Classification of three forms of regulations on emotional/autonomic nervous system by slow wave sleep

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ABSTRACT
Clinically, it has long been shown that the slow wave sleep (SWS) may adjust the emotional balance against depression. In this article, it is classified three types of regulations on emotional/autonomic nervous system by SWS. (1) In the initial stage of SWS, it is the lower ratio of respiratory inspiration/expiration that delivers the signal of tiredness, as the result of decrease in excitation from inspiratory motoneurons more than that from expiration in SWS. It is pointed out that this characteristic decrease in ratio of inspiration/expiration begins to influence the sensory posterior palate and maxillary sinuses by the corresponding air pressures, regulating the vascular circulations from mouth to eye early in SWS, accompanying the bodily relaxation in SWS, whereas without requiring the participation of forebrain slow wave. (2) After the delta slow wave increases in SWS, it favors long term depressions (LTD) to balance the increase in neural activities by long term potentiations (LTP) acquired in waking, adjusting the emotional balance to normal, especially against depression. (3) It is pointed out that the noradrenaline (NA) in locus coeruleus (LC) can antagonize the cholinergic (ACh) hyperactivity and depression, implicating that the noradrenergic LC might be regulated in SWS by neuronal plasticity in the limbic structures including the hippocampus, hypothalamus and epithalamus to orient the forebrain against noise and depression. It is expected that this classification helps clarify the complex regulations on emotional/autonomic nervous system by SWS. It is delighted if new discoveries could supplement this classification.

Keywords: Slow wave sleep, depression, ratio of inspiration/expiration, delta slow wave, long term depression, noradrenaline

INTRODUCTION

There are two different forms of sleep, the slow wave sleep (SWS) and the rapid eye movement (REM) sleep. SWS is the period of sleep occurring on the early stage of sleep and producing slow waves with a range of frequency from 0.5Hz to 4Hz plus peak-to-peak amplitude greater than 75µV.

The role of SWS in emotional regulation against depression was postulated by Cai together with memory processing (Cai, 1991, 1995, 2016), while by Kupfer and Reynolds together with aging and dementia (Kupfer & Reynolds, 1989). Despite the difference in theoretical account, clinical observations and behavioral experiments supporting the role of SWS in emotional regulation have accumulated for a long time in many aspects. On the one hand, shorter duration of SWS has been reported to be frequently associated with depression for decades of years up to now (Baglioni et al., 2014; Medina, Lechuga, Escandón & Moctezuma, 2014; Mendlewicz & Kerkhofs, 1991). Whereas, it has also been shown that sleep deprivation frequently results in negative mood disturbances characterized as depression, anxiety, frustration, tension and so on in healthy adults (Kahn-
Especially, it was reported that selective deprivation of stage 4 SWS in humans produced a depressive or hypochondriacal state (Agnew, Webb & Williams, 1967). Obviously, impairment of SWS would cause depression. On the other hand, it has been successfully adopted for decades of years to help ameliorate depression by increasing the duration of SWS in early sleep with phase advance of sleep (Bunney & Bunney, 2012; Wehr, Wirz-Justice, Goodwin, Duncan & Gillin, 1979). In consistency, it was also reported that the high delta sleep ratio might help prevent the early recurrence of unipolar affective disorder (Kupfer, Frank, McEachran & Grochocinski, 1990). Obviously, normalization of SWS could help ameliorate or prevent depression.

Even though the abundance of clinical and experimental demonstrations for SWS on regulation of emotional balance especially against depression has been accumulated for decades of years, there has not been neurobiological considerations on how SWS regulates the emotional/autonomic nervous system in mechanisms. In this article, it is reviewed the relevant achievements and classified three types of regulative mechanisms by which SWS regulates the emotional/autonomic nervous system.

The Decrease in Ratio of Inspiration / Expiration in SWS

Before SWS to occur, the body turns to rest and relaxed, while the eye closes, which is the common knowledge for SWS induction. Whereas, besides these relaxations, it is necessary to pay special attention to respiratory changes for the induction of SWS, because of yawning.

Yawning is the correlative behavior of sleep in humans, frequently occurs before and after sleep. Yawning consists of an involuntary sequence of mouth opening, deep inspiration, brief apnea, and slow powerful expiration (Cai, 2018a; Corey, Shoup-Knox, Gordis & Gallup, 2012; Guggisberg, Mathis, Schnider & Hess, 2010), driven by the movements of mouth and respiration. In contrary to the drastic and powerful respiratory movements (Cai, 2018a; Corey, Shoup-Knox, Gordis & Gallup, 2012; Guggisberg, Mathis, Schnider & Hess, 2010), a little increase in heart rate and eye muscle tension has been reported during or immediately following yawning (Corey, Shoup-Knox, Gordis & Gallup, 2012).

SWS manifests decrease in blood pressure (Silvani & Dampney, 2013) and moderate but complex regulation of heart rate (Burgess, Holmes & Dawson, 2001). On respiration, it has been demonstrated in electrophysiology that the sleep-wake state can modulate the inspiratory motoneurons of respiration, while the tonic expiratory units are largely unaffected by the sleep-wake state (Horner, 2009; Trinder, Jordan & Nicholas, 2014). Especially, the pharyngeal muscle, genioglossus muscle and intercostal muscle decrease much in sleep (Horner, 2009; Trinder, Jordan & Nicholas, 2014), while the diaphragm muscle remains unchanged across sleep-wake cycle (Horner, 2009). Grossly in effects, the ratio of inspiration/expiration decreases in SWS. Besides, it has also been demonstrated that the obstructive sleep apnea is mainly related to expiratory breath in assaying (Bikov, Hull & Kunos, 2016; Oliveira, et al., 2011). Both of these electrophysiological and pathological observations demonstrate that the ratio of inspiratory/expiratory activity decreases in SWS (Cai, 2018a).

The air flow of inspiration/expiration in SWS can certainly press against the sensory posterior palate and maxillary sinuses, which can in turn signal and elicit neurovascular regulation in head (Cai, 2018a). It has been reported that the palate may cause snoring and obstructive sleep apnea (MacLean, Fitzsimons, Fitzgerald & Mbbs, 2017), while the maxillary expansion can treat the obstructive sleep apnea (Vale et al., 2017), demonstrating the presence of pressure from the inspiratory/expiratory air flow in SWS onto the posterior palate and maxillary sinuses (Cai, 2018a).

In the induction or initiation of SWS, this decrease in ratio of inspiratory/expiratory pressure of air against the sensory posterior palate and maxillary sinuses can be relayed in head up to the vascular circulation in eye (Cai, 2018a), necessary for eye closure in SWS. For evidence, on the one hand, it has been demonstrated that the
 closure or tiredness of eyelids manifests the extent of drowsiness and sleepiness (Alvaro, Jackson, Berlowitz, Swann & Howard, 2016; Filtness et al., 2014). On the other hand, the inspiration/expiration in SWS can really regulate the vascular circulation in eyes, as it has been demonstrated that many vascular diseases of eyes are associated with the obstructive sleep apnea, such as the glaucoma, retinal vein occlusion, nonarteritic anterior ischemic optic neuropathy, central serous chorioretinopathy, floppy eyelid syndrome and so on (Huon, Liu, Camacho & Guilleminault, 2016; Skorin & Knutson, 2016).

Obviously, from decrease in ratio of inspiration/expiration to regulation of vascular circulation in eye (Cai, 2018a; Huon, Liu, Camacho & Guilleminault, 2016; Skorin & Knutson, 2016), it constitutes one form of regulation on the autonomic nervous system by SWS. This form of regulation on the autonomic nervous system does not require the participation of slow wave in the forebrain in SWS. Accordingly, also in light of yawning before sleep, this form of regulation on the autonomic nervous system begins early at the initial stage or even inductive stage of SWS, accompanying the bodily relaxation.

It is interesting to note that the neuronal plasticity may as well occur in the autonomic nervous system. It has been demonstrated that the long term potentiations (LTP) occur in the mammalian autonomic ganglia (Alkadhi, Alzoubi & Aleisa, 2005; Cifuentes, Arias & Morales, 2013) and vagus nerve (García Ramos et al., 1994), while the long term depression (LTD) in vagus nerve (García Ramos et al., 1994). Because the respiratory regulation of autonomic nervous system by SWS does not require the participation of slow wave in the forebrain, it deserves more investigations on whether these various neuronal plasticities in autonomic nervous system also occur and participate in the autonomic regulation in SWS.

The LTDs in SWS to Balance the Acquired LTPs and Adjust the Emotional Balance

Delta waves have the frequency between 0.5 and 4 Hz (Amzica & Steriade, 1998). After the delta slow wave increases in SWS, the forebrain changes in state and exerts different influence on the neuronal plasticity and emotional regulation.

Learning and memory occurs as LTP at the neuronal level in waking (Moser, 2014). Because of potentiation of synaptic transmission in long term (Moser, 2014), the accumulation of LTPs in the emotional limbic structures such as hippocampus (Moser, 2014) would shift the balance of emotion (Cai, 1991, 1995).

On the other hand, in SWS the slow delta wave is present in both cortex and hippocampus (Mitra et al., 2016). It was early demonstrated that SWS was a state unfavorable to the formation of LTP in hippocampus grossly (Bramham & Srebro, 1989; Leonard, McNaughton & Barnes, 1987), therefore also unfavorable to further consolidate the hippocampal LTPs acquired in waking. Recently, it was reported that the sleep pressure and slow wave mimicking the endogenous oscillations of SWS favored the formation of LTD in hippocampus (Yang, Zhang, Wang, Ruan & Chen, 2012a, 2012b). In this regard, SWS favors the neuronal plasticity as LTD rather than LTP.

The contrast of LTP formation in hippocampus during waking (Moser, 2014) to LTD formation there during SWS (Yang, Zhang, Wang, Ruan & Chen, 2012a, 2012b) implicates that their influences are opposite in effects on the overall hippocampal activities. The acquired hippocampal LTPs during waking (Moser, 2014) would potentiate the overall hippocampal activities, whereas the formed LTD in the slow wave of SWS (Yang, Zhang, Wang, Ruan & Chen, 2012a, 2012b) would decrease the overall hippocampal activities. Because the environmental events are irregular, the acquired hippocampal LTPs in waking (Moser, 2014) would tend to disorganize the emotional balance following random accumulation (Cai, 1991, 1995). In contrast, SWS reversely favors the formation of LTD to adjust the emotional balance back to normal (Cai, 1991, 1995, 2016).

It is necessary to note that in the cortex there are spindles at the frequencies from 12 to 14 Hz occurring in SWS (Himanen, Virkkala, Huhtala & Hasan, 2002) in addition to delta slow wave at frequencies from 0.5 to 4 Hz (Amzica & Steriade, 1998). It was demonstrated that
LTP could form from action potential associating with spindle spike at the background of delta slow wave in somatosensory cortex (Czarnecki, Birtoli & Ulrich, 2007; Rosanova & Ulrich, 2005), but LTD form from spindle spike alone (Czarnecki, Birtoli & Ulrich, 2007; Rosanova & Ulrich, 2005). Recently, it was also demonstrated that the slow wave mimicking the SWS alone resulted in LTD in cortex (González-Rueda, Pedrosa, Feord, Clopath & Paulsen, 2018), but together with postsynaptic spiking it could not cause LTD (González-Rueda, Pedrosa, Feord, Clopath & Paulsen, 2018). These complex cortical manifestations of LTP and LTD in SWS lie beyond the limbic emotional regulations, which requires further investigation.

It has been shown that the SWS might help retention of declarative memory in humans (Inostroza & Born, 2013; Rasch & Born, 2013). Some authors have argued that the increase in ratio of synaptic signal/noise during SWS, favored by the contrast of LTP to LTD, could account for the retention of declarative memory (Tononi & Cirelli, 2003, 2014). Such explanation requires some time duration for SWS to accomplish the task. However, it was reported that, after a midday nap or after relaxation-hypnosis, the declarative memory was also improved as compared to that after wakefulness (Schichl, Ziberi, Lahl & Pietrowsky, 2011), demonstrating the time duration of SWS not required for accomplishing the task. In this regard, a nonspecific state of reduced mental noise may account for this effect of sleep on declarative memory, such as the decrease of cholinergic activity before and during SWS (Gais & Born, 2004).

The Emotional Regulation via Locus Coeruleus in SWS

Ripples are another kind of oscillations in hippocampus occurring during SWS, with frequencies ranging from 140 to 220 Hz (Sullivan et al., 2011). There have been a lot of evidences indicating that the hippocampal ripples couple to the cortical spindles for memory processing in SWS (Clemens et al., 2007; Siapas & Wilson, 1998). Besides, it was even reported that it was able to induce LTP at synapses between hippocampal CA3 and CA1 cells but only if accompanied by synaptic activity of sharp-wave ripples (Sadowski, Jones & Mellor, 2016). Obviously, the memory processing in hippocampus via ripples would regulate the emotional balance in different manners than the LTD forming there during SWS.

Recently, it was newly reported that the ripple/spindle coupling was affected by stimulation of Locus coeruleus (LC) rich in noradrenaline (NA) (Novitskaya, Sara, Logothetis & Eschenko, 2016). Low-frequency (20 Hz) stimulation had no effect, while higher-frequency (100 Hz) trains transiently blocked the ripples, spindles, and the generation of ripple-associated cortical spindles, causing a reference memory deficit (Novitskaya, Sara, Logothetis & Eschenko, 2016). Accordingly, the NA of LC affected the forebrain ripples, spindles, and their coupling.

The forebrain in SWS is characterized as decrease in vigilance (Cai, 2016, 2017, 2018a) with orientation to processing irregularly acquired memories (Cai, 1991, 1995; Inostroza & Born, 2013; Rasch & Born, 2013). In waking, the reticular noradrenergic (NA), serotonergic (5-HT), acetylcholinergic (ACh) and dopaminergic (DA) systems are all active (Foote, Bloom & Aston-Jones, 1983; Kayama & Koyama, 2003; McGinty & Szymusiak, 1988), so are the nonspecific intralaminar/midline nuclei of thalamus (Cai, 2017; Van der Werf, Witter & Groenewegen, 2002). In SWS, the NA and 5-HT systems decrease somewhat in discharge (Foote, Bloom & Aston-Jones, 1983; Kayama & Koyama, 2003; McGinty & Szymusiak, 1988), while the ACh system (Cai, 2017; Kayama & Koyama, 2003) and nonspecific intralaminar/midline nuclei of thalamus (Cai, 2017; Van der Werf, Witter & Groenewegen, 2002) decrease more.

NA and ACh are usually opposite in roles in regulating the emotional balance, whereas 5-HT is complex in its effects. The deficiency of brain NA or 5-HT or both may cause depression (Kidman, 1985; Nutt, 2002; Savitz, Lucki & Drevets, 2009), while hyper- and hypo-cholinergic states may result in depression and mania respectively (Dilsaver, 1986). Correspondingly, the effects of NA, 5-HT and ACh on the limbic activities are also different. NA is usually inhibitory and increases the ratio of signal/noise to environmental input (Madison & Nicoll,
whereas ACh is excitatory (Fisahn, Pike, Buhl & Paulsen, 1998). 5-HT influences the activity in the limbic forebrain in a more complex way, excitatory to some and inhibitory to others (Schmitz, Gloveli, Empson & Heinemann, 1998).

Cai has suggested that in waking the hippocampus and amygdala regulate such descending limbic structures as the mammillary bodies, septum, hypothalamus and epithalamus to regulate the ascending NA, 5-HT, ACh and DA systems, accomplishing declarative memory consolidation and recall (Cai, 1990, 2018b). In SWS, although the ACh system (Cai, 2017; Kayama & Koyama, 2003) and nonspecific intralaminar/midline nuclei of thalamus (Cai, 2017; Van der Werf, Witter & Groenewegen, 2002) decrease much in discharge, the NA and 5-HT systems only decrease somewhat in discharge (Foote, Bloom & Aston-Jones, 1983; Kayama & Koyama, 2003; McGinty & Szymusiak, 1988), therefore favorable in state to external orientation while against depression. Via the mutual interactions of NA/5-HT systems with the subcortical limbic structures (Cai, 1990, 2018b; Foote, Bloom & Aston-Jones, 1983; Kayama & Koyama, 2003; McGinty & Szymusiak, 1988), the SWS may orient the forebrain to increase the ratio of signal/ noise to environmental input after awake (Madison & Nicoll, 1986), while adjust the emotional balance against depression (Kidman, 1985; Nutt, 2002).

It is noted that, except the common LTDs (Yang, Zhang, Wang, Ruan & Chen, 2012a, 2012b) and even the rare LTPs (Sadowski, Jones & Mellor, 2016) forming in hippocampus in SWS, the neuronal plasticity in the lower portion of the subcortical limbic structures, such as those reported in the hypothalamus (Nisikawa, Shimazoe, Shibata & Watanabe, 2002; Panatier, Gentles, Bourque & Oliet, 2006; Qi & Yang, 2015) and epithalamus (Park et al., 2017), may lie even beyond the influences from the forebrain delta slow waves, spindles and ripples in SWS, which deserves more investigations. Notably, the LTP in suprachiasmatic nucleus (SCN) can be induced with different conditions modulated by day-night cycle (Nisikawa, Shimazoe, Shibata & Watanabe, 2002), implicating that the SCN LTP may possibly occur in SWS.

**Brief Perspectives**

The clinical observations on the regulation of SWS against depression has been accumulated for decades of years (Baglioni et al., 2014; Bunney & Bunney, 2012; Cai, 2016; Medina, Lechuga, Escandón & Moltó, 2014; Mendlewicz & Kerkhofs, 1991; Wehr, Wirz-Justice, Goodwin, Duncan & Gillin, 1979). Whereas, the underlying neurobiological processes of SWS to adjust the emotional balance have not been reviewed in detail up to now. In this article, it is reviewed the various neurobiological mechanisms of SWS involved in the regulation of the emotional/autonomic nervous system. It is classified these mechanisms into three types, as (1) the decrease in ratio of inspiration/expiration on regulating the vascular circulations in head from mouth to eye beginning early in SWS (Cai, 2018a); (2) the formation of hippocampal LTDs in SWS (Yang, Zhang, Wang, Ruan & Chen, 2012a, 2012b) to balance the increase in neural activities by LTPs acquired in waking (Moser, 2014); (3) the upregulation of NA in LC by SWS. Prospectively, this classification can help clarify the complex regulations of SWS on the emotional/autonomic nervous system, and promote the further investigations on this subject.

In this article, it is reviewed many types of neuronal plasticity in various locations of emotional/autonomic nervous system. (1) The LTP in mammalian autonomic ganglia (Alkadhi, Alzoubi & Aleisa, 2005; Cifuentes, Arias & Morales, 2013)/vagus nerve (García Ramos et al., 1994) and the LTD in vagus nerve (García Ramos et al., 1994) are related to the respiratory regulation without requiring the participation of forebrain slow wave of SWS, which deserves more investigations. (2) The hippocampal LTDs forming in the delta slow wave of SWS (Yang, Zhang, Wang, Ruan & Chen, 2012a, 2012b) can balance the increase in neural activities by LTPs acquired in waking (Moser, 2014), and adjust the emotional balance against depression (Cai, 1991, 1995, 2016). More investigations are required to look for LTD and even LTP in amygdala, septum, cingulate cortex and so on other forebrain limbic structures during SWS. (3) The hippocampal LTD (Yang, Zhang, Wang, Ruan & Chen, 2012a, 2012b) in SWS, as well as the neuronal plasticity in
the hypothalamus (Nisikawa, Shimazoe, Shibata & Watanabe, 2002; Panatier, Gentles, Bourque & Oliet, 2006; Qi & Yang, 2015) and epithalamus (Park et al., 2017), may all be related to the upregulation of NA in LC by SWS, while more investigations are required to look for neuronal plasticity in the hypothalamus and epithalamus during SWS.

It is noted that the delta slow wave predominates in the frontal lobe during SWS and secondly in occipital lobe (Happe et al., 2002). Neither of these cortical regions can voluntarily control the autonomic nervous system below the hypothalamus/epithalamus. Thus, more investigations are required on the neuronal activity, balance and plasticity in these lower structures of autonomic nervous system.

During the regulation of SWS on the emotional/autonomic nervous system, the neuronal plasticity forming in SWS may also affect the acquired memories in waking. SWS might help retention of declarative memory in humans (Inostroza & Born, 2013; Rasch & Born, 2013). It was reported that the declarative memory was improved by a nap or hypnosis (Schichl, Ziberi, Lahl & Pietrowsky, 2011), without requiring the time duration of SWS. In this regard, a nonspecific state of reduced mental noise, such as the decrease of ACh activity (Gais & Born, 2004) or speculative upregulation of NA in LC by SWS, may account for this effect of SWS on declarative memory. Obviously, more investigations are required on this issue.

CONCLUSIONS

For demonstration of the abundant clinical and experimental observations that SWS may adjust the emotional balance against depression, this review article classifies three types of regulations on emotional/autonomic nervous system by SWS. (1) In the induction of SWS as enlightened by yawning, the decrease in ratio of inspiration/expiration begins to influence the sensory posterior palate and maxillary sinuses, regulating the vascular circulations from mouth to eye in SWS, without requiring the participation of forebrain slow wave. (2) The delta slow wave in SWS causes LTDs to balance the LTPs acquired in waking, adjusting the emotional balance to normal, especially against depression. (3) The noradrenergic LC might be regulated in SWS by the neuronal plasticity in the limbic structures including the hippocampus, hypothalamus and epithalamus to orient the forebrain and increase the ratio of signal/noise to environmental input after awake, while adjust the emotional balance against depression. This classification helps clarify the complex regulations of SWS on the emotional/autonomic nervous system.

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