which means that the traits distinguishing the multiple environmental, internal, and constitutional aspects of REMS are unimportant. The single exception for this conclusion is the already mentioned aquatic mode of life: the thermal properties of water are of paramount importance and, therefore, forces the suppression of REMS.

8. The evolution of waking states and the function of NREMS and REMS

The function we propose for the phasic signs of REMS observed in immature mammals, as well as the REMS anomalies observed in vertebrate embryos, primitive mammals, marine mammals, and in pharmacologically treated humans is not speculative. At variance with any other presumed adaptive functions of REMS, the proposed here is consistent with experimental evidence, with the epistemic roots of science and with the current knowledge of population genetics. Furthermore, our proposal constitutes the single explanation that, for the time being, consistently explains why the NREMS and REMS cycles persist in adult mammals. Such consistency adds a strong support to the assumption that NREMS and REMS appeared because of obliterating the motor output of the reptilian BB and GDB (Rial et al., 1993, 2007, 2008, 2009, 2011; Nicolau et al., 2000).

9. Sleep and wakeful idleness

In a previous report (Rial et al., 2022) we observed the growing interest of researchers on the Wakeful Idleness (WI), a state different from sleep and from active wakefulness. Furthermore, we remarked that sleep and WI meet, at least, seven out of the eight traits used to define the behavioral sleep: quiescence, modified sensory thresholds (depending on the state of the reticular formation) easy reversibility, preferred resting places and body positions as well as circadian organization of the

preferred time for resting. In addition, both are highly pleasing for humans and animals with capacity for hedonic experiences. In summary, only the homeostatic regulation seemed to be absent from the wakeful rest. However, we recently presented significant evidence showing that the wakeful idleness is regulated, not only from physiological constraints, but also from strong cultural and legal commands that, obviously, cannot oppose the natural forces (Rial et al., 2022).

Indeed, a world of permanent utilitarian activity is unimaginable, both for humans and animals. So, sleep and idling waking are hardly distinguishable. The single distinctive trait seems to be the consciousness, obviously present in idling animals and humans and seemingly absent during NREMS and REMS. However, this last assertion is relative. In fact, the dreams observed during REMS (Kahn et al., 1997; Hobson, and Friston, 2012; Scheinin et al., 2021), as well as during NREMS (Siclari et al., 2018) have been considered as indicative of partial consciousness. So, we dared to affirm that sleep is an upgrade of waking idleness (Rial et al., 2022).

We observed that sleep was the result of blocking the behavioral output during light time in early pre-mammals devoid of the ocular filters avoiding blindness (Rial et al., 2022). But we may remember that the behavioral output of REMS was suppressed in marine mammals because of the incompatibility between life in the water as well as the poikilothermic incompatibility achieved through the inhibitory activity of medullar glycinergic and GABAergic neurons. Likewise, the behavioral output of NREMS was blocked by GABAergic neurons of the substantia nigra pars reticulata (Lai et al., 2021). Therefore, we see that, in the three states, sleep appears after inhibiting the behavioral output, i.e., after forcing rest. Indeed, we saw that the change to and from behavioral activity and simple rest, or even to and from sleep, was astoundingly simple: switching off or on the behavioral output using a neural mechanism that pre-existed since long. In our previous report (Rial et al., 2022) and agreeing with many authors (Webb, 1974; Meddis, 1975, 1983, 2018; Rial et al., 1997, 2007, 2010; Siegel, 2009, 2011) it was proposed that the main function of sleep consists in guaranteeing the behavioral rest. This proposal receives further support from the present review.

Furthermore, we would dare to affirm that the primary need forcing the invention of the mammalian sleep was the relegation of the two types of subcortical wakefulness - rhombencephalic and diencephalic – to sleep, a kind of junkyard. We imagine the horrified face of the readers. Of course, affirming that sleep must provide with some vital, yet unknown advantage is a kind of inviolable dogma between sleep scholars. We should note, however, that the suppression of a disadvantage is also an advantage. In fact, early mammals invented sleep to escape from two dangers: blindness and terrific competitors. Contrasting, transforming sleep into simple immobility, by using any available process other than sleeping would cause, as far as it is known, no problem at all. As a matter of fact, Mother Nature found an elegant solution to succeed in both tasks – avoiding blindness and the dinosaurs' predation, by inventing sleep, i.e., blocking the reptilian behavioral output, which is, possibly, an advantage that surpass, by far, the eventual advantages proposed up to now by sleep researchers. Imagine, as an alternative, that Mother Nature would allow the persistence, in modern mammals, of the three types of wakefulness: spinal-rhombencephalic, brainstem-diencephalic and cortical. It seems that Mother Nature succeeded in suppressing such madness by relegating them to what we qualified as a junkyard: sleep. Obviously, Mother Nature only allowed attenuated forms of such madness: suppressing the behavioral output, i.e., inventing sleep. Otherwise, the coexistence between cortical and spinal-rhombencephalic wakefulness extinction would be catastrophic for the survival.

10. A final caution

We should note that the present report only deals with the waking states of vertebrates and its relationships with the mammalian sleep. Obviously, our results cannot be applied neither to birds in which no nocturnal bottleneck has been described. For the same reason, the evolutionary pathway we propose for the mammalian sleep cannot be applied for the sleep of invertebrates and poikilothermic vertebrates. Therefore, the sleep of non-mammalian animals must have appeared as result of evolutionary convergence that remains to be explained. But we know that, in essence the most tangible function of the mammalian sleep consists in suppressing the behavioral output during a part of the daily cycle.

Data availability

No data was used for the research described in the article.

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