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Delta Wave Power: An Independent Sleep Phenotype or Epiphenomenon?

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SUPPLEMENT

Electroencephalographic (EEG) δ waves during non-rapid eye movement sleep (NREMS) after sleep deprivation are enhanced. That observation eventually led to the use of EEG δ power as a parameter to model process S in the two-process model of sleep. It works remarkably well as a model parameter because it often co-varies with sleep duration and intensity. Nevertheless there is a large volume of literature indicating that EEG δ power is regulated independently of sleep duration. For example, high amplitude EEG δ waves occur in wakefulness after systemic atropine administration or after hyperventilation in children. Human neonates have periods of sleep with an almost flat EEG. Similarly, elderly people have reduced EEG δ power, yet retain substantial NREMS. Rats provided with a cafeteria diet have excess duration of NREMS but simultaneously decreased EEG δ power for days. Mice challenged with influenza virus have excessive EEG δ power and NREMS. In contrast, if mice lacking TNF receptors are infected, they still sleep more but have reduced EEG δ power. Sleep regulatory substances, e.g., IL1, TNF, and GHRH, directly injected unilaterally onto the cortex induce state-dependent ipsilateral enhancement of EEG δ power without changing duration of organism sleep. IL1 given systemically enhances duration of NREMS but reduces EEG δ power in mice. Benzodiazepines enhance NREMS but inhibit EEG δ power. If duration of NREMS is an indicator of prior sleepiness then simultaneous EEG δ power may or may not be a useful index of sleepiness. Finally, most sleep regulatory substances are cerebral vasodilators and blood flow affects EEG δ power. In conclusion, it seems unlikely that a single EEG measure will be reliable as a marker of sleepiness for all conditions.

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High amplitude electroencephalographic (EEG) δ waves (0.5-4 Hz) characterize mammalian non-rapid eye movement sleep (NREMS). EEG δ wave power is the parameter used to model process S in the two-process model of sleep,[1] although EEG δ waves can correlate with processes seemingly unrelated to sleep, e.g., cerebral atrophy.[2] It is used because in many circumstances it is a good correlate of sleep duration and intensity. For instance, after sleep loss both EEG δ power during NREMS episodes and duration of NREMS are enhanced.[3] Further, as a model parameter, it works remarkably well. Nevertheless there is a large literature indicating that EEG δ power (often called slow wave activity or SWA) is regulated independently of sleep.

Phylogenic and ontogenetic evidence: Poikilotherm EEG δ power is maximum during waking and decreases during sleep (reviewed[4]). In human neonates, there are periods of an almost flat EEG during NREMS.[5] In fact, if neonate rabbits are given muramyl dipeptide, a substance that promotes both NREMS and EEG δ power in adults, only NREMS is enhanced.[6] EEG δ waves are also suppressed with the onset of puberty and into the early 20s.[7,8] Similarly, elderly people often loose their stage 4 NREMS, hence much reduced EEG δ power, yet retain substantial NREMS. Sleep mechanisms in the elderly remain intact to the extent that they are responsive to sleep regulatory substances such as glucocorticoids.[9]

Physiological evidence: Repeated sleep restriction of rats causes an enhanced EEG δ power during the first recovery period; on subsequent days after repeated sleep deprivations, EEG δ power is not enhanced although sleep duration is.[10] In contrast, in humans similar experiments result in enhanced δ power following each sleep deprivation period.[11] If rats are provided a tasty diet, they consume much food and have excessive NREMS during the days they are on the diet. However, during that time their EEG SWA during NREMS is reduced.[12] Anterior hypothalamic lesions are associated with reduced NREMS and reduced EEG SWA; if the animals are permitted to recover, duration of NREMS returns to near normal values while the reductions in EEG SWA are permanent.[13] Similarly, if basal forebrain cholinergic neurons are lesioned using IgG-saporin there is a permanent reduction in EEG SWA without much long-term affect on duration of NREMS.[14] Hyperventilation by human adolescents for a few seconds is associated with high amplitude EEG δ waves without changes in state[15] although in some individuals there is altered responsiveness.[16] Finally, EEG δ power varies in different strains of mice independently of duration of sleep.[17]

Pharmacological evidence: Systemic atropine induces high amplitude EEG slow waves without affecting state.[18,19] Benzodiazepines enhance NREMS but inhibit EEG δ power.[20] Several sleep regulatory substances enhance duration of NREMS and EEG δ power, e.g., tumor necrosis factor (TNF), growth hormone releasing hormone, interleukin-1 (IL1) (reviewed[21]), while others decrease EEG δ power while increasing the duration of NREMS, e.g., nerve growth factor, neurotrophin-4,

obestatin.[22] Some sleep regulatory substances if applied directly to the cortex, e.g., TNF and IL1, induce localized enhancement of EEG δ power[23,24] without changing the duration of organism sleep. Collectively these studies clearly indicate an independent regulation of EEG δ power and NREMS.

Local use-dependent sleep mechanisms: In all of the studies mentioned thus far, state was defined at the whole animal level. It seems likely that if state had been characterized at the cortical column level there may be a closer association between EEG SWA and cortical column state. Indeed, Yoshida et al.[23] and Yasuda et al.[24] interpreted their data as evidence of a more intense local sleep in the cortical columns affected. Further, brain-derived neurotrophic factor (BDNF), if given intracerebroventricularly, enhances duration of NREMS but decreases EEG δ power during NREMS.[25] In contrast, direct application of BDNF to the cortex enhances EEG δ waves.[26] Similarly, TNF enhances EEG δ power if given intracerebroventricularly, or applied directly to the cortex but if given intraperitoneally, it reduces EEG δ power during NREMS.[27]

The regulation of EEG SWA and NREMS duration share some mutual mechanisms; we posit that changes in EEG SWA are tied to the mechanisms responsible for local neuronal network sleep. A sleep-like state of cortical columns is characterized by higher amplitude evoked response potentials (ERP) than are observed during wakefulness.[28] The higher amplitude ERPs likely result from individual neurons going from a hyperpolarized state to a depolarized state, as opposed to going from a state of resting membrane potential to a depolarized state during wakefulness. Sleep regulatory substances, such as TNF, applied directly to cortical columns enhance ERPs suggesting that TNF directly enhances the probability of neuronal assemblies being in the functional sleep state.[29] Further, TNF applied in this localized fashion to the cortex enhances local EEG SWA.[23] The release of sleep regulatory substances, including TNF, IL1, nitric oxide, and adenosine, increases as a result of neuronal activity within neuronal networks (reviewed[30]). Further, neuro- and glio-transmissions are associated with ATP release into the extracellular space. Extracellular ATP in turn induces IL1, TNF and BDNF release from glia. ATP agonists promote sleep while ATP antagonists inhibit sleep.[31] Such processes occur during both sleep and wake because thalamic input to the cortex is not blocked during sleep as previously proposed (thalamic gating). This is evident since evoked response potentials are easily observed during sleep.

We posit that as synchronization of state between columns is achieved, there is a greater effect on EEG δ power. If there is disruption of cortical column state coordination pathways, e.g., thalamic lesions, sleep persists at the local level but with lower δ activity, e.g., stage 1 NREMS.[32] Further, because there is an association of reduced metabolic activity during NREMS, there is reduced blood flow. Cerebral blood flow is inversely correlated with EEG δ power although the direction of the effect is region-dependent.[33] Thus, although EEG δ power can be separated from organism sleep regulation, there is nonetheless, clear links between δ power and sleep due to the metabolic-linked sleep mechanisms at the local neuronal assembly level.

The idea that EEG SWA is dependent on regional neuronal use is consistent with the observation that most sleep regulatory substances are cerebral vasodilators. As mentioned, increased blood flow (to accommodate use-dependent cellular respiration) affects EEG δ power. Peripheral tactile stimulation-induced neural activity leads to increased EEG δ power in subsequent NREMS in the contralateral somatosensory cortex.[34] In contrast, the reduction of afferent neural activity attenuates EEG δ power in subsequent sleep.[35,36] Such effects are likely due to activity-induced changes in sleep regulatory substance release and blood flow.

Sleep function: The separation of duration of NREMS and EEG δ activity has bearing on the mechanisms posited to be responsible for sleep function. Thus, Kavanau's[37] and Tononi's[38] theories propose that intrinsic field potentials play a role in sleep function. For example, Tononi proposes that EEG slow waves cause synaptic downscaling (a term used to describe the mechanisms that counter positive Hebbian plasticity (fire together-wire together). In contrast, in the Krueger/Obal[39] theory the sleep/synaptic stabilization mechanisms are posited to result from activity-dependent induction of substances that alter cell receptivity within the neuronal network they are produced and thereby alter network state, i.e., network input-output relationships shift from being adaptive during waking to being unrelated to the environmental real time events during sleep. For example, TNF production is enhanced in cortical columns if afferent activity is increased and if TNF is applied to a cortical column, it induces a sleep-like state in the column.[29] TNF can cause synaptic up-scaling (via AMPA receptors[40]) or down-scaling (via adenosine A1 receptors[41]). In the Krueger/Obal theory, organism sleep is an emergent property of the synchronization of the sleep-like state of multiple networks.[42] The greater the number of cortical columns with phase-locked sleep-like states the greater EEG SWA. Thus, unlike the Kavanau/Tononi theories, the Krueger/Obal theory does not regard the EEG SWA as a causative agent, but rather as a correlate of the processes responsible for sleep. Further, the Krueger/Obal theory allows for both up-scaling and down-scaling to occur during sleep depending upon whether there was positive or negative synaptic weight change within local circuits during waking.

Conclusions: EEG δ power is regulated independently of sleep duration. It seems unlikely that a single EEG measure can be used as a marker of sleepiness in all conditions. However, used in conjunction with other tests such as the multiple sleep latency test or the maintenance of wakefulness test, EEG δ power remains a useful index of sleepiness or sleep intensity.

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.