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The Cerebellar Dentate Nucleus

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Abstract

The dentate nucleus is the largest and phylogenetically youngest nucleus of the cerebellum. It has a tooth-like shape and is located within the deep white matter of each cerebellar hemisphere. The dentate nucleus contains two main morphological types of neurons, large polyhedral ones which are either Glutaminergic or Glycinergic, and small round shaped one which are GABAergic. The dentate nucleus can be divided into different functional areas, which are related to different parts of the cerebellar cortex and the cerebral hemispheres. Although it was thought that the dentate nucleus was solely related to the development and integration of motor tasks, recent evidence gave new insights into its function, and it is now widely accepted that the dentate nucleus is additionally related to the learning procedure, to short-term memory and to high cognitive functions in general.

Key words: Cerebellar Dentate Nucleus, GABAergic, High cognitive functions.

Introduction

The cerebellar dentate nucleus (DN) is the largest and phylogenetically the youngest cerebellar nucleus, the others being the fastigial, the globose and the emboliform nuclei. The dentate nucleus has a tooth-like or serrated edge and is located within the deep white matter of each cerebellar hemisphere. DN contains two main types of neuronal cells; large polyhedral neurons which are glutaminergic, or glycinergic and form the macrocellular peripheral region and small GABAergic neurons, which form the microcellular region. Neurons from the macrocellular area of the DN are connected to the Purkinje cells of the cerebellar cortex. The size of the glutaminergic neurons varies between 40-50μm, while their shape is in consistence with the brain area to which they are connected. The glutaminergic neurons from the area of the DN which is connected to the cerebellar tonsils are large, polyhedral and bear two or three primary dendrites which form a circular dense dendritic field around the cell body. The neurons from the area of the DN which is connected to the posterior lobe of the cerebellar cortex are characterised by marked pleomorphism. Their cell bodies are polyhedral, fusiform or triangular, and they have multiple short branches and an apical dendrite. The neurons from the area of the DN which is connected to the anterior lobe of the cerebellum are ovoid, or semi-ovoid, and they have four to six branches that form asymmetric dendritic fields. The microcellular region of the DN receives collaterals from the axons Purkinje cells of the flocculonodular lobe of the cerebellum which terminate in the fastigial nucleus. Each one of the glutaminergic cells from the macrocellular region forms synapses with 860 Purkinje cells (Palkovits et al., 1977, Chan-Palay, 1977).

Connections

The cerebellum can be divided into three regions based on phylogenetic and functional criteria. The vestibulocerebellum or archicerebellum is consisted by the flocculonodular lobe and the immediately adjacent vermis is related to balance and eye movements. The archicerebellum receives input from the semicircular canals, the vestibular nuclei, the superior colliculi and the visual cortex, and sends fibres back to the medial and lateral vestibular nuclei. Lesions of this region cause balance impairment and gait disturbance (Kingslay, 2000).

The spinocerebellum, or paleocerebellum, is consisted by the vermis and the intermediate parts of the hemispheres and is functionally related to the regulation of movements of the limbs and the trunk and modulates the descending functional systems. It receives inputs from the dorsal columns of the spinal cord and the trigeminal nerve, as well as from the visual and the auditory system, and sends fibres to the deep cerebellar nuclei, and more specific the fastigial nucleus which in turn projects to the cerebral cortex, the reticular formation and the vestibular nuclei. The spinocerebellum elaborates the proprioceptive input in order to anticipate the future position of a body part during the course of a movement, in a "feed forward" manner (Kingslay, 2000).

The cerebrocerebellum, or neocerebellum is consisted from the lateral parts of the hemispheres and is involved in the planning of movements and the evaluation of the incoming sensory information. The neocerebellum receives input almost exclusively from the cerebellar cortex, via the pontine nuclei and the dentate nucleus, and sends fibres to the ventrolateral thalamus which is connected to motor areas of the premotor cortex and primary motor areas of the cerebral cortex and to the red nucleus which is in turn connected to the inferior olivary nucleus. The neocerebellum is involved in the planning of future movements and is also involved in pure cognitive functions (Kingslay, 2000).

The DN receives afferent fibres from the neocerebellum and paleo (macrocellular region) and secondarily to the archicerebellum (microcellular region). The axons of the large glutaminergic neurons of the DN are concentrated inwards forming the gate of the nucleus, and then they follow their pathway through the anterior cerebellar peduncles to the red nucleus (rubber), the thalamus and through that to the cerebral cortex, playing an important role in the development and the elaboration of the voluntary motor programs. It was initially thought that the DN is solely related to the frontal central gyrus and thus to the motor functions (Asanuma et al., 1983), however recent evidence has shown that it is also indirectly connected with the frontal eye fields, the premotor cortex and the parietal cortex (Middleton and Strick 1998a, 1998b, 2000, 2001, Clower et al., 2001, Lynch et al., 1994).

Dum and Strick have shown that the glutaminergic neurons from the caudal area of the DN are related to the upper limbs motor area, while the glutaminergic neurons of the DN which are related to the lower limbs motor cortex are located caudally and anteriorly to them. The motor cortex of the face is related to glutaminergic neurons which are found in the posterior-caudal margin of the dentate nucleus (Dum and Strick, 2003). Furthermore the inferior area of the DN is related to the cerebral cortex of the parietal lobe, while the middle lateral area is related to the 46 Brodmann field. The ventral area of the DN is related to the 12 Brodmann field or the cerebral cortex (Gao et al., 1996; Ivry, 2003, Zemanick et al., 1991; Hoover and Strick, 1999; Lynch et al., 1994; Dum and Strick, 2003).

Dentate nucleus and thalamus

The DN is connected to the ventrolateral thalamic nucleus, which in turn is connected with the primary motor area of the cerebral cortex, through the dentatorubrothalamic tract. Furthermore it is connected with the posterior ventral thalamic nucleus, which in turn is connected with the sensory cortex (3,1,2 Brodmann fields). Last but not least, recent evidence has shown that the dentate nucleus is linked to the lateral-central thalamic nucleus. The anterio-posterior and rostro-caudal topographic distribution of the dentate nucleus corresponds to the latero-medial topographic distribution of the thalamus (Kievit and Kuypers, 1977, Miyata and Sasaki, 1983, Vitek et al., 1994).

Dentate nucleus and brainstem

The ventral area of the dentate nucleus, including the microcellular region, sends fibres to the superior colliculi, through the superior cerebellar peduncles (Hirai et al, 1982). Fibres from the caudal area, after crossing to the opposite half in the midbrain, at the level of the superior colliculi, terminate at the red nucleus, the periventricular grey matter, and the tegmentum, whereas other fibres terminate to the inferior part of the brainstem, and more specifically to the inferior olivary nucleus and the macrocellular area of the reticular formation. Fibres from the ventral area of the DN terminate in the area around the red nucleus and in the auxiliary occulomotor nuclei, and in the pre-tegmental region (Teune et al., 2000).

Studies in cats have demonstrated the existence of fibres starting from the macrocellular region and the posterolateral area of the dentate nucleus, terminate in the vestibular nuclei, while fibres from the microcellular region terminate in the superior and inferior vestibular nuclei, and in addition to that the dentate nucleus receives afferent fibres from the vestibular nuclei (Delfini et al., 2000).

The dentate nucleus sends fibres to the tegmental reticular formation with a topographic distribution. The inferio-superior distribution in the dentate nucleus corresponds to a antero-posterior distribution in the reticular formation (Stanton, 2001).

Figures

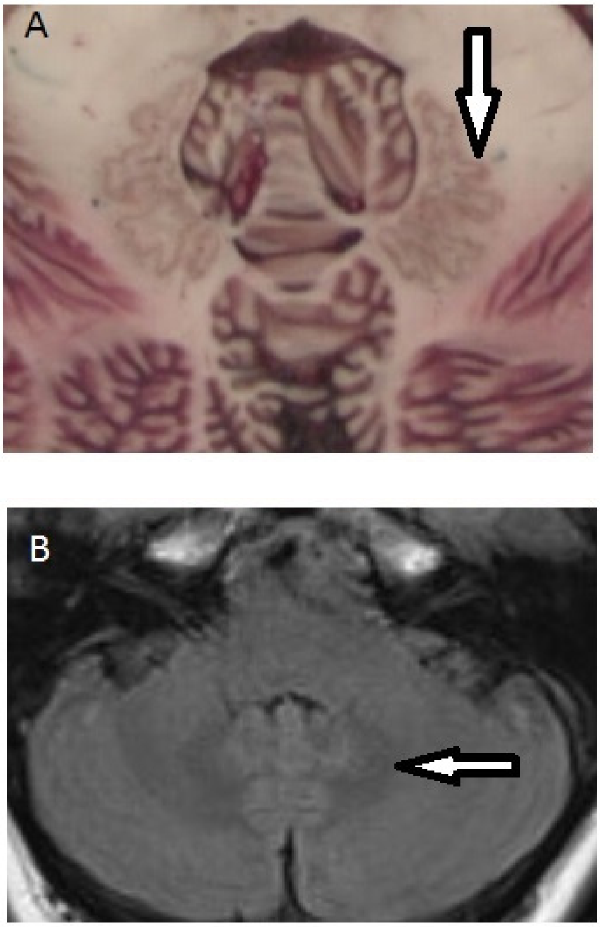

Figure 1: Horizontal section through the middle of the cerebellum **(A)**, and MRI brain, Flair sequence **(B)**. The dentate nucleus appears as a tooth-like shaped structure located in the deep white matter of each hemisphere (arrows).

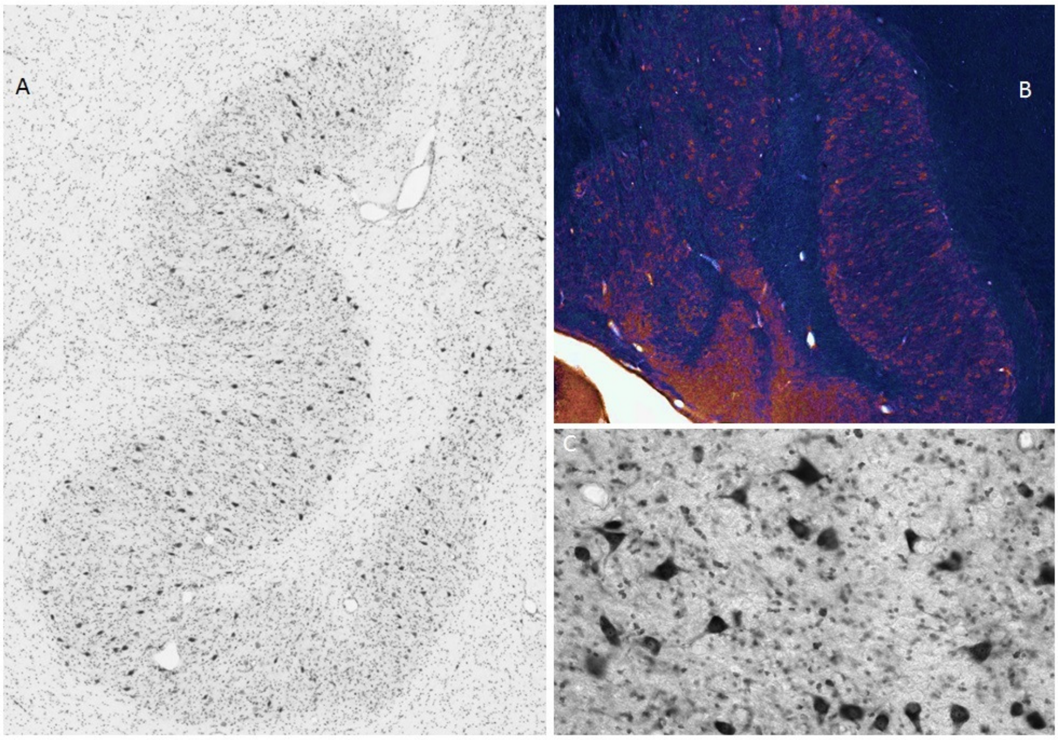

Figure 2: **(A)** Nissl staining, through the middle of the dentate nucleus Magnification 50X, **(B)** Weil method, with modified picture polarization through the middle of the dentate nucleus, Magnification 50X, **(C)** Polyhedral neurons from the macrocellular region of the dentate nucleus, Nissl staining, Magnification 100X

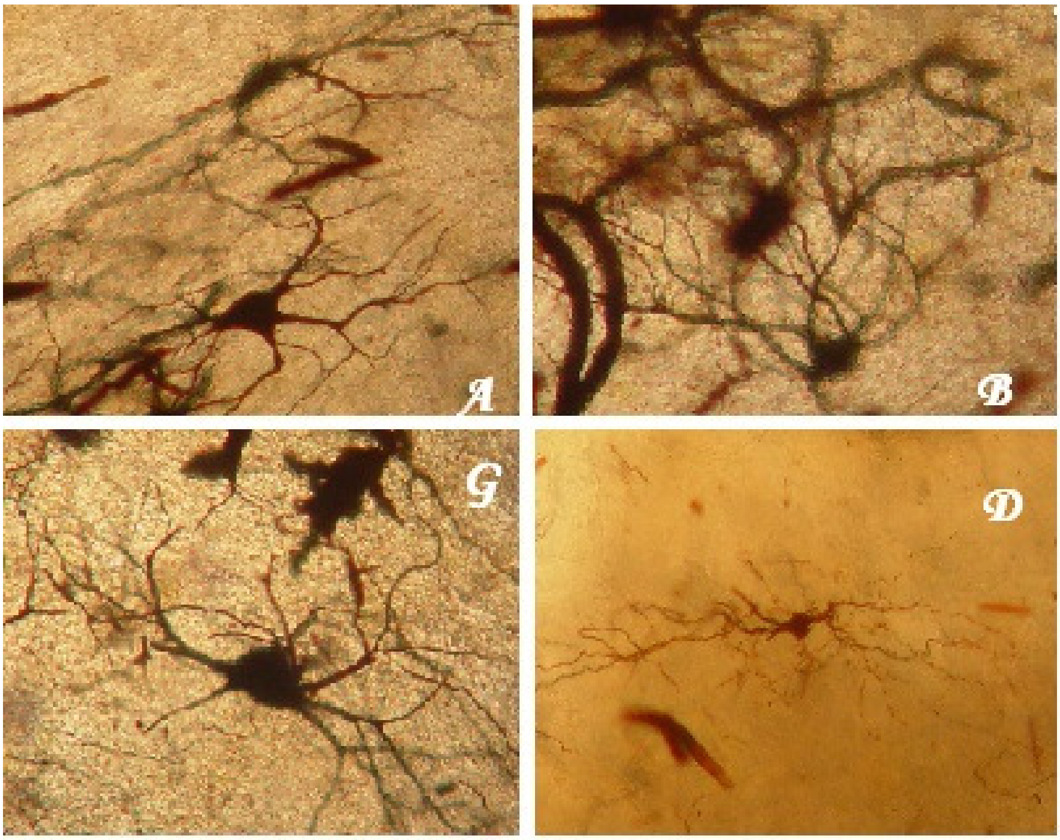

Figure 3: Large polyhedral neurons from the macrocellular region of the dentate nucleus **(A, B, C)**, and a small GABAergic neuron from the microcellular region **(D)**, Golgi method, Magnification 200X

Function

It is now widely accepted that the cerebellar dentate nucleus is related to eye movements, to the integration of sensory input, to short term memory, learning and future planning, in addition to the critical role in the motor schemes (Kim et al., 2018, Jueptner et al., 2001, Liu et al., 2000). Moreover it is believed that the dentate nucleus can be functionally divided into two main parts, the inferior-caudal region which is connected to the frontal central gyrus and therefore to voluntary motor schemes, while the superior-ventral region is related to the learning process and eye movements (Clower et al., 2001, Middleton and Strick 2001, Kim et al., 2018, Jueptner et al., 1997, Liu et al., 2000).

Furthermore the dentate nucleus is a critical part of Guillain-Mollaret triangle or myoclonic triangle which is an important feedback circuit of the brainstem and deep cerebellar nuclei, responsible for modulating the spinal cord motor activity.

It is important to emphasize that beyond the role of the cerebellum and the cerebellar dentate nucleus in the improvement and amplification of motor tasks, they play a crucial role in the procedure of learning, and high brain functions, by modifying the already learned tasks, and amplifying the new ones, always working in collaboration with the basal ganglia, the thalami, the brainstem nuclei and the cerebral cortex.

The cerebellum, as a whole and the dentate nucleus in specific, is a critical part in the distributed neural circuits participating not only in the motor function but also in autonomic, limbic and cognitive behaviours. Lesions of the motor cerebellum, mostly in lobules III-V in the anterior lobe and the secondary sensorimotor region in lobule VIII and the corresponding dentate nucleus, result in dysmetria of movement, however lesions of the cognitive and limbic cerebellum in the posterior lobe, represented in lobules VI, VIIA (including lobules VIIAf and VIIAt at the vermis, and crus I and crus II in the hemispheres) and VIIB, and possibly in lobule IX, and the corresponding area of the dentate nucleus, are followed by dysmetria in the realms of intellect and emotion (Schmahmann, 1991, 1997, 1998).

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