Session 686 - Mechanisms of Synaptic and Neuronal Plasticity

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686.01 / G48 - Unveiling neuronal differences in chloride extrusion capacity

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Presenter at Poster
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Poster

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Abstract
The strength of synaptic inhibition in the adult neurons relies on their capacity to maintain intracellular chloride (Cl^-) concentration, and the main regulator of intracellular Cl^- concentration is the K^+-Cl^- co-transporter 2 (KCC2). As KCC2 function is not homogenous across the CNS, these differences may significantly affect the integration of inhibitory inputs. Here we combined different approaches to explore the impact of variable Cl^- extrusion capacities in nociceptive neurons of the superficial spinal dorsal horn, which includes projections neurons in lamina I and interneurons in lamina II. By imposing a Cl^- load, E_{GABA} recorded in lamina I was more depolarized than in lamina II, indicating a weaker Cl^- extrusion capacity in the former. Notably, we did not observe any difference when E_{GABA} was measured under low chloride conditions (including by gramicidin-perforate patch clamp), suggesting that a Cl^- load is required to detect apparently subtle differences. These data were replicated by performing Cl^- imaging in MQAE-loaded spinal cord slices. Indeed, when synaptic activity was completely blocked, no interlaminar differences in Cl^- concentration were detected in dorsal horn, conversely in presence of normal synaptic activity a clear gradient in Cl^- concentration was observed. The gradient was further increased by enhancing synaptic activity with capsaicin. We confirmed that the lower Cl^- extrusion capacity in lamina I neurons affects synaptic inhibition in an activity dependent manner by stimulating high frequency inhibitory activity. These experiments showed that under sustained inhibitory input, lamina I neurons accumulate Cl^- faster than lamina II. Functional experiments were mirrored by immunohistochemical analysis of KCC2 expression which confirmed a lower level of KCC2 in lamina I under the control of TrkB receptor signaling. Following nerve injury, KCC2 expression strongly decreased in both laminae, but still KCC2 in lamina I was the lowest. Our computer simulation indicated that such a low KCC2 level in lamina I of nerve injured rats fails to maintain Cl^- gradient when synaptic activity increases. Thus, constitutive differences of KCC2 activity has a strong impact on the efficiency of enhanced inhibition under both normal and pathological settings.