Chapter 39
Oscillation in the Inferior Olive Neurons: Functional Implication

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Abstract The inferior olives represent one of the omnipresent bulbar nuclei in vertebrates.

Their axonal projection to cerebellar nuclei, and its powerful synaptic input to Purkinje cells, (the so-called climbing fibers), serve as a powerful excitatory input deeply related to the timing of motor execution. Inferior olive neuronal activity is synchronized by intrinsic membrane oscillatory activity, via voltage dependant calcium channel activation, and their interconnectivity via neuronal electrical coupling.

39.1 The Olivocerebellar System

The inferior olive nuclei, a set of two symmetrical neuronal groups, located on each side of the bulbar region, are the cells of origin of the cerebellar climbing fiber system (Szentagothai and Rajkovits 1959) and are one of two major afferent pathways on to the cerebellar cortex (Cajal 1904). Their axons traverse the midline to enter the cerebellum via the inferior peduncle where they form climbing fiber contacts on Purkinje cells (PC) establishing the most powerful chemical synaptic contact in the central nervous system (Eccles et al. 1966). Each inferior olive (IO) neuron generates ten or so climbing fibers that, in addition to innervating the cerebellar cortex, also produce collateral branches that terminate in all cerebellar nuclei. The conduction times of climbing fibers are modulated such that their activation of Purkinje cells are independent of location and distance in the cerebellar cortex (Sugihara et al. 1993).

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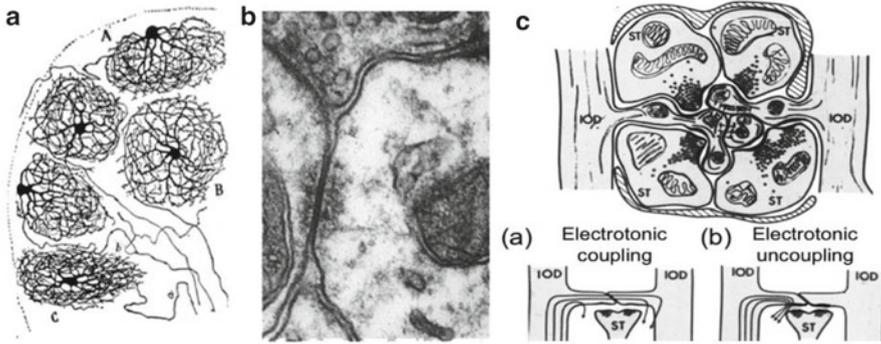e-mail: Rodolfo.llinas@med.nyu.edu

Fig. 39.1 Inferior olivary neurons. (**a**) Golgi stain of IO neurons in the IO nucleus. Note that cell bodies are located in the center of an spherically distributed dendritic tree, except when the cell body is next to the outer limit of the nucleus (Cajal 1888) (**b**) Electron micrograph showing gap junction at a point of contact between IO dendritic branches (Sotelo et al. 1974). The synaptic shunting occurs due to the increased membrane conductance. (**c**) Drawing of an IO glomerulus showing inhibitory synaptic terminal (ST) arising from the cerebellar nuclei. The glomerulus is the site of electrical junction junction. The diagrams below show electronic coupling between IO dendrites (*a*) and it's shunting by synaptic inhibition (*b*)

39.2   IO Single Cell Anatomy

IO neurons are characterized by their spherical dendritic trees (Fig. 39.1a). Within the IO nucleus their dendrites intermingle and are electronically coupled via gap junctions (Llinas et al. 1974; Sotelo et al. 1974) (Fig. 39.1b). The point of electrical junction between dendrites (Fig. 39.1c) is surrounded by inhibitory terminals arising from the cerebellar nuclei neurons. These junctions modulate electrotonic coupling by shunting current through an increase in membrane conductance (Llinas 1974; Lefler et al. 2014) (Fig. 39.1a–c).

39.3   Single Cell Electrophysiology

IO neurons fire spontaneously at 4–10 Hz and can exhibit rhythmic oscillatory activity near 10 Hz (Llinas and Yarom 1981a, b). The fact that IO neurons are electrically coupled and tend to fire in groups lends support to the proposal that climbing fibers have a timing function in motor coordination (Llinas 1974). Furthermore, simultaneous recordings from multiple PCs have shown that complex spikes occur synchronously within groups of PCs (Fig. 39.2).

The synchronous nature of IO oscillations have been shown to be important in determining the timing and spatial organization of motor sequences (Llinas 1988; Lampl and Yarom 1997; Welsh and Llinas 1997). In addition, a temporal correlation between the firing of the olivocerebellar system and the execution of movements
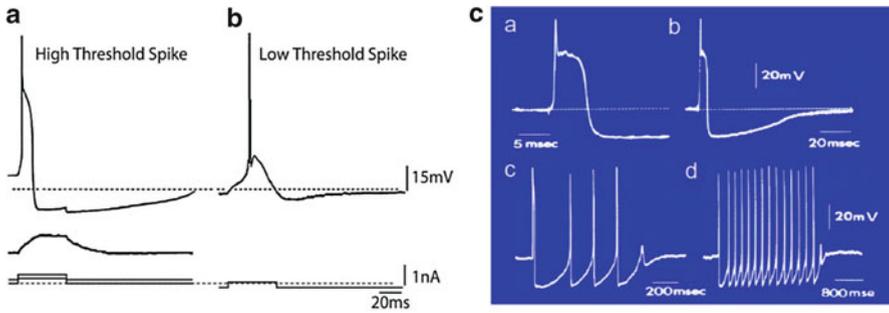
Fig. 39.2 Electrical characteristics of IO neurons. (**a**, **b**) Two levels of IO spike activation. (**a**) From the resting membrane potential (*dashed line*) the high threshold spike has a large afterdepolarization generated by activation of a P-type calcium current followed by a prolonged afterhyperpolarization activated by a calcium-gated potassium conductance (*top* trace). No spike is elicited when a lower intensity current pulse is applied (*middle* trace). *Bottom* traces show injected current pulses. (**b**) The low threshold calcium spike is generated by activation of a T-type calcium current when the cell is depolarized from a hyperpolarized membrane potential. (**c**) High threshold IO spikes (*a*, *b*) producing spontaneous spike firing involving both low and high threshold calcium currents (*c*, *d*). Action potentials shown in *a* and *b* are the first action potential in *c* and *d*, respectively

has been demonstrated experimentally (Welsh et al. 1995). The ability of the olivo-cerebellar system to generate synchronous rhythmic activity has been attributed to the intrinsic oscillatory properties of the IO neurons (Llinas and Yarom 1981a, b; Benardo and Foster 1986; Bal and McCormick 1997) and their electrotonic coupling (Llinas 1974; Sotelo et al. 1974; Llinas and Yarom 1981b; Lampl and Yarom 1997; Makarenko and Llinas 1998; Yarom and Cohen 2002). In particular, several types of voltage-dependent calcium and potassium conductances, in addition to those involved in action potential generation, enable IO cells to oscillate and fire rhythmically at 1–10 Hz. These conductances include a high-threshold calcium conductance (P-type channels), a low-threshold calcium conductance (T-type channels), a calcium-gated potassium conductance, and a hyperpolarization-activated cationic conductance (Llinas and Yarom 1981a, b, 1986; Bal and McCormick 1997).

39.4   Electrical Coupling

Electrical coupling between IC neurons has been assumed to play a crucial role in synchronizing IO oscillations and in generating groups of concurrently oscillating neurons (Llinas and Yarom 1986). Originally, the degree of coupling was proposed to be controlled by return glomerular inhibition (Llinas 1974) that served to shunt the electronic coupling between IO dendrites. The pathway was found to originate from cerebellar nuclear GABAergic neurons (Sotelo et al. 1986; de Zeeuw et al.
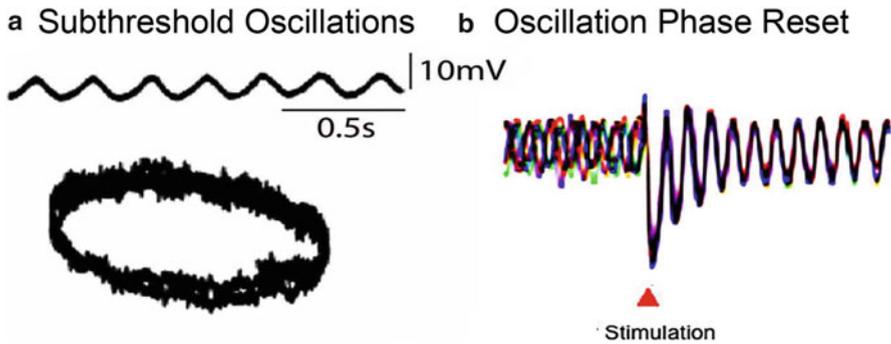
Fig. 39.3 Oscillations in IO cells recorded in vitro. (**a**) *Top trace*. Intracellular recording from IO neurons demonstrate regular the existence of spontaneous subthreshold membrane potential oscillations. (**a**) *Bottom*. The oscillation is regular enough in amplitude and frequency that a Lissageu figure could be generated. (**b**) A second property, quite fundamental to IO function is the ability to reset its phase following extracellular stimulation. Note that extracellular stimulation only modified the phase of the spontaneous oscillations without affecting their amplitude or frequency. (Superposition of six individual intracellular traces of stimulus-evoked oscillations reset) (Modified from Choi et al. 2010)

1989, 1996; Fredette and Mugnaini 1991; Medina et al 2002) and, surprisingly, represent almost 50 % of the total neuronal population of the cerebellar nuclei.

39.5   Membrane Potential Subthreshold Oscillation and Phase Resetting

In addition to uniform membrane potential oscillatory properties, IO neurons have the unique ability to reset their oscillatory phase when activated (Leznik et al. 2002; Lefler et al. 2013).

The functional significance of the oscillatory properties illustrated in Fig. 39.3 is an increased probability of PC complex spike activation relating to rapid recovery of motor execution following stumbling, or other unpredicted motor events.

39.6   Pathology

The single neurological condition related to the inferior olive is IO hypertrophy, associated with large synchronous movements of both midline musculature (palatal myoclonus) and multi-limb abnormal motricity especially in progressive supranuclear palsy.

39.7   Functional Implications

Four main issues are central of IO neurons: (1) their subthreshold oscillatory properties, relating to the control of motor timing. (2) The intrinsic electrical properties with electrical coupling allowing neuronal synchronization clusters. (3) The electronic decoupling by inhibition and (4) the resetting of oscillatory phase by synaptic input. These four elements allow simultaneous temporal control supporting rapid correction such as on the fly recovery from stumbling.

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