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ORIGINAL PAPER

Hypothalamic Histaminergic and Orexinergic Modulation on Cerebellar and Vestibular Motor Control

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Abstract Somatic–nonsomatic integration is critical for generation and execution of an appropriate and coordinated behavioral response to changes in internal and external environments. However, the underlying neural substrates and mechanisms are still enigmatic. Intriguingly, the central histaminergic and orexinergic systems originating from the hypothalamus, a high autonomic regulatory center, innervate almost the whole brain including various subcortical motor structures, particularly the cerebellum and vestibular nuclei. Here, we suggest that the hypothalamic histaminergic and orexinergic system bridging the nonsomatic center to somatic motor structures may actively modulate the cerebellar and vestibular nuclear neurons and subsequently participate in motor control and somatic–nonsomatic integration.

Keywords Histamine · Orexin · Hypothalamus · Cerebellum · Vestibular nuclei · Motor control

An intact behavior comprises not only somatic (motor) but also nonsomatic components, including visceral, emotional, cognitive, and other high functions. Therefore, a somatic–nonsomatic integration is critical for generation of an appropriate and coordinated behavioral response to changes in the internal and external environment [1, 2]. In fact, several cases of simultaneous somatic and visceral dysfunction have been reported. Two patients with lesions restricted in the cerebellum showed classic somatic motor symptoms (a severe gait ataxia or terminal tremor), but accompanied by other nonsomatic visceral symptoms, such as bradycardia, respiratory alkalosis, and hyperventilation [3]. Particularly, it is noteworthy that when ataxia slowly improved, hyperventilation and bradycardia also resolved in [3]. However, the neural substrates and mechanisms responsible for somatic–nonsomatic integration are still largely unknown.

Interestingly, neuroanantomical studies have revealed direct, bidirectional connections [3, 4] between the hypothalamus, a high center for autonomic (nonsomatic) regulation, and the cerebellum, an important somatic motor structure. We speculate the direct, bidirectional cerebellar–hypothalamic circuits may be potential pathways underlying the somatic–nonsomatic integration [1]. A series of studies from our and other laboratories have demonstrated that the cerebellum may actively participate in many nonsomatic basic functions, such as feeding, cardiovascular, and osmotic regulations, through the direct cerebellohypothalamic projections [1, 2, 5]. On the other hand, the hypothalamus may also modulate the cerebellar cortical and nuclear neurons and influence the cerebellar motor control, via the direct hypothalamocerebellar projections, especially histaminergic [1, 6, 7] and orexinergic [8]. Besides, the hypothalamic histaminergic and orexinergic systems innervate other important subcortical motor structures, such as the vestibular nuclei, basal ganglia, and even spinal cord [9, 10].

While the central histaminergic system solely originates from the tuberomammillary nucleus of the hypothalamus [9], the central orexinergic system strictly originates from the perifornical area and lateral hypothalamic area [10]. But both of these systems project widely to almost the whole brain and participate in various nonsomatic basic functions, thus may act as general modulators for whole brain activity.

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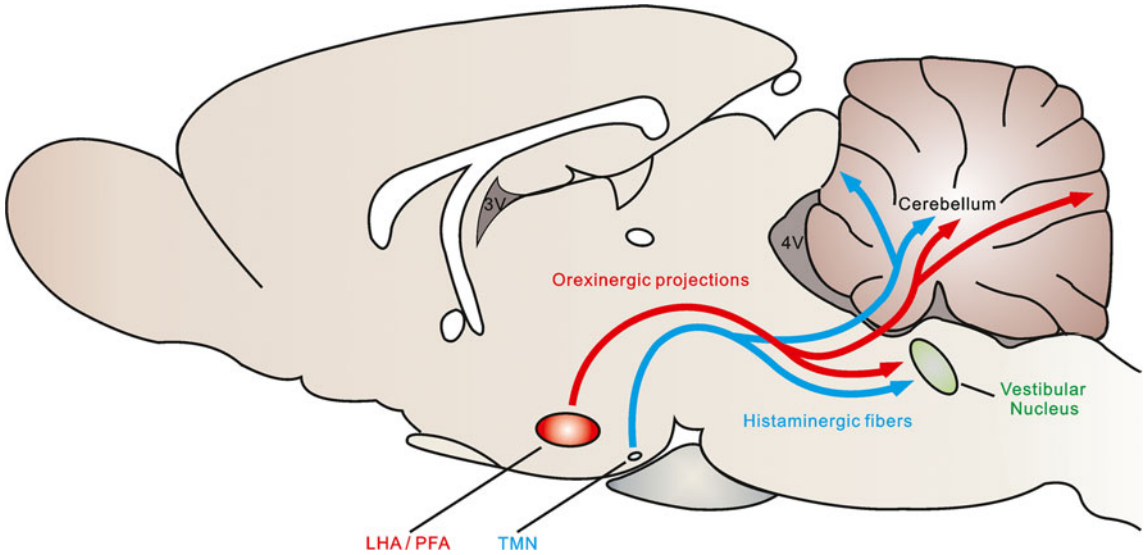

Fig. 1 Hypothalamic histaminergic and orexinergic projections to the cerebellar cortex and nuclei, as well as to the vestibular nuclei. *LHA* lateral hypothalamic area, *PFA* prefornical area, *TMN* tuberomammillary nucleus

Intriguingly, we have found that the central histaminergic and orexinergic systems are both also actively involved in central motor control and somatic motor behaviors. In the cerebellum, an important motor structure ensuring that movements are performed with spatial and temporal precision, histamine exerts an excitatory effect on cerebellar cortical Purkinje cells, granule cells, and nuclear neurons via postsynaptic histamine H_2 or H_2 and H_1 receptors [1, 7]. Especially, the excitatory effect of histamine on the cerebellar nuclear neurons is selective, i.e., histamine only excites projection neurons rather than interneurons in the cerebellar nuclei (manuscript in preparation). Furthermore, by activation of H_2 receptors in the cerebellar fastigial and interpositus nuclei, hypothalamic histaminergic afferents may modulate the final outputs of the spinocerebellum and subsequently regulate activity of the proximal and distal muscles and promote cerebellar-mediated motor balance and coordination [6, 7]. In addition, histamine also excites all major subnuclei (lateral, medial, superior, and inferior) in the vestibular nuclear complex [11–13], a sensorimotor complex integrating vestibular, visual, and motor signals to make compensatory eye and head movements as well as postural adjustments. Actually, the hypothalamic histaminergic projections may even directly innervate and modulate spinal motoneurons [14], the final common path for motor commands from various high motor centers and reflective signals from spinal itself.

On the other hand, the central orexinergic system, which has been traditionally implicated in many nonsomatic basic functions, including the feeding, sleep/wake states, and reward processes, is also closely related to motor control, since orexin deficiency may result in cataplexy, a motor deficit which is characterized by sudden loss of muscle tone, in humans, dogs, and rodents [10]. We have reported that orexin increases the activity and sensitivity of projection neurons in the lateral vestibular nucleus via OX1 and OX2 receptors and consequently regulates central vestibular-mediated posture, motor balance, and negative geotaxis [15]. More interestingly, the hypothalamic orexinergic innervation on the lateral vestibular nucleus is more critical when animals facing a major motor challenge as opposed to during rest and general movements [15], which may account for why the absence of orexin results in cataplexy. Besides, orexin also homogeneously depolarizes neurons in the medial vestibular nucleus (manuscript in preparation) and the cerebellar interpositus nucleus [8].

In conclusion, the hypothalamic histaminergic and orexinergic innervations and modulations on cerebellum and vestibular nuclei (Fig. 1) bridge the nonsomatic center to somatic motor structures. These projections may be important components of the neural substrates responsible for somatic–nonsomatic integration. Lack or dysfunction of the histaminergic and/or orexinergic modulations may result in a simultaneous somatic and nonsomatic dysfunction, such as narcolepsy–cataplexy [15], in which nonsomatic activities (sleep and emotional) and somatic responses (motor) are not correctly integrated and coordinated.

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