Cerebellar connections: hypothalamus

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Morphological studies have described reciprocal cerebello-hypothalamic projections in various species. These connections provide evidence for the key role of the cerebellum and hypothalamus in physiological regulatory processes such as autonomic and endocrine homeostasis. Our recent study using horseradish peroxidase (HRP) retrograde axonal transport technique showed cerebellar connections with the posterior and the dorsomedial hypothalamic nuclei. Further, we have demonstrated regional differences of the connections of the dorsomedial hypothalamic nucleus in rat. The results of HRP labelling showed that afferent pathways originating from the anterior and posterior parts of dorsomedial hypothalamic nuclei indicate a number of differences in the projections. The posterior part of the dorsomedial hypothalamic nucleus and the posterior hypothalamic nucleus receives direct distinct projections from the cerebellum, whereas the anterior part of the dorsomedial hypothalamic nucleus does not. Moreover, the posterior part of the dorsomedial nucleus of the hypothalamus when compared to the posterior hypothalamic nucleus has more intense connections with the cerebellum. These observations bring a new perspective on the question of how the cerebellum is involved in the regulation visceromotor functions.

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**Introduction**

Evidence for the involvement of the cerebellum in various functions comes from numerous data in different species. In addition to the role of the cerebellum in the coordination of somatic motor activity, the regulation of muscle tone and mechanisms that influence and maintain equilibrium, several studies also indicate a general cognitive and sensory role of the cerebellum in behavioural functions and memory.1–6

The afferent and efferent projections of the cerebellum provide strong evidence to its functional role. Numerous morphological studies using retrograde and anterograde tract tracing techniques showed connections of the cerebellum to cortical, subcortical and brainstem structures.4,6–9 The cerebellum has long been regarded as involved in the control of movements, primarily through its connections with the cerebral cortex.

**Cerebello-thalamo-cortical connections**

It is well established that inputs to the cerebellum arise from large areas of the cerebral cortex, including the frontal, parietal and temporal cortices.8,10–12 Inputs from the cortical areas to the cerebellum make a loop known as cerebro-cerebellar circuitry. If the cerebellum influences cognition or perception, as well as motor control, it must be through projections from the deep cerebellar nuclei to thalamo-cortical circuit. However, the thalamic relays of cerebellar efferents reaching the cortex are not clearly defined in various species. Early investigations showed the output of the cerebellum from the deep cerebellar nuclei to a single region of the ventrolateral thalamus.13 This thalamic region was believed to project exclusively upon a single cortical area, the primary motor cortex. It is now apparent that cerebellar projections to the thalamus are not limited to a single region of the ventrolateral thalamus, but these projections target other thalamic nuclei as well.14,15 Yamamoto et al. used a double staining technique to reveal thalamic connections of deep cerebellar nuclei in monkey and showed that ventral thalamic nuclei, and the ventrolateral part of mediodorsal thalamic nucleus are the thalamic relays of cerebello-cortical circuit.14 Person et al. described connections of the medial cerebellar nuclei with paraventricular complex and mediodorsal nucleus; central medial, paracentral, parafascicular, central lateral, ventral medial, ventral lateral nuclei of the thalamus.16 Further, Liu et al. demonstrated the possible pathways of cerebellum via parafascicular nucleus of the thalamus in modulating nociceptive inputs.17

The cerebellar output project via the thalamus to multiple cortical areas, including frontal eye field, supplementary motor area, frontal association cortex, primary motor, premotor, prefrontal, and parietal cortices.18–20 The projections to these cortical areas appear to originate from distinct regions of the cerebellar nuclei. These observations have led to the proposal that cerebel-
lar output is composed of a number of separate “output channels” each of which projects to a distinct cortical area which are thought to be concerned with different aspects of motor or cognitive behaviour. Further, Tamada et al. proposed a laterality index method and revealed that the simple and semilunar lobe of the lateral cerebellum have connections with the pars opercularis and pars triangularis in the inferior frontal gyrus. They concluded that cerebello-cerebral communication loop is tool usage, which is in between the cognitive and motor functions of the human cerebellum.

In addition to the indirect cerebellar pathways (cerebello-thalamo-cortical) that target various cortical areas, direct connections between cerebellum and cortex were also described. Stepniewska et al. determined the relative contributions of transthalamic cerebellar and pallidal projections to the primary motor cortex of the monkey. These results indicate that the motor cortex is influenced by both the cerebellum and globus pallidus in the monkey. Further, the cerebello-thalamo-cortical circuit is believed to play a crucial role in movement and also influences motor control as well as cognition. The organization and the strength of the connections that link the cerebellum with areas of the cerebral cortex are known to be concerned with higher order behaviours rather than with motor control.

The cerebellar outputs are relayed via thalamus to the appropriate cortical area, however, cerebellar connections with the reticular nucleus of the thalamus have received less or no attention. Our previous study on the connections of the reticular nucleus of the thalamus showed that the lateral, anterior and posterior interposed but not the medial cerebellar nuclei which have connections with specific regions of the reticular nucleus of the thalamus in varying density. Although numerous data has been collected on the function of the reticular nucleus of the thalamus, the precise role is still being debated. Crick postulated that the reticular nucleus of the thalamus acts to mediate selective attention in particular, to specifically gate dorsal thalamic input to the cerebral cortex. These results may indicate that the cerebello-recticular nucleus of the thalamus fibers system connecting the two parts of the central nervous system may provide a control circuit through which the cerebellum may influence cognition, visceral control, behavioural function and memory as well as motor control via the reticular nucleus of the thalamus.

Cerebellar-subcortical connections

The traditional view that the basal ganglia and cerebellum are simply involved in the control of movements has been challenged in recent years. New information about reciprocal discrete circuits concerning basal ganglia and cerebellar connections with the cerebral cortex has been put forward. The neuronal activity within basal ganglia and cerebellar loops with motor areas of the cerebral cortex is highly correlated with parameters of movements, while neuronal activity within basal ganglia and cerebellar loops within areas of the prefrontal cortex is more related to aspects of cognitive functions. Mitrofanis and de Fonseka demonstrated reciprocal connections with the zona inserta and cerebellum (a diencphalic nucleus deriving from the ventral thalamus) suggesting that zona inserta integrates cerebellar information to other cortical and subcortical structures. Further, electrophysiological studies showed connections of the cerebellum with the hippocampus. The stimulation of the fastigial nucleus evoked the discharge of hippocampus on both sides of the brain. The cerebello-hippocampal connections were thought to play an important role in the behavioural expression of learning.

Cerebello-brainstem connections

The strongest projections to the cerebellum and from the cerebellum, are to the brainstem structures. The primary connections of all the cerebellar nuclei are to the inferior olivary complex. Dense cerebello-olivary connections are reciprocal. The inferior olivary and the cerebellar nuclei are considered to be folded but continuous sheets of gray matter and complete nucleo-olivary projections can be described as a simple transformation. The cerebellar nuclei connections are generally very widespread and found throughout the brainstem (Figure 1). The different regions of the same cerebellar nucleus shows important differences in the distribution of projections. Teune et al. demonstrated the connections of the cerebellar-brainstem structures in the rat. The rostral part of the medial cerebellar nucleus is mostly found to be connected to the caudal half of the brainstem, whereas its caudal part is connected to midbrain areas. The medial part of the posterior interposed nucleus sends most projections to the red nucleus, prerubral region and parvicellular reticular formation, the lateral part to the inferior olivary complex, rostral half of the brain stem, superior colliculus and zona inserta. The anterior interposed nucleus targets inferior olivary nucleus, red nucleus, pontine reticulo-tegmental nucleus and pretecum. The lateral cerebellar nucleus is characterized by a widespread distribution. In conclusion, different regions of the same cerebellar nucleus may show important differences in distribution of labelled terminals. On the other hand, injections placed in different cerebellar nuclei may result in similar labelled terminals. Further, Kawamura et al. studied the cerebellar projections to the superior colliculus and pretecum in the cat. Their results showed that cerebello-tectal projections arise from two different regions of the cerebellar nuclei: the caudal half of the medial nucleus and the ventrolateral part of the posterior interposed nucleus. Fibers arising from the medial cerebellar nucleus are distributed bilaterally in the superficial zone of the intermediate gray layer of the superior colliculus, while those originating from the