Chapter 6
The Olivocerebellar Tract

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Abstract Neurons in the inferior olive nucleus, the sole origin of cerebellar climbing fibers, project their axons to the cerebellum through the olivocerebellar tract. A single olivocerebellar axon gives rise to multiple climbing fibers (about seven in rat) which typically terminate into longitudinal compartments in the cerebellar cortex. These compartments match with the longitudinal striped arrangement of aldolase C-positive and -negative Purkinje cell subsets. As a result of this topographic arrangement, the olivocerebellar projection relays the synchronous activity of the electrically coupled adjacent inferior olive neurons to complex spike firing of Purkinje cells in a narrow longitudinal stripe. Olivocerebellar axons show a dynamic morphogenetic process. An immature axon has abundant terminal branches that innervate multiple Purkinje cells. Several terminal branches (climbing fibers) grows to eventually establishing a powerful one-to-one synaptic connection between a single climbing fiber terminal and a single target Purkinje cell. Furthermore, these axons are capable of strong compensatory re-innervation after lesion even in adult.

Keywords Inferior olive • Climbing fibers • Branching • Collaterals • Purkinje cells • Reinnervation • Compartments

6.1 Introduction

The olivocerebellar tract is the axonal path of inferior olive neurons, which project to the cerebellum. This projection system is peculiar in morphological, physiological and developmental aspects, which contribute significantly to characterizing the cerebellar system. In this short article, we summarize these aspects based on relevant studies, including our own work.

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D.L. Gruol et al. (eds.), *Essentials of Cerebellum and Cerebellar Disorders*,
DOI 10.1007/978-3-319-24551-5_6

6.2 Gross Morphology of the Olivocerebellar Tract

The inferior olive nucleus, located in the caudoventral medulla, or between rhombomeres 8–10, is a complex of multi-lamella structure packed with small-sized neurons with round somata and curved dendrites. All neurons in the inferior olive nucleus, except for a very small number of scattered GABAergic neurons, project to the cerebellum terminating as climbing fibers. The inferior olive is the sole origin of climbing fibers. Therefore, functionally, the inferior olive can be regarded as a part of the cerebellum.

The olivocerebellar tract is the bundle of axons of the inferior olive neurons projecting to the cerebellar cortex. The axons run medially crossing the midsagittal plane, and continuing through or above the contralateral inferior olive, before entering the white matter under the lateral surface of the medulla that connects to the inferior cerebellar peduncle (Sugihara et al. 1999). Prior to entering the cerebellum through the inferior cerebellar peduncle, the axons that terminate in the vermis pass through the rostral most part of the cerebellar peduncle dorsal to the superior cerebellar peduncle intermingled with the uncinate fasciculus and the ventral spinocerebellar tract. Other olivocerebellar axons pass through the conventional inferior cerebellar peduncle.

Upon entering the cerebellum, each axon gives rise to collaterals to the cerebellar nuclei and branches into multiple (seven on average in rat) branches that terminate on a single adult Purkinje cell as climbing fibers (Fig. 6.1). Thus, “climbing fibers” which were discovered by Ramón y Cajal are terminations of the multiple branches of the olivocerebellar axons. Besides giving rise to branches that terminate as climbing fibers, olivocerebellar axons also give rise to several thin collaterals mainly terminating in the granular layer with a small number of swellings. Synaptic contact and functional significance of these collaterals are not well clarified (Sugihara et al. 1999). The multiple climbing fibers originating from a single axon are usually distributed in a narrow longitudinal band-shaped area (Sugihara et al. 2001). The olivocerebellar axon’s longitudinal projection pattern is in contrast with the transversely wide projection pattern of mossy fiber axons (Quy et al. 2011).

6.3 Topography in the Olivocerebellar Tract

The entire olivocerebellar pathway is topographically arranged. The topography has been resolved in detail. The inferior olive is subdivided into many subareas, usually a portion of a single lamella. Neurons in each subarea of the inferior olive project topographically to a particular subarea in the cerebellar nuclei and a particular striped area in the cerebellar cortex (Sugihara and Shinoda 2004, 2007). These specific subareas in the cortex and nuclei are also topographically connected by the corticonuclear Purkinje cell projection (Sugihara et al. 2009). Specific subareas in the cerebellar nuclei also topographically project to a precise subarea in the inferior

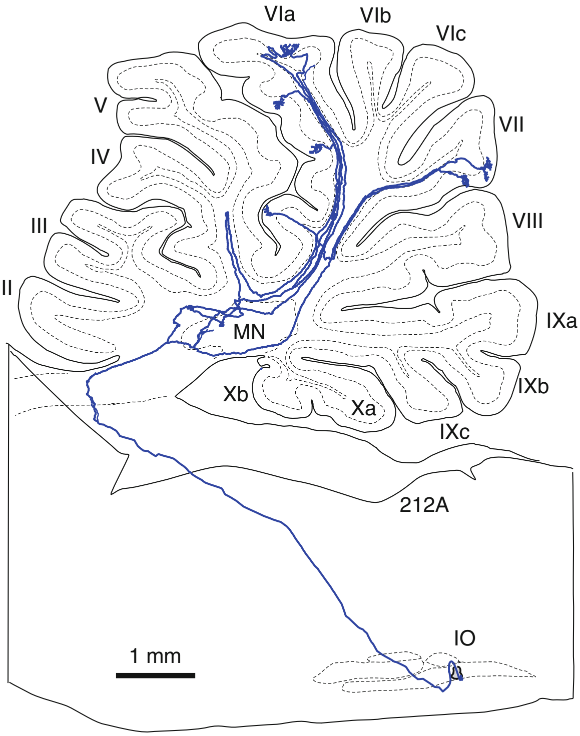

Fig. 6.1 Lateral view of a trajectory of a reconstructed single olivocerebellar axon. This axon originated from the medial and caudal part of the medial accessory olive, a subnucleus of the inferior olive, and terminated in lobules VI and VII in the vermis. Abbreviations, *II–Xb* lobule II – lobule Xb, *IO* inferior olive, *MN* medial nucleus

olive (Ruigrok and Voogd 1990). As a whole, a triangular topographic loop of neuronal connection is formed among subareas in the inferior olive, cerebellar cortex and cerebellar nuclei. Each set of topographically connected subareas in the cerebellar cortex, cerebellar nuclei and inferior olive is designated as a cerebellar module (Ruigrok 2011). A standing question of how many modules the entire cerebellum is divided into remains. Conventionally, modules A, B, C1, C2, C3 and D have been recognized (Voogd and Bigare 1980). However, most of these modules have been further subdivided into smaller modules (Ruigrok 2011; Sugihara et al. 2009). In addition, there are other modules that are not involved in these sets of modules in the flocculus and nodulus (Sugihara et al. 2004). Most cerebellar modules are consistent with the cortical compartments defined by the molecular expression profile in Purkinje cells (Sugihara and Shinoda 2004, Sugihara et al. 2009). More specifically, modules linked with aldolase C-positive and –negative compartments are all located in the caudoventral and rostrodorsal parts of the cerebellar nuclei, respectively (Sugihara and Shinoda 2007). Generally, modules are involved in different aspects of motor control and other cerebellar functions presumably due to different connections that each module has with other parts of the CNS (Horn et al. 2010).

6.4 Physiological Properties

The inferior olive neurons show oscillatory fluctuation of membrane potential at about 10 Hz (Llinas and Yarom 1986). This activity is synchronized among nearby neurons through dendro-dendritic gap junction (Llinas and Yarom 1986; Long et al. 2002). Excitatory input to the inferior olive, which originate from the somatosensory and vestibular systems in the medulla and spinal cord and from midbrain nuclei (see Sugihara and Shinoda 2004), may reset the oscillatory rhythm to evoke firing (Leznik and Llinás 2005). Olivary cells may fire at the peak of the oscillation of one action potential or a few action potentials in burst. The firing of an action potential (or a brief burst of action potentials) occurs solitary or in sequence with about 100 ms interval (Marthy et al. 2009). On the average, the firing frequency of the olivary neuron is one in a second (Eccles et al. 1966).

Firing of olivary neurons is conveyed all the way to the axon terminals, i.e., climbing fiber terminals, with a conduction time of approximately 4 ms (in rat, Sugihara et al. 1993). An action potential (or a brief burst of action potentials) in the climbing fiber produces a complex spike response in target Purkinje cells (Eccles et al. 1966). Olivocerebellar axon collaterals elicit an excitatory effect in the cerebellar nuclei (Llinás and Mühlethaler 1988; Blenkinsop and Lang 2011). However, its effect in the granular layer is yet unclear.

Since adjacent inferior olive neurons generally project to a narrow longitudinal striped area in the cerebellar cortex, it often matches with a single aldolase C stripe (Sugihara et al. 2007). Because of this property in the olivocerebellar projection, Purkinje cells arranged in the longitudinal band (width = ~0.25 mm) tend to fire complex spikes synchronously in awake and anaesthetized states (Sasaki et al. 1989; Lang et al. 1999). The band of complex spike synchrony generally matches with a single aldolase C stripe (Sugihara et al. 2007). This synchronous complex spike firing of Purkinje cells may be functionally important to form cerebellar output in the cerebellar nuclei (Blenkinsop and Lang 2011).

6.5 Morphological Development of the Olivocerebellar Tract

The immature olivocerebellar axonal projection is formed in the late embryonic stage when Purkinje cells are arranged in clusters before settling into striped compartments (Fujita et al. 2012). Basic topographic projection pattern is already established in the olivocerebellar bundle at this stage (Chédotal and Sotelo 1992). Axonal terminals form fine plexus with abundant branching known as the creeper terminal (Sugihara 2005). In accordance with the development of Purkinje cells in the second postnatal week, axonal branches are pruned to leave only those that begin to form a dense arbor around a single Purkinje cell soma (nest terminal). The nest terminals grow to a full climbing fiber terminal in the following few weeks. Besides the above local refinement of climbing fiber-Purkinje cell contact, the compartmental topographic projection pattern of axons may also be refined during development.

The above process of climbing fiber development leads to the establishment of a one-to-one synaptic connection between a single climbing fiber terminal and a single target Purkinje cell. A loss of granule cells and some genetic mutations prevent normal development of climbing fibers (Sugihara et al. 2000). Together with abnormal immature morphology of climbing fibers, impairment of one-to-one innervation can occur in these situations. A Purkinje cell may be innervated by multiple climbing fibers that originate from one olivocerebellar axon (pseudo-multiple innervation) of different olivocerebellar axons (true multiple innervation, Sugihara et al. 2000).

6.6 Morphological Plasticity of the Olivocerebellar Tract

Since the normal olivocerebellar projection is nearly exclusively contralateral, increase of ipsilateral projection can be used to measure plastic change in the projection. Such plastic change is seen after unilateral cut of the cerebellar peduncle in neonatal stage (Sugihara et al. 2003). A similar transcommissural olivocerebellar projection to the ipsilateral cerebellum is seen even in adult after administration of substances that can facilitate axonal plasticity (Dixon and Sherrard 2006).

Semitotal lesion of the inferior olive by neurotoxin 3-aminopyridine (3-AP) induce axonal sprouting of remaining olivary neurons to compensate the loss of many olivocerebellar axonal terminals (Rossi et al. 1991). Axonal sprouting occurs only in their terminal portions, mainly in the terminal arbor of climbing fibers and possibly also at the terminal of thin collaterals in the granular layer and cerebellar nuclei. However, no axonal sprouting from the stem axon in the cerebellar white matter was evident at least in adult (Aoki and Sugihara 2012).

6.7 Conclusion

The above is a brief summary of our knowledge on the morphological, physiological and developmental aspect of the olivocerebellar tract. The projection is highly organized and comprises an important element of the cerebellar system. The activity of the olivocerebellar system produces significant modulatory changes in Purkinje cell properties at the cellular and molecular levels, which were not the focus of this article. The general morphological properties of the olivocerebellar system summarized here are important when considering the effect of olivocerebellar activity on cerebellar function as a whole.

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