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Serotonergic hypothesis of sleepwalking

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Summary Despite widespread prevalence of sleepwalking, its etiology and pathophysiology are not well understood. However, there is some evidence that sleepwalking can be precipitated by sleep-disordered breathing. A hypothesis is proposed that serotonergic system may be a link between sleep-disordered breathing and sleepwalking. Serotonergic neurons meet basic requirements for such a role because they are activated by hypercapnia, provide a tonic excitatory drive that gates afferent inputs to motoneurons, and the activity of serotonergic neurons can be dissociated from the level of arousal. This paper discusses also drug-induced somnambulism and co-occurrence of sleepwalking and other disorders such as migraine and febrile illness.

The characteristic of sleepwalking

Sleepwalking (somnambulism) is one of the most common parasomnias and refers to various complex motor behaviours, including walking, that are initiated during deep (stages 3–4) non-rapid-eye-movement (NREM) sleep. Some episodes may be limited to sitting up, fumbling, picking at bedclothes, and mumbling but usually sleepwalkers usually stand up and walk around quietly and aimlessly. Occasionally, they become agitated, with thrashing about, screaming, running, and aggressive behavior [1]. The concurrence of abrupt motor activity with diffuse, rhythmic, high-voltage bursts of delta electroencephalographic (EEG) activity indicates dissociation between mental and motor arousal during sleepwalking episodes [1].

Etiology of sleepwalking

Despite widespread prevalence of sleepwalking, its etiology and pathophysiology are not well understood [2,3]. To date, genetic, developmental, organic, and psychological factors have been proposed as causes of sleepwalking and somnambulism episodes can be triggered by fever, medication with some drugs, stress and major life events [4]. Recently, Bassetti et al. [1] proposed that sleepwalking could result from activation of thal-

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amocingulate pathways and persisting deactivation of other thalamocortical arousal systems. Evidence is starting also to accumulate that sleepwalking can be precipitated by sleep-disordered breathing (SDR) in adults [5] and in children [6]. In fact, research carried out by Guilleminault et al. [6] revealed that somnambulism is not only often accompanied by sleep-disordered breathing but also that successful treatment of SDR results in disappearance of parasomnias. Therefore, it can be inferred that there is a neural mechanism that is triggered by hypercapnia, can release motor activity but does not lead to full arousal.

The role of serotonergic neurons in chemoreception

Cell bodies containing serotonin (5-hydroxytryptamine; 5-HT) are localized in two major groups in or near the brain stem raphe nuclei [7]. The rostral group, localized in the pons/mesencephalon, contains the dorsal (DRN) and the median (MRN) raphe nuclei whereas the caudal group, localized in the medulla, is comprised primarily of the nuclei raphe magnus, obscurus and pallidus (NRM, NRO and NRP, respectively). Medullary 5-HT neurons are located proximally within the vascular tree, close to large blood vessels, thus enabling them to sense blood CO_2 [8]. Recently, it has been shown that serotonergic neurons are stimulated by hypercapnic acidosis thus implicating 5-HT neurons in central chemoreception [8]. In vitro recordings revealed that the mean firing rate of the acidosis-stimulated 5-HT raphe neurons increases between 240% and 300% of control in response to P_{CO_2} changes between 3% and 9% [8]. Similar results were also obtained under physiological conditions using in vivo recordings that revealed that neurons both in the DRN and in the NRO/NRP are activated by hypercapnia [7].

The role of serotonin in control of motor activity

According to Jacobs and Fornal [9], the primary role of brain serotonergic system is facilitation of gross motor movement. It has been shown, using various methods, that serotonin exerts facilitatory effects on motoneurons. In vivo application of 5-HT in the vicinity of spinal motoneurons or systemic injection of 5-HT precursors leads to an increase in motoneuronal excitability, increases tonic muscle electromyogram (EMG) activity and facilitates some spinal motor reflexes [10]. Large body of evidence indicates that there is a general relationship between 5-HT neuronal activity across all groups of 5-HT neurons and the level of tonic motor activity [9]. During an undisturbed waking state of a cat, brain 5-HT neurons in all raphe nuclei discharge in a slow and rhythmic manner and this clock-like activity is a manifestation of an endogenous pacemaker activity. This regular firing of serotonergic raphe neurons during waking creates a steady synaptic release of 5-HT which provides a tonic excitatory drive that modulates motor system neuronal activity and gates afferent inputs to motoneurons. During gross repetitive motor behaviors subpopulations of 5-HT neurons are activated, attaining discharge levels several times greater than that observed during undisturbed waking. Conversely, as the animal becomes drowsy and enters slow-wave sleep, 5-HT neuronal activity displays a gradual decline and falls silent during rapid eye movement sleep. This general pattern of activity across the sleep-waking cycle is seen in all major groups of brainstem 5-HT neurons. The decrease in the activity of serotonergic neurons is paralleled by a decrease in muscle tonus [9].

The limited role of serotonin in arousal

Although the discharge rate of raphe 5-HT neurons is grossly correlated with level of arousal across the sleep-wakefulness cycle, it has also been shown that activity of serotonergic neurons modulating the motor system can be dissociated from the arousal. In cats with lesions of the dorsomedial pons, the activity of DRN 5-HT neurons was similar to that in normal cats during waking and NREM sleep and these pontine lesioned animals displayed normal waking behavior [11]. However, during REM sleep the activity of DRN 5-HT neurons in those cats considerably increased instead of falling silent and there were often periods when the discharge rate approached that observed during waking [11]. The increase in activity of 5-HT neurons during REM sleep did not lead to awakening, as demonstrated by the fact that the animals, although they displayed complex motor behaviour, were unresponsive to bright lights and mild tactile stimuli.

The opposite situation, when arousal is accompanied by dramatic decrease in activity of 5-HT neurons, is also possible. For example, microinjections of carbachol into the pontine tegmentum during waking reduced the activity of DRN serotonergic neurons by 97% below pre-drug baseline rates

[12]. This dramatic decrease was accompanied by muscle atonia lasting for 50—70 min but did not result in loss of arousal, as evidenced by the fact that the animals were able to visually track moving objects. Similar results were obtained using mephenesin, a centrally acting muscle relaxant, which also suppressed the activity of 5-HT neurons without affecting arousal [12]. Profound decrease in discharge rate of serotonergic neurons can also be seen under physiological conditions. During orienting reaction, when animals are highly attentive, the activity of DRN and 5-HT neurons also falls silent [9]. These data provide evidence that the arousal per se is independent of the 5-HT neurons activity.

The role of serotonin in pathophysiology of sleepwalking

We would like to put forward a hypothesis that serotonergic system may be a link between abnormal breathing and motor activity during sleep. The 5-HT neurons can play such a role because serotonin provides a tonic excitatory drive that gates afferent inputs to motoneurons, the activity of raphe neurons can be dissociated from the level of arousal, and raphe neurons are activated by hypercapnic acidosis. Normally, the responsiveness of 5-HT neurons to systemic CO_2 stimulation is greatly reduced or abolished during sleep [7]. It is known that activity of serotonergic neurons is regulated by endogenous pacemaker [7] and is modulated by afferents from other parts of brain [13]. To date, it has been shown that activity of 5-HT neurons is regulated by GABAergic and noradrenergic systems [14,15], opioids [16], orexins [17], neurokinins [18], neurotensin [19], glutamine [9] and glycine [20]. It is, therefore, conceivable that in somnambulists there is an impairment in regulation of 5-HT activity that leads to transient increase in the excitability of serotonergic neurons. If such a state occurs along with abnormal breathing, it can lead to further increase in 5-HT neurons activity. This, in turn, can result in increased excitability of motoneurons and release of gross movements, which normally do not occur during sleep. It is worth noting that somnambulism is most common in children and recedes with age [4]. Therefore, it is conceivable that impairments in regulation of 5-HT activity may be related to brain maturation. The need for concomitantly increased excitability of 5-HT neurons and acidosis explain why abnormal breathing during sleep only rarely induces sleepwalking.

This hypothesis is congruent with original suggestion by Barabas et al. [21] that serotonin can play role in etiology of somnambulism. Their conclusion was drawn from the fact that there is a high incidence of sleepwalking among patients suffering from migraine that was thought to be related to intermittent serotonin depletion. That observation is only seemingly inconsistent with the hypothesis that a transient increase in activity of 5-HT neurons is responsible for triggering episodes of sleepwalking. There is growing body of evidence that migraine is associated with a chronically reduced serotonergic neurotransmission and migraine attacks result in fact from a massive release of 5-HT in the brain [22].

The notion of increased activity of 5-HT neurons during episodes of sleepwalking can be supported by the electro-encephalographic characteristic of sleep architecture in sleepwalkers. It has been reported that there is an increase in the slow wave sleep (stages of 3 and 4 of NREM) in somnambulists compared with normal controls and that the slow wave activity (SWA) during 2 min immediately preceding an episode of parasomnia is significantly higher than the SWA during 2 min in the same stage 10 min before an episode of parasomnia [23]. This observation is congruent with the effect of serotonin on slow wave sleep (SWS). Research carried out by Cape and Jones [24] revealed that microinjections of serotonin during sleep into the cholinergic basalis neurons increase EEG delta activity in rats. Moreover, in one-half of rats injected with serotonin, these authors observed anomalous wake episodes associated with high delta activity. These wake episodes were characterized by open eyes and quiet behaviour and, in fact, resembled sleepwalking in humans.

Recently, it has been also reported that treatment with paroxetine in the evening can trigger episodes of somnambulism [25]. Paroxetine is a potent selective serotonin reuptake inhibitor [26] and is known to increase SWS in healthy individuals [27]. This observation further substantiates the hypothesis of increased activity of 5-HT neurons in somnambulists. There are also reports of lithium-induced somnambulism [28,29]. Studies in humans and animals indicate that lithium has a net enhancing effect on the serotonin function and increases 5-HT release in some areas of the brain [30,31]. Therefore, it is likely that serotonin can play role also in the lithium-induced somnambulism. Finally, it has been also reported that febrile illness can be a precipitating factor for sleepwalking [32] and there are data implicating serotonin in pathophysiology of fever. It has been shown, for example, that treatment with lipopolysaccharide

(LPS) produces marked increase in the concentration of serotonin in the brain and depletion of 5-HT causes attenuation of LPS-induced fever [33,34]. Therefore, serotonin can also constitute a link between fever and sleepwalking.

Conclusions

In summary, cerebral serotonergic system may play an important role in pathophysiology of sleepwalking. This hypothesis is supported by the fact that several factors known to precipitate episodes of sleepwalking activate serotonergic system. The higher prevalence of other sleep disorders, including night terrors and enuresis, in sleepwalkers suggest that sleepwalking may be a part of a more generalized sleep disturbance and can share a common pathophysiological substrate [35]. Therefore, serotonin may be implicated also in occurrence of other parasomnias.

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