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Plasticity of the axon initial segment in the mouse barrel cortex

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The axon initial segment (AIS) is a highly specialized microdomain at the proximal axon of neurons. It is characterized by a local protein scaffold that tethers a high density of sodium channels to the axonal membrane, making it the primary site of action potential (AP) initiation. A decade ago, two hallmark publications uncovered a phenomenon called AIS plasticity, where changes in AIS length and / or location in respect to the soma occurred in response to changes in synaptic input. This plasticity was in turn associated with alterations to intrinsic cellular excitability, leading to the hypothesis that the AIS plays a homeostatic role in the regulation of neuronal input - output function. At that point, it remained unclear whether AIS plasticity can occur under physiological conditions in behaving animals. In the present thesis, it was investigated whether AIS plasticity occurs in the developing and adult mouse somatosensory system and whether it can be altered by sensory deprivation. Using multichannel immunofluorescence, confocal microscopy, Western blot analysis, and whole-cell patch clamp recordings, structural and functional AIS changes were investigated in pyramidal neurons of layer II/III and layer V of the barrel field in primary somatosensory cortex (S1Bf), which consists of the cortical area representing the mouse whisker pad. During early postnatal development, AIS length significantly elongated and shortened in distinct time windows and was associated with changes in protein expression levels. Additionally, an increase in intrinsic excitability, neuronal firing properties and synaptic input were measured. Using whisker trimming as a deprivation paradigm, it was found that the developmental plasticity was in part dependent on sensory input, as long-term whisker trimming lead to an increased AIS length and increased excitability in layer II/III pyramidal neurons. Interestingly, a lower AP threshold was directly correlated with longer AIS, suggesting a link between structure and function Strikingly, the same deprivation period was able to elicit AIS plasticity in adult mice. Lastly, restoration of sensory input by regrowth of whiskers rescued normal AIS length, indicating the lack of a critical period of sensory input for developmental AIS plasticity. Taken together, the findings support the hypothesis that AIS plasticity serves as a homeostatic mechanism to regulate neuronal excitability in response to prolonged changes of synaptic input.