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Parasagittal Zones in the Cerebellar Cortex Differ in Excitability, Information Processing, and Synaptic Plasticity

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Abstract At the molecular and circuitry levels, the cerebellum exhibits a striking parasagittal zonation as exemplified by the spatial distribution of molecules expressed on Purkinje cells and the topography of the afferent and efferent projections. The physiology and function of the zonation is less clear. Activity-dependent optical imaging has proven a useful tool to examine the physiological properties of the parasagittal zonation in the intact animal. Recent findings show that zebrin II-positive and zebrin II-negative zones differ markedly in their responses to parallel fiber inputs. These findings suggest that cerebellar cortical excitability, information processing, and synaptic plasticity depend on the intrinsic properties of different parasagittal zones.

Keywords Parasagittal zones · Cerebellar cortex · Parallel fibers · Purkinje cells · Zebrin II

Introduction

Purkinje cells (PCs), the sole output neurons of the cerebellar cortex, express a multitude of molecules in either a zebrin II-positive or zebrin II-negative parasagittal banding pattern [1, 2]. Both the climbing fiber projection from the inferior olive and the PC projection to the cerebellar nuclei are organized in matching parasagittal zones [3]. Mossy fibers also terminate in longitudinal zones. Climbing and mossy fiber afferents show spatial correspondence with the molecular markers [1]. However, the functional implications of this parasagittal architecture remain elusive [1]. While cerebellar afferents generate parasagittally oriented responses in the cerebellar cortex [1] and synaptic plasticity appears to vary among zones [4], a greater understanding is needed of the physiological properties of the parasagittal zones and how any differences relate to the underlying molecular and cellular architecture. Studies using flavoprotein optical imaging are helping to shed light on the physiological characteristics of the parasagittal zones.

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Parasagittal Organization of Molecular Layer Inhibition

Flavoprotein imaging revealed that low-frequency stimulation (10 Hz) of parallel fibers (PFs) evokes not only the expected "beam" of increased fluorescence along the activated PFs but also parasagittal bands of decreased fluorescence [5]. Where the bands cross the beam, there is a relative decrease in fluorescence. Blocking $GABA_A$ receptors abolishes the bands of decreased fluorescence [5, 6]. Furthermore, PF stimulation evokes a decrease in simple spike firing in PCs located within an inhibitory band but not in PCs located between the bands. Also, intracellular Ca^{2+} decreases within the bands. Together, these findings demonstrate that the bands of decreased fluorescence are due to GABAergic molecular layer inhibition that generates both "off-beam" inhibition lateral to the beam and local "on-beam" inhibition [5].

The inhibitory bands are structural, extending across a folium and align with zebrin II-positive bands [5]. The inhibitory bands are evoked by peripheral stimulation (e.g., stimulation of the ipsilateral vibrissal pad) and modulate the responses to peripheral stimulation, suggesting a role in controlling the spatial patterning of cerebellar cortical activity. Although the signaling mechanism that generates the parasagittal inhibition is not known, newer findings suggest a key role for excitatory amino acid transporter type 4 (EAAT4) [7].

Importantly, EAAT4 is expressed parasagittally on PCs in zebrin II-positive bands [1]. The inhibitory bands may have implications for cerebellar disease. In a transgenic mouse model of spinocerebellar ataxia type 8, the inhibitory banding pattern is lost as is the normal responsiveness to $GABA_A$ antagonists [6]. The reduction in molecular layer inhibition likely disrupts cerebellar cortical function and contributes to the striking motor phenotype in SCA8 mice.

Parasagittal Organization of Long-latency Patches

Flavoprotein imaging uncovered another functional parasagittal compartmentalization. In addition to the beam-like response at a short latency, high-frequency PF stimulation evokes patches of increased fluorescence along the beam at 20–25 s latencies [8]. Consistent with the dependency on high-frequency PF stimulation, these long-latency patches are abolished by type 1 metabotropic glutamate receptor ($mGluR_1$) antagonists. Ionotropic glutamate receptor antagonists have no effect. The long-latency patches are evoked in zebrin II-positive parasagittal bands. The long-latency patches reflect the release of Ca^{2+} from intracellular stores as blockers of phospholipase C β (PLCβ) and ryanodine receptors completely suppress the long-latency patches. The long-latency patches exhibit a robust, $mGluR_1$-dependent long-term potentiation to high-frequency PF stimulation demonstrating that synaptic plasticity differs among the zones [8, 9].

The finding that the long-latency patches are mediated by $mGluR_1$ receptors and the release of internal Ca^{2+} suggests a possible mechanism. Both $mGluR_1$ receptors and the downstream signaling cascade in PCs are organized parasagittally [10]. The PLCβ3 isoform is found on PCs in zebrin II-positive bands while the PLCβ4 isoform and the splice variant, $mGluR_{1b}$, are found on PCs in complimentary zebrin II-negative bands [10]. The $mGluR_{1b}$ isoform has less potency in coupling to the PLC downstream signaling pathway than does the $mGluR_{1a}$ isoform and these differences in potency may be involved in the expression and unique properties of the long-latency patches [8].

In summary, parasagittal zones respond differentially to PF stimulation, including excitability and synaptic plasticity that likely underlies distinct functions. The next challenge is to understand the implications for cerebellar function.

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