EDITORIAL

WIDESPREAD MEMBRANE POTENTIAL CHANGES AND CARDIORESPIRATORY SYNCHRONIZATION INVOLVED IN ANXIETY AND SLEEP-WAKE TRANSITIONS

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Located within the ascending reticular activating system are nuclei which release neurotransmitters such as acetylcholine, serotonin, dopamine, and norepinephrine. These nuclei have widespread projections that extend into the limbic system and throughout cortex. Activation of these neurotransmitters during awake states leads to arousal, while inhibition leads to the loss of consciousness experienced during slow-wave sleep. Previously, we proposed a mechanism in which cardiorespiratory synchronization may underlie the widespread hyperpolarization that occurs throughout the brain during slow-wave sleep. We further propose that a similar homeostatic mechanism may be involved in sleep-wake transitions and maintaining various arousal states including rapid eye movement sleep, waking, and anxiety. Widespread depolarization associated with more rapid, shallow breathing and desynchronized cardiorespiratory oscillatory activity may underlie waking, anxiety, and rapid eye movement sleep states. The exact voltage values of these widespread membrane potential changes remain unknown and possibly highly variable between different neural areas and cell types. Here, we place these consciousness states on a spectrum of approximated widespread membrane potential values with anxiety states being the most depolarized, followed by waking states, and rapid eye movement sleep. We propose that although these widespread membrane potential changes are minor, they may underlie transitions between and maintenance of varying levels of arousal. Further research on these mechanisms could provide insights into how the brain functions. This homeodynamic arousal mechanism involves the established feed-forward and feedback signaling between the ascending reticular activating system and the hypothalamus, as well as the modulation by cardiorespiratory oscillatory feedback from the body. Understanding the basic mechanisms responsible for the states of sleep, waking, and anxiety could lead to better treatment options in health and disease.

Although extant knowledge about the ascending reticular activating system (ARAS) provides evidence of its involvement in regulating sleep and wake cycles, exactly how these processes work is ambiguous. In this paper, we further expand on our previously proposed model of cardiorespiratory synchronization, and propose that high levels of cardiorespiratory synchronization can modulate various brainstem nuclei and lead to the widespread hyperpolarization that occurs throughout the brain during slow-wave sleep. We apply this theory to other states of consciousness including rapid eye movement (REM) sleep, waking, and anxiety. We suggest that widespread depolarization may underlie

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various degrees of rapid and shallow breathing and decreased levels of cardiorespiratory synchronization that occur during states of REM sleep, waking, and anxiety. These consciousness states may be better understood on a spectrum raking hyperpolarization and depolarization of neuronal membrane potential. This spectrum places slow-wave sleep on the more hyperpolarized end of the spectrum, and places REM sleep, waking, and anxiety on the more depolarized end of the spectrum. We propose that widespread homeodynamic membrane potential changes may correspond with, and could likely underlie the various states and associated neural activity of the aforementioned states of consciousness.

Ascending reticular activating system

The ARAS consists of a group of nuclei in the brainstem (such as the locus coeruleus, raphe nuclei, pedunculopontine nucleus (PPN), and parabrachial nucleus; as well as various thalamic nuclei, the hypothalamus, and basal forebrain) (1) responsible for transitions in waking and sleeping. Consciousness is a result from activation of the ARAS and the subsequent changes in the brainstem and cortex (2). This system connects the brainstem and the cortex and extends from the pontine reticular formation through the mesencephalic tegmentum and ends in the intralaminar nuclei of the thalamus (3).

The ARAS and brainstem are made up of various nuclei that are involved in neurotransmitter systems that spread throughout the brain (Fig. 1). The release of neurotransmitters by these nuclei can launch rapid and widespread changes throughout the brain. The cardiovascular and respiratory centers are also located in the medulla adjacent to these other nuclei. The respiratory center consists of the nucleus of the solitary tract, nucleus ambiguous, and other pons nuclei. Neurons from the nucleus of the solitary tract innervate the reticular formation, hypothalamus, thalamus, limbic system, and other areas throughout the brain (4).

Neurotransmitters and the sleep-wake cycle

Changes in the sleep-wake cycle are initiated, maintained, and regulated by neurotransmitters (produced by neurons) and located within the brainstem and hypothalamus (5) (Fig. 2). Acetylcholine (Ach) is released by the central nervous system and has both excitatory and inhibitory effects (6), and levels are higher during REM sleep (7).

Gamma-amino butyric acid (GABA) in the "pontine reticular formation can promote wakefulness and inhibit REM sleep" (7), as can serotonin and dopamine.

Norepinephrine is more active during wakefulness and less active during slow-wave sleep, and helps regulate REM sleep (8), but initiates deactivation of REM sleep when it is activated in the locus coeruleus (9). In response to stimuli, norepinephrine neurons in the locus coeruleus react either by: i) exhibiting moderate tonic firing and phasic firing during non-stressed waking states, or ii) exhibiting high tonic firing and phasic firing dysregulation during stress (10).

Analogously related, epinephrine is active during wakefulness, and elevated levels are associated with stress and the sympathetic response (11). Injection of epinephrine into the locus coeruleus results in fewer REM periods but an overall extension of the sleep cycle (12).

Lastly, orexin neurons are also important in sleep because they help to: i) modulate sleep-wake transitions; ii) transitions between the sleep states (13); and iii) innervate areas throughout arousal pathways (14).

Nuclei in the VLPO contain neurons that use GABA, and fire only during NREM and REM sleep, and vagal outflow to the heart and body is dominated by the parasympathetic system during NREM sleep, while sympathetic dominance occurs during REM (15). Furthermore, EEG evidence has shown that during slow-wave sleep, parasympathetic vagal activity of the heart and slow waves strongly interact (15).

Cardiorespiratory synchronization and slow-wave sleep

Most studies on the control of arousal and sleep-wake cycles focus on the role of efferent signaling from various areas of the brain, such as the

hypothalamus (Fig. 3). We recognize the important role of these brain structures in these sleep processes and transitions; however, we focus on the proposed modulation of these sleep processes via afferent feedback such as cardiorespiratory signaling to the brainstem, which is largely ignored. Brain structures such as the hypothalamus are also involved in modulating breathing (16) therefore influencing this afferent signaling, but detailed discussion of modulation through higher brain areas is beyond the scope of this paper.

Bartsch et al., found that the degree of cardiorespiratory phase synchronization (defined as consistency of number of heartbeats with breathing cycles during the same phases) increased by 400% during the transition from REM to deep sleep (17). There are also strong hyperpolarizing forces that lead to widespread inhibition throughout the brain within the cortex, thalamus, ARAS, hypothalamus, and amygdala that prevent external stimuli from reaching the cerebral cortex in order to provide the body with protection while sleeping (18).

This widespread hyperpolarization could result from modulation of brainstem nuclei by slow, deep breathing and high levels of cardiorespiratory synchronization (15), and could partly stem from hyperpolarizing currents originating from slowly adapting stretch receptors in the lungs (19), and widespread inhibition during prolonged inspirations of slow, deep breathing (20).

Cardiorespiratory synchronization and widespread hyperpolarization

We propose that widespread hyperpolarization may underlie the restorative properties of slow-wave sleep, as well as the propagation of delta waves, and functional disconnection of the thalamus and cortex that occur in slow-wave sleep. During slow-wave sleep, when the ARAS is inhibited (18), there is a decrease in the release of acetylcholine, norepinephrine, and serotonin (9). As a comparison, during REM sleep, the cholinergic nuclei from the pons-midbrain junction are active while serotonin is inactive. Furthermore, synchronous oscillations within spindle and delta frequencies takes place

when thalamic neurons hyperpolarize during the onset of sleep, and shift to burst firing mode (21).

During slow-wave sleep the thalamus transitions from tonic firing to burst firing mode synchronizing with the cortex. During awake states, tonic firing from the thalamus transmits information to the cortex (22). This rhythmic bursting is thought to play an important role in promoting the slow-waves observed during slow-wave sleep (23).
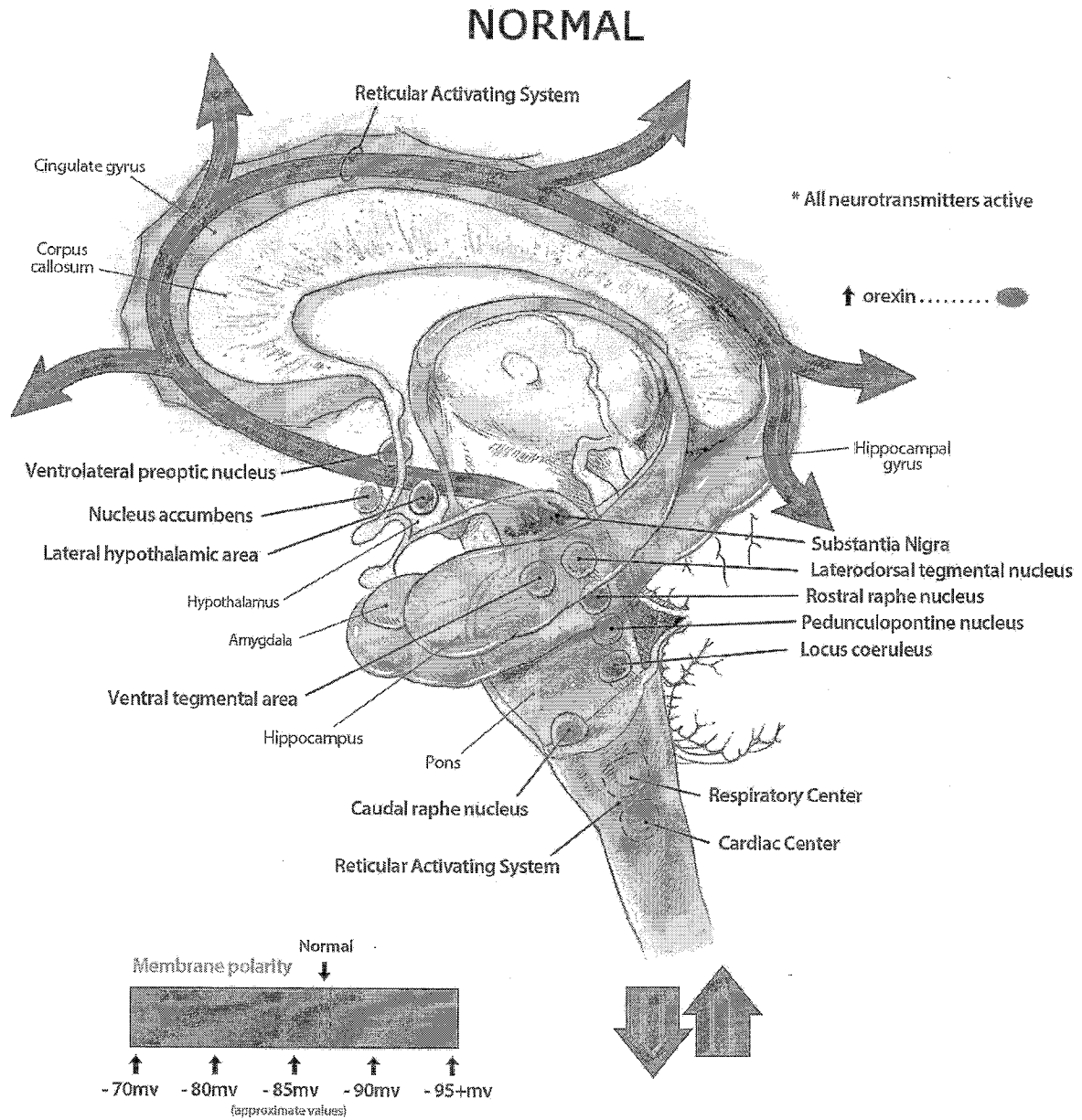
Widespread depolarization and REM

REM sleep is characterized by increased parasympathetic activity and variable sympathetic activity associated with an increased activation of certain brain functions. During REM sleep there is widespread depolarization throughout the brain. The ARAS depolarizes (24) and activates other brain regions such as the thalamus (25). The beta-gamma band activity may be generated by the membrane potential responsiveness of PPN neurons that fire at gamma band frequency when depolarized during waking and REM states (26), and hyperpolarization of these neurons via GABAergic inhibition may promote slow-wave sleep. There is also increased activity in the limbic system and cardiac and respiratory centers of the brainstem (27).
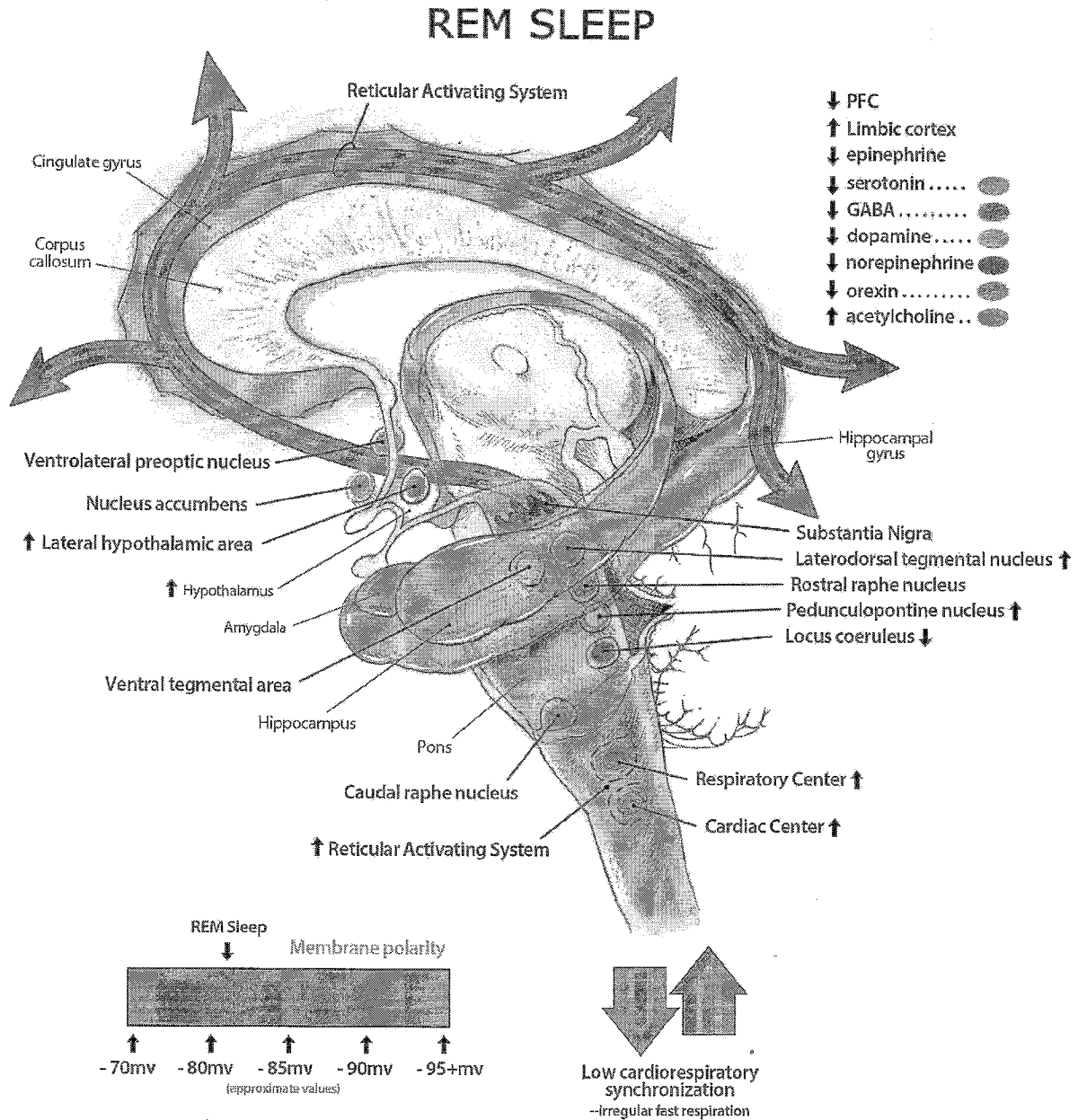
During REM sleep cardiorespiratory synchronization decreases and breathing becomes more shallow and rapid than in slow-wave sleep (28). We propose that REM sleep is initiated when limbic and amygdala activity synchronize with the cardiorespiratory system, leading to widespread depolarization within the ARAS via a cholinergic system. This leads to activation of visual and parietal responses without the activation of certain waking cognitive areas and processes. We suggest that the hypothalamus is highly involved in maintaining normal REM and slow-wave sleep by increasing the frequency and depth of breathing—which in turn leads to widespread modulation of resting membrane potentials throughout the brain—and modulates shifts in sleep cycle phases.

Waking and paradoxical sleep

Waking and REM sleep states are characterized

NORMAL

Reticular Activating System

Cingulate gyrus

Corpus callosum

* All neurotransmitters active

↑ orexin .... ●

Hippocampal gyrus

Ventrolateral preoptic nucleus

Nucleus accumbens

Lateral hypothalamic area

Hypothalamus

Amygdala

Ventral tegmental area

Hippocampus

Pons

Caudal raphe nucleus

Reticular Activating System

Substantia Nigra

Laterodorsal tegmental nucleus

Rostral raphe nucleus

Pedunculopontine nucleus

Locus coeruleus

Respiratory Center

Cardiac Center

Normal

Membrane polarity ↓

↑ ↑ ↑ ↑ ↑

-70mv   -80mv   -85mv   -90mv   -95+mv
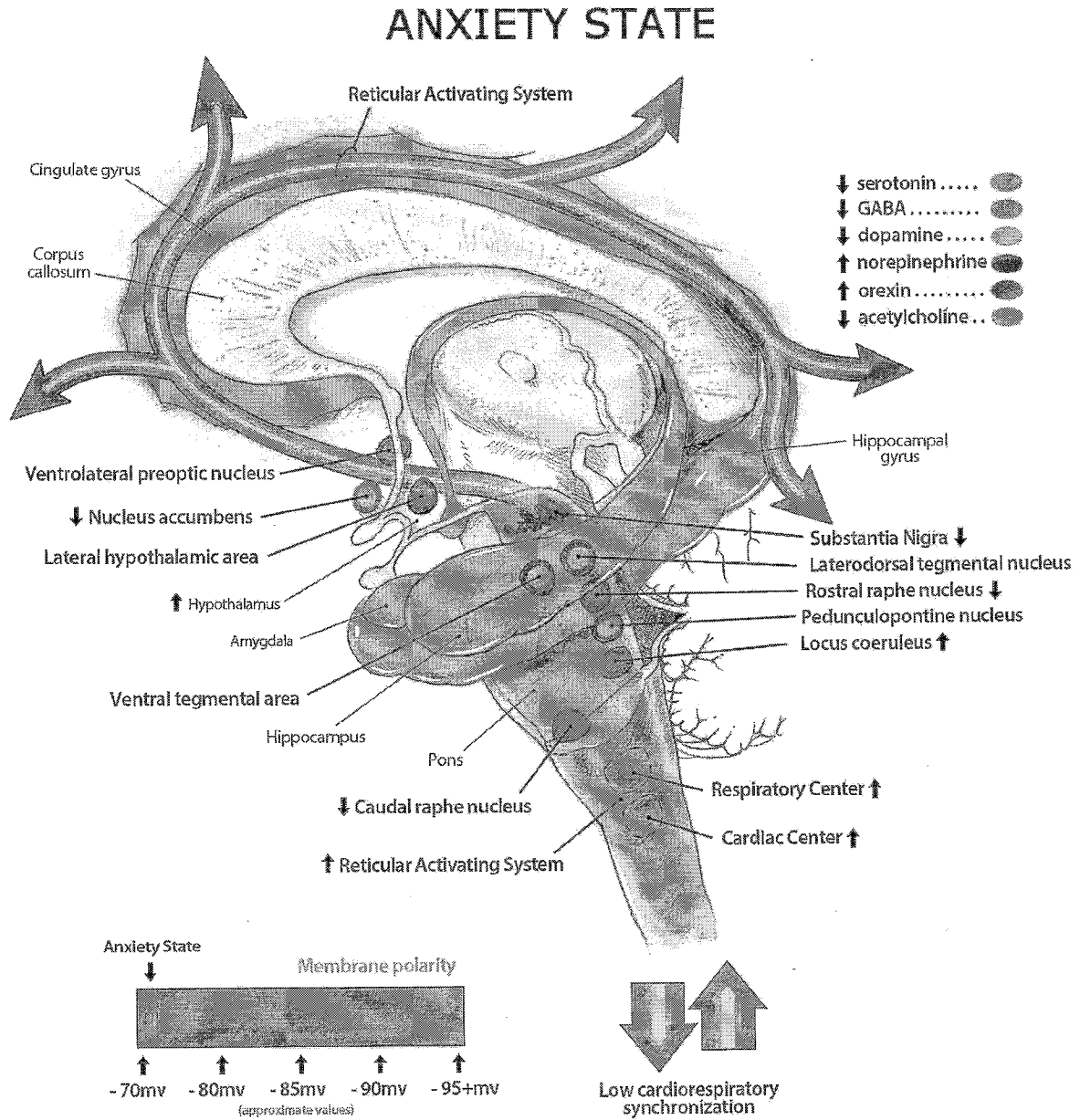
(approximate values)

Fig. 1. *Ascending Reticular Activating System Activity in Normal States. During normal states, there are average levels of cardiorespiratory synchronization and respiratory and heart rates. There is increased orexin activity and all other neurotransmitters are active. The cardiorespiratory and brainstem activity exhibited during awake states likely results in a normal baseline membrane polarity throughout the ARAS, limbic system, and the rest of the brain which can be compared to other consciousness states. (Approximate membrane potential values shown are used to demonstrate the degree of the shift in membrane potentials between states. Actual membrane potential values likely vary amongst different cell types.)*

REM SLEEP

Reticular Activating System

Cingulate gyrus

Corpus callosum

↓ PFC
↑ Limbic cortex
↓ epinephrine
↓ serotonin .....
↓ GABA ....
↓ dopamine .....
↓ norepinephrine
↓ orexin ....
↑ acetylcholine ..

Hippocampal gyrus

Ventrolateral preoptic nucleus
Nucleus accumbens
↑ Lateral hypothalamic area
↑ Hypothalamus
Amygdala
Ventral tegmental area
Hippocampus
Pons
Caudal raphe nucleus
↑ Reticular Activating System

Substantia Nigra
Laterodorsal tegmental nucleus ↑
Rostral raphe nucleus
Pedunculopontine nucleus ↑
Locus coeruleus ↓

Respiratory Center ↑
Cardiac Center ↑

REM Sleep
↓
Membrane polarity

↑   ↑   ↑   ↑   ↑
-70mv   -80mv   -85mv   -90mv   -95+mv
(approximate values)

Low cardiorespiratory synchronization
--Irregular fast respiration

Fig. 2. *Ascending Reticular Activating System Activity in REM Sleep States. The light coloring of the brainstem and ARAS illustrate the relatively depolarized state exhibited during REM sleep. REM sleep states exhibit widespread depolarization but are slightly less depolarized than anxiety states (approximately -80 mV). During REM sleep, levels of cardiorespiratory synchronization are low and respiratory and heart rates are high and more chaotic. During this state there is increased activity in the limbic system but the prefrontal cortex remains deactivated. There are decreased levels of most neurotransmitters; however, there is acetylcholine activation. Low levels of cardiorespiratory synchronization and fast, irregular breathing may underlie the widespread depolarization throughout the ARAS, limbic system, and some other areas of the brain during REM sleep. (Approximate membrane potential values shown are used to demonstrate the degree of the shift in membrane potentials between states. Actual membrane potential values likely vary amongst different cell types.)*
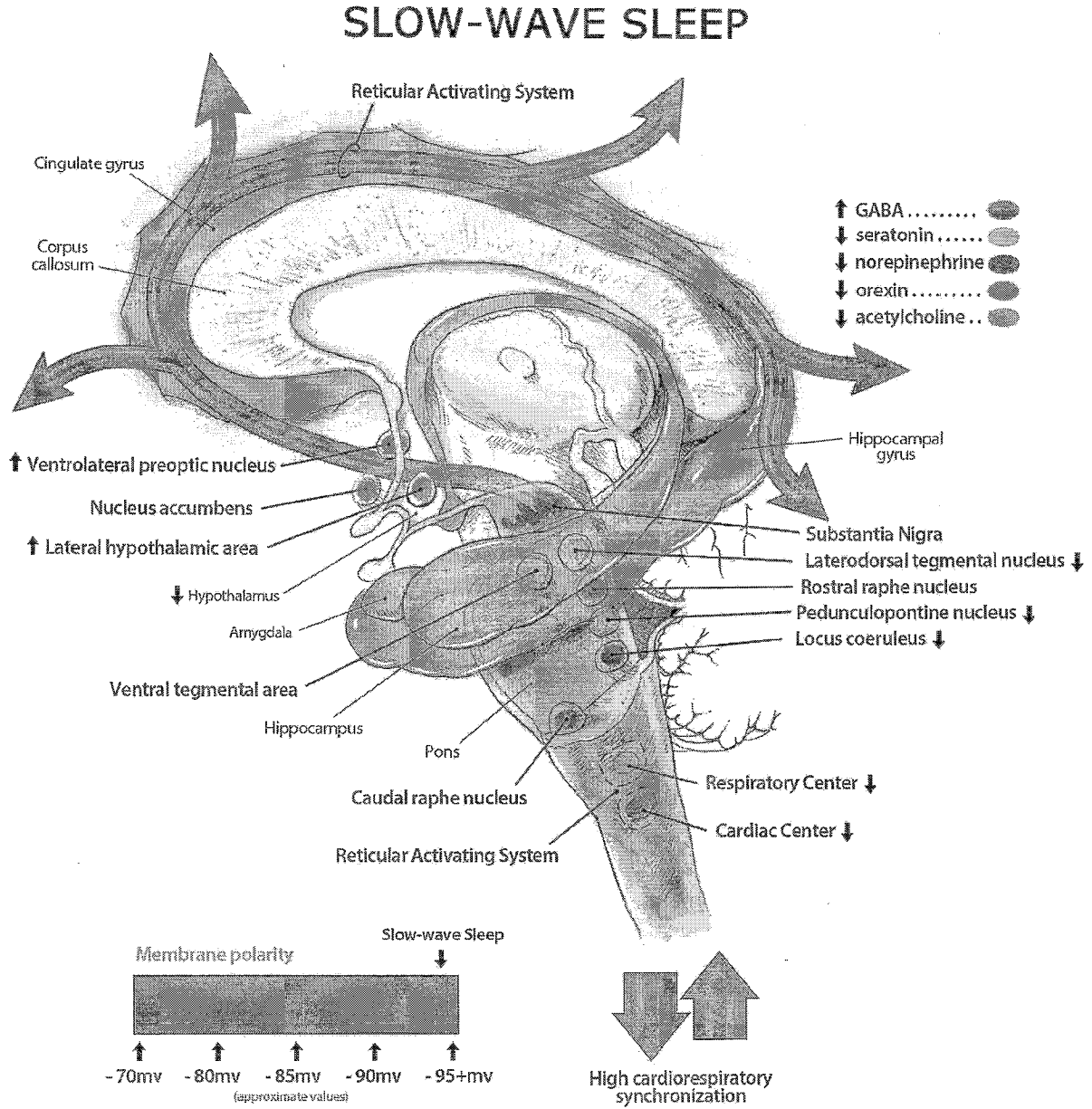
Fig. 3. *Ascending Reticular Activating System Activity in Slow-Wave Sleep. The light coloring of the brainstem and reticular activating system illustrate the widespread hyperpolarization that occurs throughout the brain during slow-wave sleep (at approximately -95 mV). The highest levels of cardiorespiratory synchronization are experienced during slow-wave sleep and respiratory and heart rates are very low during this state. This leads to increased levels of GABA and decreased levels of norepinephrine, orexin, serotonin, and acetylcholine. These changes may underlie the widespread hyperpolarization that occurs throughout the ARAS, limbic system, and cortex during slow-wave sleep. (Approximate membrane potential values shown are used to demonstrate the degree of the shift in membrane potentials between states. Actual membrane potential values likely vary amongst different cell types.)*

Fig. 4. *Ascending Reticular Activating System Activity in Anxiety States. The dark coloring of the brainstem and ascending reticular activating system illustrate the relatively depolarized state exhibited during anxiety states. Anxiety states lie on the farthest end of the membrane polarity spectrum and exhibit the greatest depolarization of all states described (at approximately -70 mV). During anxiety states, levels of cardiorespiratory synchronization are low and respiratory and heart rates are higher and more chaotic. This leads to increased levels of norepinephrine and orexin while levels of serotonin, GABA, dopamine, and acetylcholine decrease. This may result in widespread depolarization throughout the ascending reticular activating system, limbic system, and rest of the brain. (Approximate membrane potential values shown are used to demonstrate the degree of the shift in membrane potentials between states. Actual membrane potential values likely vary amongst different cell types.)*

by high frequency beta-gamma band activity, and are modulated by part of the ARAS called the pedunculopontine nucleus (PPN) (26). Recent studies have shown that cholinergic neurons: i) synchronize with theta oscillations; ii) fire during active waking and paradoxical sleep, modulating cortical activation and plasticity; and iii) cease firing during slow-wave sleep (29). Furthermore, wakefulness and paradoxical sleep both show higher levels of high-frequency activity in areas of the thalamus and cortex than in slow-wave sleep. Wakefulness results from the modulation between monoaminergic and cholinergic cells, with thalamic and cortical neurons becoming hyperpolarized when these cells decrease their firing rates, eventually leading to slow-wave sleep.

However, paradoxical sleep results from an increase in firing rates of cholinergic neurons that release neurotransmitters in the thalamus and cortex, depolarizing them and interrupting slow-wave sleep to an almost awake state. It is possible that this state creates an altered perceptual experience due to a lack of full spatio-temporal binding, and when combined with levels of high-frequency activity in the medial pulvinar nucleus, creates dreams (30). Therefore, we suggest that vagal and cholinergic activity can lead to dreaming during paradoxical sleep because of synchronization between basal forebrain neurons bursting rates and theta oscillations during waking and paradoxical sleep.

GABA and vagal innervation

Several vital organs are innervated by the vagus nerve, which relays sensory, visceral, and physiological information to the central nervous system (31). Vagal nerves are the primary nerves for the parasympathetic system and project into the SA and AV nodes, and the cardiac muscle and the brain receives more vagal afferent information cardiovascular system than from any other organ (32). The cardiac vagal neurons modulate heart rate and production of respiratory sinus arrhythmia, and vagal activity can slow down or stop the heart (due to a decrease in spontaneous depolarization of SA and VA nodes upon release of Ach) (32).

GABA is the primary "inhibitory transmitter in central nervous system," and nearly 20% of the brain's neurons are GABAergic (33). During inspiration, GABAegic neurons in the ventral medulla receive bursts of excitatory neurotransmission (34). When respiration rates become fewer than 8.5 breaths per minute, during sighing, or during deep breaths, low frequency heart rhythm oscillations are generated by vagal activity, suggesting sympathetic activity and perhaps providing an assessment of sympathetic and parasympathetic system balance (32).

Cardiorespiratory synchronization and anxiety

We propose that cardiorespiratory synchronization is on the opposite end of the spectrum, and is the mechanism that underlies the symptoms of anxiety. Our theory suggests that widespread depolarization throughout the brain during REM sleep can also occur during times of stress and states of anxiety, caused by rapid and shallow breathing, along with low levels of cardiorespiratory synchronization. We propose that the rapid, shallow breathing that occurs in both REM (35) and anxiety states may underlie widespread neural depolarization that simultaneously occurs with hypothalamic modulation and neurotransmitter release in the ARAS. This process is homeodynamic, and overall changes occur through: i) feed-forward controls from the hypothalamus and ARAS; and ii) feedback controls from the cardiorespiratory system.

The autonomic nervous system and respiratory activity are interrelated, and are based on membrane potential changes (36). Anxiety states are associated with rapid breathing, while slow, deep breathing (*Pranayama* and meditation) has been shown to attenuate symptoms (36). It has been shown that meditation increases the parasympathetic component of heart rate variability (37), reflecting increased vagal activity. We suggest this indicates that stimulation of the vagus nerve via *Pranayama* and meditation techniques may lead to widespread neural inhibition via modulation of the ARAS, and increasing levels of inhibitory GABA.

We hypothesize that widespread depolarization of the ARAS activates the cholinergic system and the associated limbic and striate cortical activity and

subsequent dream sleep (Fig. 4). Stimulation of the cholinergic neurons of the pons-midbrain junction causes desynchronization of EEG oscillatory activity, and wakefulness while stimulation of the thalamus causes sleep (9). Therefore anxiety states and REM sleep states likely exhibit more widespread neural depolarization, while slow-wave sleep states exhibit more widespread hyperpolarization and inhibition via ARAS modulation and cardiorespiratory oscillatory activity.

CONCLUSION

Previously we proposed that high levels of cardiorespiratory synchronization influence brainstem nuclei and lead to the widespread hyperpolarization that occurs throughout the brain during slow-wave sleep. In this paper, we have further expanded on this model to explain neural activity during other conscious states including REM sleep, normal awake states, and anxiety. Furthermore, more shallow, rapid breathing and unsynchronized cardiorespiratory oscillations may lead to the slight but widespread depolarization that occurs during REM sleep, waking, and anxiety states, with REM states being the most depolarized, followed by anxiety and waking states. Further study of these possible homeodynamic neural membrane potential changes and their role in maintaining states of consciousness and transitions between states would allow for a better understanding of widespread neural processes, as well as how the brain functions as a whole.

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