Simulated relations of molecular, cellular, and neuronal network dynamics in a hippocampal network

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The Hyperpolarization-activated cation (HCN) channel (Ih current) has been hypothesized to facilitate short-term memory storage in the brain via a cascade of signalling events involving second messengers including protein kinases and intracellular calcium accumulation. Interestingly, this memory mechanism is effected not through synaptic changes (Hebbian rule) but via alterations in the dynamics of the network, two scales above the underlying molecular level. Pathologically, HCN plays a similar cross-scale role in the production of epileptiform activity.

We have designed a network model utilizing cells with an HCN channel activated by the intracellular level of calcium-bound cAMP. We asessed influences between network dynamics and intracellular signalling, to isolate the source or sources need for emergence of memory representations. The network consisted of 800 five-compartment pyramidal cells, 200 one-compartment basket cell interneurons, and 200 one-compartment oriens lacunosum-moleculare (O-LM) interneurons. All cells contained leak current, transient sodium current and delayed rectifier current. Pyramidal cells contained IA potassium current and both pyramidal and OLM cells had Ih current. Cell classes were interconnected probabilistically with AMPA/NMDA, and GABAA synapses.

At baseline, OLM cells fired preferentially at the theta frequency, causing periodic inhibition/disinhibition of pyramidal cells. The network also displayed emergent gamma rhythms. Lowering the HCN channel conductance of pyramidal cell dendrites delayed pyramidal cell synchronization onset. This in turn delayed the emergence of pyramidal interneuron network gamma (PING; in PING, pyramidal cells drive basket cells via AMPA/NMDA receptors and basket cells in turn inhibit the pyramidal cells through GABAergic synapses). Changes in HCN channels modulated hippocampal network rhythms and altered network synchrony. We predict that hippocampal networks may become more prone towards epilepsy with alterations in the level of HCN channel expression. These effects could be tested *in-vivo* and *in-vitro*, under neuromodulatory or pharmacological control.