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The Pathogenesis of Continuous Spike and Waves during Slow Sleep Syndrome: Short Communication

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Abstract

Continuous spikes during slow wave sleep (CSWS) syndrome is an age-related and self-limited severe epileptic encephalopathy characterized by electrical status epilepticus in sleep (ESES) on electroencephalogram, seizures, and developmental regression. The mechanisms that lead to the development of CSWS syndrome are complex and not clear. Surprisingly, steroids and benzodiazepines offer a good treatment outcome compared to conventional anti-epileptic drugs. Of concern, this condition has a long-term poor prognosis due to the persistence of neuropsychological impairment. Many questions are yet to be answered in this syndrome. Why epileptiform discharges are age-related and self-limiting? Why spike wave discharges occur during non-rapid eye movement sleep and not during the rapid eye movement sleep? Why steroids and benzodiazepines are more efficacious compared to conventional anti-epileptic drugs? In this article, we attempt to discuss these questions by studying the relationship between sleep and hormones, cytokines, and neurotransmitters. Low levels of growth hormone and melatonin, as well as high levels of IL-6 in cases with CSWS syndrome unpin the pathomechanisms. The transient expression of GluN2A subunit, decreased GABAergic inhibition during brain development, declination of non-rapid eye movement sleep in favor of rapid eye movement sleep due to decrease of growth hormone releasing hormone in aging, neuronal loss or decrease in synaptic strength could explain the disappearance of CSWS syndrome in adolescence. Steroids seem to work in CSWS syndrome via: enhancement of GABAA inhibition, suppression of IL-6, and by favoring rapid eye movement sleep which is seizure free.

Keywords: Continuous spikes during slow wave sleep syndrome; Pathomechanisms; Hormones; Cytokines; Neurotransmitters; Steroids

Introduction

Continuous spikes during slow wave sleep (CSWS) syndrome is an age-related and self-limited severe epileptic encephalopathy characterized by electrical status epilepticus in sleep (ESES) on electroencephalogram (EEG), seizures, and developmental regression in, at least, two domains of development [1]. The epileptiform activity occurs in non-rapid eye movement sleep (NREMS) (stage 2), it decreases in slow wave sleep (SWS), and disappear in rapid eye movement sleep (REMS) [2]. This condition has been observed to occur more in males compared to females, usually in the first decade of life [3]. It is estimated to contribute about 0.4–1.3% of all children with epilepsy [4]. The advent of modern imaging methods have revealed malformations of cortical development or vascular insults as a leading causes of CSWS syndrome in approximately 50% of all cases [3-7]. The polymicrogyria, thalamic lesions, hydrocephalus, focal cortical dysplasia and stroke are the leading structural causes. In addition, *GRIN2A*, *SCN2A*, *KCNQ2*, *KCNB1*, *KCNA2* mutations have been reported in cases with CSWS syndrome [8].

The mechanisms that lead to the development of CSWS syndrome are complex and unclear. Importantly, this condition associate with long-term poor prognosis due to the persistence of neuropsychological impairment [6].

Surgery, steroids, and benzodiazepines seem to offer good treatment outcome [9-11]. van den Munckhof B, et al performed a pooled analysis of 575 cases of CSWS syndrome in which antiepileptic drugs were associated with improvement in 49% of patients, benzodiazepines in 68%, steroids in 81% and surgery resulted in improvement in 90% of patients [11]. Their consecutive study revealed steroids to be more effective as compared to non-steroids [12]. It has been demonstrated that prednisone, methyl prednisone, and adrenocorticotrophic hormone can stop ESES and improve neuropsychological functions [12]. Ketogenic diet [13,14] and immunoglobulins are the additional options that have been used with no enough evidence. Overall, immune-modulating drugs such as corticosteroids or intravenous immunoglobulins and ketogenic diet seem to offer better efficacy than conventional antiepileptic drugs [11-16]. The facts that epileptiform discharges are age-related and self-limiting, occurs mostly during NREMS and responds to steroids suggest the role of hormones and/or cytokines in the pathomechanism of CSWS syndrome. The knowledge regarding changes in the brain's hormonal activity and levels of cytokines during normal sleep cycles can be linked to pathophysiology of CSWS syndrome. For instance, Ayça et al. studied the role of melatonin in CSWS syndrome recently whereby cases were found to have low levels of melatonin compared to controls [17]. Iyoda et al. investigated the levels of growth hormone (GH) in two cases diagnosed with CSWS syndrome, in which they found low levels [18].

This article attempts to explain the possible underlying mechanisms of CSWS syndrome. It describes the relationship between sleep and hormones, cytokines and neurotransmitters in relation with CSWS syndrome. In addition, it gives an insight about the mechanisms of steroids and benzodiazepines in treatment of CSWS syndrome. A better understanding of mechanisms provides additional therapeutic targets that can improve the outcome of seizures, ESES pattern, and cognitive development. In addition, this review identifies the existing gaps for future research exploration. Other reviews tempted to summarize the relationship between epilepsy in general and sleep pattern, hormones, cytokines and anti-epileptic drugs. However, none tried to explore such relationship in CSWS syndrome, and specifically the mechanisms of steroids.

Sleep Regulation and Epilepsy

Sleep is regulated by interaction between hormones, cytokines and neurotransmitters. These include hormones such as GH, cortisol, and melatonin, cytokines such as interleukin (IL)-1, IL-12, IL-6, tumor necrosis factor (TNF)-α and of Th1 cytokines like interferon (IFN)-γ, and neurotransmitters such as GABA and glutamate. They all work together to regulate sleep, and dysfunction of any can lead to epileptic activity.

Sleep and neurotransmitters and epilepsy

Studies on animal models revealed that the expression of many neurotransmitter receptors including GABAA as well as ion channels such as voltage dependent potassium and calcium channels are regulated by circadian rhythm [19,20].

GABA system and sleep and CSWS syndrome: There are several populations of GABAergic neurons that control sleep [21], some enhance sleep while others promote wakefulness. Reticular-thalamic GABAergic neurons play role in inducing sleep and maintain it, together with generation of spindles and delta activity [21]. However, the reticular-thalamic neurons can be inhibited by GABAergic neurons found in lateral hypothalamic area, and by other inhibitory inputs from serotoninergic, cholinergic, noradrenergic and histaminergic system to promote wakefulness [21]. GABAA and GABAB receptors have a significant role in regulation of sleep in normal physiology and pathological conditions respectively. GABAA receptors are composed of five subunits [22]. The α5 and δ are highly expressed in hippocampus and thalamus thus regulate GABAergic tonic inhibition [23,24]. In addition, the α1 and α3 are predominant in the thalamo-cortical network [21]. Recent study indicated reduced expression of α5 and δ subunit for the sleep deprived mice [25].

The GABAA receptor complex consists of a chloride ionophore which can bind to GABA, steroid, benzodiazepine, and barbiturate [26]. GABAergic transmission through the GABAA receptors has several effects on sleep; it increases spindles (stage 2 of NREMS) and decreases delta activity (stage 3 of NREMS), it shortens sleep onset latency and increases sleep continuity, and it inhibit REMS [21]. The highest GABAA release from the cortex correlate with cortical synchrony of natural sleep [27], so it favors NREMS [28]. Several anti-epileptic drugs work through GABAA receptor to enhance sleep. For instance, benzodiazepine which increases NREMS, decreases wakefulness and, suppresses REMS in EEG [28-30]. Steroids also enhance sleep by binding to GABAA receptors [26]. Consequently, we hypothesize that one of the mechanisms of steroids in CSWS syndrome is attributed by its action on GABAA receptor.

The GABAB is coupled with calcium and potassium

ion channels and has low affinity to GABA as compared to GABAA [31]. GABAB favors EEG desynchronization [27]. It has been shown that GABAB receptor-mediated inhibitory postsynaptic potentials could be responsible for ESES [3]. In summary, GABAA neurotransmission is crucial for physiologic oscillation while GABAB neurotransmission enhance pathological oscillations. Reduced GABAA inhibition can be among the underlying mechanisms for CSWS syndrome. NREMS is crucial for memory consolidation, therefore, the pathological oscillations during this particular time can explain long term poor cognition observed in affected children.

Glutamatergic system and sleep and CSWS syndrome

Glutamatergic reticular neurons have a critical role in regulating REMS [32]. Glutamate enhances REMS and is responsible for cortical desynchronization [27]. Rats treated with monosodium glutamate display decrease in NREMS similar to rats with GHRH receptor deficiency [33]. The interaction of brain stem GABAergic, aminergic, and cholinergic neurons can control the activity of glutamatergic reticular neurons [32]. Importantly, the cyclical interaction between glutaminergic excitatory thalamocortical neurons, and inhibitory GABAergic reticular thalamic neurons is the basis for production of spindle waves during NREMS [3]. Thus, we propose the excessive glutaminergic excitation to be among the underlying mechanisms of occurrence of epileptiform discharge during NREMS as seen in CSWS syndrome. 36.6% of the cases with *GRIN2A* mutations have CSWS syndrome [34]. *GRIN2A* encodes a subunit of glutamate-gated N-methyl-d-aspartate (NMDA) receptors which is expressed postnatally. Salmi et al. proposed Grin2a KO mice as animal model for CSWS syndrome of which showed a similar phenotype as in human being [35]. Interestingly, amantadine which is weak NMDA receptor antagonist, has been reported as a good treatment option for CSWS syndrome, and it seems to be a promising first choice treatment [36]. Further studies will reveal more drugs targeting this receptor of which will minimize the utilization of steroids that are accompanied by many side effects. Several cases diagnosed with CSWS syndrome and yet discovered to have gain-of-function mutations in *SCN2A* [37], *KCNB1* [8], and *KCNA2* [38] have been reported suggesting NMDA-pathy can result to CSWS syndrome. Consequently, in addition to NMDAR antagonist, sodium and potassium channels are promising targets for drugs development.

Hormones and sleep and CSWS syndrome

Studies have shown the role of hormones in sleep. Some enhance sleep while others inhibit sleep. These hormones work through either GABAergic or glutamatergic neurons to enhance NREMS or REMS respectively. Some of those hormones have been linked with epilepsy thus act as promising drug targets. Studies have shown that the suprachiasmatic nucleus regulates the circadian oscillations that most hormones display including GH, cortisol, ghrelin, galanin and neuropeptide Y which commonly act through GABAA receptor [39]. The reciprocal interaction of the hypothalamo-pituitary-somatotrophic (HPS) and the hypothalamo-pituitary-adrenocortical (HPA) systems hormones, particularly GH-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) plays a critical role in sleep regulation. The GHRH surge during the NREMS while the CRH is high during the REMS [39]. GH levels are high during the first half of the night while adrenocorticotrophic hormone (ACTH) and cortisol release is low, and opposite happens during the second half of the night; ACTH and cortisol surge, whereas GH release is low. In total, the peptides and hormones of the HPA axis inhibit sleep, whereas activation of the HPS axis facilitate sleep [40]. Prolonged activation of the HPA axis leads to suppression of GH release, most likely through modulating GHRH secretion [41].

Growth hormone releasing hormone and sleep and CSWS syndrome: GH and GHRH promote sleep as discussed before. The synchronous activity of GHRH neurons in the hypothalamus reasons the mechanisms underlying the relationship between SWS and GH secretion [42]. GHRH specifically promotes NREMS in mice, rats, rabbits as well as humans [43]. Administrations of GHRH enhance NREMS duration and intensity through activation of ventrolateral preoptic area and median preoptic nucleus (MnPO) neurons [43,44]. And injection of GH increases REMS by affecting dorsal raphe and locus coeruleus neurons, which have the GH receptors [45].

GH acts through GABAA receptors to enhance the inhibitory tone in GABAergic neurons [39,46] thus, suggests its anti-epileptic activity. GH deficiency has been shown to induce seizures [47]. Tang et al. demonstrated the existing interactions between GHRH and GABAA receptors in both human being and animal model of epilepsy [46]. Iyoda et al. investigated the levels of GH in two cases diagnosed with CSWS syndrome [18], whereby they found low serum levels of GH during NREMS when there was maximum epileptic discharges, on contrary, the high levels were found at the beginning of REMS. Their study suggested that the GH deficiency associate with CSWS syndrome, despite of the small sample size. Future research might delineate the role of this hormone in CSWS syndrome, and it could stand as a drug target.

Cortisol hormone and sleep and CSWS syndrome: The HPA system is responsible for production of cortisol hormone. This system is activated by acute physical and psychological stress. Production of cortisol hormone begins with the release of corticotrophin releasing hormone (CRH) from the hypothalamus. Cortisol has a widely distributed receptors in the body of which influence the endocrine and immune systems [48]. This hormone plays a major role in the onset of wakefulness [49]. High cortisol hormone has multiple transition activities during sleep: waking to sleeping around two hours after sleep onset, NREMS to REMS after 6 hours of sleep, sleep stage 1 or 2 to SWS around 2, 4 or 6 hours later and SWS to sleep stage 1 or 2 about 2 hours later [39]. Cortisol is very important for initiation and maintenance of REMS [50]. Nevertheless, excessive cortisol associate with decrease of SWS, disturbances of sleep continuity and REMS disinhibition [51]. Studies have shown that injection of CRH hormone in both humans and animals results to decrease of SWS during NREMS in contrast of increase of sleep latency and REMS [39]. Acute CRH enhance wakefulness and suppresses NREMS, via hypocretin and locus coeruleus activation, whereas chronic use of CRH increases REM sleep through activation of laterodorsal tegmental area/pendunculopontine tegmentum [45]. And acute administration of cortisol and glucocorticoids decreases REMS while chronic administration of methylprednisolone induces REMS [52].

Cortisol has multiple receptors in the brain. It can acts through GABAA receptors to prevent epilepsy through the enhancement of inhibitory tone in GABAergic neurons in reticular system [39]. Nevertheless, high levels of cortisol during stress can induce seizures [53]. We hypothesize that high cortisol-induced seizures might results from low levels of GHRH which associate with epilepsy as discussed before. Low GHRH is due to the reciprocal interaction between HPS and the HPA systems as mentioned before [39]. Since steroids can act through GABAA receptors, we hypothesize its anti-seizure effect in CSWS syndrome is attributed by its actions on this particular receptor. In addition, since cortisol has anti-inflammatory effect, we hypothesize that it inhibit seizure through its anti-inflammatory effect. Two cases-control studies based on cases with CSWS syndrome revealed high inter-ictal levels of IL-6 [54,55], of which were decreased upon the usage of steroids. However, these theories need more confirmatory studies.

Melatonin hormone and sleep and CSWS syndrome: Melatonin is important as it provides sleep signal [56]. Studies have shown that melatonin enhances REMS [57-59]. Lower levels of melatonin have been found in children with drug resistant epilepsy compared with healthy controls [60]. Ayça et al. studied the role of melatonin in CSWS syndrome recently whereby cases were found to have low levels of melatonin compared to controls [17]. Melatonin has anti-epileptic activity, and it works through NMDA receptor [61]. As a result, melatonin stands as a promising treatment option for the cases with CSWS syndrome.

Neurosteroids and sleep and CSWS syndrome: Neurosteroids belong to the group of steroids that are synthesized in the brain. These include alopregnanolone (ALO), pregnanolona (PNA) and pregnenolone (PNE) [62]. PNA and ALO act through GABAA receptors by increasing the conductance of chloride channels thus increasing SWS while PNE is an antagonist of the GABA-A receptor, as a results it acts through cholinergic system to increase REM [62]. Thus PNA and ALO analogues can help to minimize seizures.

Cytokines and Sleep and CSWS Syndrome

The close relationship between sleep and cytokines has been proposed recently. Some of the cytokines favors NREMS while others favors REMS. These cytokines work through GABAergic or glutamatergic neurons. Consequently, some enhance GABAergic inhibitory tone while others favors glutamatergic excitation thus producing seizures. It has been shown that the high levels of cytokines are found during SWS in NREMS which is characterized by high GH and prolactin as well as low cortisol and catecholamine concentrations [63]. Those cytokines include pro-inflammatory ones like interleukin (IL)-1, IL-12, IL-6, tumor necrosis factor (TNF)-α and of Th1 cytokines like interferon (IFN)-γ [63]. Cortisol and catecholamines suppress the immune functions in an anti-inflammatory manner [63]. The inflammatory process (endocrine and immune rhythm) peak during the NREMS while the REMS is pronounced with anti-inflammatory activity [63].

Some of the cytokines influence the level of certain hormones which control sleep. For instance, Obal et al. [43], indicated that IL1 enhances GHRH release, synthesis of GHRHergic neurons and up-regulates GHRH receptors which in turn increases NREMS. They further indicated that injection of IL1 into the locus coeruleus or dorsal raphe enhance NREMS, on contrary, injection of IL1 into the hypothalamic paraventricular nucleus enhances REMS through activation of the CRH. GABAergic neurons contains receptors for both GHRH and IL1 and the stimulation of either receptor enhances sleep [64]. The release of IL1 is regulated negatively by soluble IL1 receptors, the IL1 RA, CRH, anti-inflammatory cytokines (IL4, 10, and 13, and TNF) of which they inhibit sleep [43]. Importantly, IL1 interacts with many other neurotransmitter systems; serotonin, and acetylcholine to regulate sleep [43]. IL1 beta and TNF induce excess NREMS in mice, rats, rabbits,

monkeys, and cats and human beings [43]. They promote NREMS by inhibiting dorsal raphe or locus coeruleus neurons, which activate preoptic sleep-active neurons respectively, and stimulate the release of sleep-inducing substances such as prostaglandin D2, adenosine, and GHRH [45].

IL-6 is among pro-inflammatory cytokine which promote SWS in NREMS [63]. However, it can induce seizures through glutamatergic receptors [65,66]. Two studies revealed high inter-ictal levels of IL-6 for the cases with CSWS syndrome [54,55], of which decreased upon usage of steroids. We hypothesize that one of the mechanism of occurrence of epileptic discharge in this condition is attributed by the action of IL-6 on glutamatergic neurons as proposed before by other studies [65,66]. And another possible mechanism is through the activation of HPA axis, which results in high levels of cortisol, and low levels of GHRH which can produce seizures even in CSWS syndrome. IL-6 activates the HPA axis and is regulated partly by glucocorticoids and catecholamines [40]. Consequently, steroids suppress the levels of IL-6 and thus minimize seizures in CSWS syndrome. This is alternative mechanism, in addition to its direct inhibitory activity on GABAA receptors. More research will unveil the role of IL-6 in the pathomechnism of CSWS syndrome.

CSWS Syndrome and Age-relation, Self-limitation and Sex Predominance

Both hormones and dynamic expression of receptors during brain development can explain the age-related, self-limiting and sex predominance phenomena in CSWS syndrome. Cases with CSWS syndrome present with seizures from the age of 3-5 years [3]. Recent study demonstrated that 36.6% of the cases with GRIN2A mutations have CSWS syndrome [34]. The same study showed that GluN2A expression increases during the second postnatal week in mice, and seizures were observed on third postnatal week which is equivalent to 2-3 years of age in humans [34]. Interestingly, the brain alteration accompanied with increased GluN2A expression were transient as they disappeared at post-natal day 30 which is equivalent to 12 years in human [34]. As a result, GRIN2A mutations can explain why CSWS syndrome is age related and self-limiting. Reduced GABAergic inhibition in immature brain can explain the age-related phenomena of CSWS syndrome [3].

High levels of GHRH is associated with high amounts of NREMS which favors epileptic discharges compared to REMS, whereas reduced levels of GHRH for instance during ageing results into declination of NREMS [67]. Declination of NREMS during puberty can also partly be explained by neuronal loss or decrease in synaptic strength [68]. Thus, we hypothesize the transient expression of GluN2A subunit, decreased GABAergic inhibition during brain development, declination of NREMS in favor of REMS due to decrease of GHRH in aging, neuronal loss or decrease in synaptic strength can explain the disappearance of CSWS syndrome in adolescence. Surprisingly, despite of age, sex has been pointed out as another determinant of the effect of GHRH on NREMS [39], of which can partly explain why males are more affected with this condition compared to females.

Treatments of CSWS Syndrome

Several antiepileptic drugs works by favoring REMS and reduce NREMS [69]. They target neurotransmission by acting on GABA and glutamate receptors or the process of release, inactivation, and reuptake of excitatory or inhibitory neurotransmitters, or channels (Na^+, Ca^{2+}, and Cl^-). Steroids and benzodiazepines seem to be the mainstay treatment for CSWS syndrome patients [11,12]. They can both bind to GABAA receptor and facilitate inhibition of thalamic relay cells [26] and thus, prevent occurrence of epileptiform discharges as those seen in CSWS syndrome. Noteworthy, the reciprocal interaction of HPS and HPA systems hormones, particularly GHRH and CRH in regulation of sleep discussed. The GHRH level is high during NREMS while CRH is high during REMS [39]. Hence, the corticosteroids in this syndrome seem to increase the REMS and decrease the NREMS through the reciprocal interaction of HPS and HPA systems. Methylprednisolone has been shown to decrease REMS latency, increases REMS in patients with multiple sclerosis [70]. EEG monitoring of the patients with CSWS syndrome and yet on steroids will reveal changes on sleep pattern.

Benzodiazepines works by binding to GABA receptor and promote inhibition and hence results to increase stage 2 sleep and sleep spindle frequency as well as decrease of SWS and sleep latency [56]. Ethosuximide reduces SWS and increases REMS and stage 1 sleep [56]. Clobazam decreases sleep latency, stage 1 sleep, SWS, and wake after sleep onset and increases stage 2 sleep [56]. Sodium valproate and phenytoin as well as ketogenic diet decrease SWS and favor REMS [56, 69]. Amantadine is a weak NMDA receptor antagonist, and it has been reported as good treatment option for CSWS syndrome [36].

Conclusion

The interactions between neurotransmitters, hormones, and cytokines can explain the occurrence of CSWS syndrome. The expression of many neurotransmitter receptors including GABAA as well as ion channels such as voltage dependent potassium and calcium channels, hormones such as GHRH, cortisol, melatonin, and cytokines such as IL-6, IL1 beta and TNF are regulated by circadian rhythm. Some of the hormones and cytokines have direct effect on GABAergic or glutamatergic system

thus can facilitate occurrence of seizures. Therefore, the dysregulation of any of them directly or indirectly can produce epileptic discharges. The transient expression of GluN2A subunit, decreased GABAergic inhibition during brain development, declination of NREMS in favor of REMS due to decrease of GHRH in aging, neuronal loss or decrease in synaptic strength could explain the disappearance of CSWS syndrome in adolescence. Steroids seem to work in CSWS syndrome via: enhancement of GABAA inhibition, suppression of IL-6, and by favoring REMS which is seizure free. Benzodiazepines work by enhancing the GABAA inhibition as well as by favoring REMS. The fact that steroids works through many ways reason out why they are more efficacious than benzodiazepines and other anti-epileptic drugs. In addition to GABAergic system, GHRH, melatonin, IL-6 and glutamatergic system are areas which need more research into relation with CSWS syndrome. They stand as promising drug targets of which might minimize the usage of steroids which associate with many side effects.

Contributors

Miriam Kessi, Yulin Tang, and Chen Chen reviewed the paper and drafted the manuscript. Lifen Yang, Jing Peng and Fei Yin gave out the idea and supervised each step involved in the preparation of the manuscript. All co-authors have read and agreed to the content of the manuscript.

Conflict of Interest

None of the authors have any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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