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Sala Seminari - VIMM

Title of the seminar: A diurnal rhythm of intracellular chloride in pyramidal neurons affects cortical dynamics and signal processing in the cortex

Abstract: Living organisms navigate through a cyclic world: activity, feeding, social interactions are all organized along the periodic daily rhythm synchronized by external environmental cues and brain function varies markedly through the day. An obvious contributory factor is the large change in the level of sensory drive from day to night. Less obvious is the degree to which intrinsic neuronal activity might vary, yet there is abundant clinical data supporting the idea that many functional neurological and psychiatric conditions have strong diurnal patterns. Additionally, basic animal research has further documented differences in the level of neuronal firing and synaptic function between periods of rest and activity. Surprisingly, we have no clear understanding of the cellular basis of the diurnal regulation of neuronal activity, but we should expect the operation of some mechanisms acting on the excitation/inhibition interplay.

The main inhibitory synaptic currents, gated by gamma-aminobutyric acid (GABA), are mediated by Cl--conducting channels, and are therefore sensitive to changes of the chloride electrochemical gradient. As GABAergic activity dictates neuronal firing, the intracellular chloride concentration ([Cl-]i) plays a major role in the regulation of neuronal activity. We measured [Cl-]i with 2-photon imaging of a genetically encoded Cl- sensor in anaesthetized young adult mice, and we found a large physiological diurnal fluctuation of baseline [Cl-]i in pyramidal neurons. This equates to a ~15mV positive shift in chloride equilibrium potential at times when mice are typically active (midnight), relative to their sleep phase (midday).

The cyclic regulation of [Cl-]i impacts on cortical processing since visually evoked gamma-band oscillations are reduced during the active phase, as it should be expected by the decreased capacity of inhibition of synchronizing large neuronal ensembles. Importantly, this can be rescued by the NKCC1 blocker bumetanide that also restores [Cl-]i to the daily levels. Finally, we determined that during the high [Cl-]i period, the cortex is more sensitive to the pro-epileptic drug 4-ammino pyridine, and again, this enhanced epileptogenicity is rescued by bumetanide.

These results strongly support the idea that the diurnal cycle of cortical excitability is mediated by a previously unknown change of GABAergic transmission due to a cyclic change of [Cl]i homeostasis in cortical pyramidal neurons.