

Calcium regulation of HCN supports persistent activity associated with working memory: a multiscale model of prefrontal cortex

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“Bump attractors” are hypothesized to enable short-term memory via persistent activation in prefrontal cortex (PFC). They have been primarily assessed in terms of electrical mechanisms, without attention to molecular events. To assess this contribution, we developed a multiscale model going from molecular to network levels, assessing contribution of calcium (Ca) release from endoplasmic reticulum (ER) to Ca regulation of hyperpolarization-activated cyclic-nucleotide gated channels (HCN) thought to provide continued activity via rebound. The network had 800 neurons arranged in 6 cortical layers. Neurons included pyramidal (E) and 2 interneuron (I) types, with Na, K, Ca, and HCN channels. Cells connected with AMPA/NMDA/GABAA synapses using data from primary motor cortex (M1). Metabotropic glutamate receptors (mGLUR) produced inositol triphosphate (IP3). Intracellular components included: Ca, Ca buffers, ER Ca stores, IP3, ER IP3 receptors (IP3Rs; release ER Ca), sarco/ER Ca-ATP-ase pumps (SERCA; pump Ca into ER), Ca extrusion pumps, and E cell HCN regulated by Ca-bound protein kinase. Stimulus-induced depolarization led to Ca influx via NMDA/L-type channels. After a delay, mGLUR activation led to ER Ca release via IP3Rs. These factors increased HCN conductance and firing (0.5-3.5 Hz), lasting 5-10 s. Non-stimulated cells were suppressed from more inhibition via extra drive from activated E to I cells. The network encoded stimulus strength in the ratio of firing rates of stimulated vs non-stimulated neurons (firing-rate distinction; FRD). Free Ca regulated FRD and was manipulated via parameter changes, e.g.,: 1. Ca extrusion pump time constant (τ) had an inverted-U relationship with FRD: slow τ caused Ca to saturate all neurons; fast τ prevented Ca from having time to regulate neurons. 2. Increasing concentration or binding rate of Ca buffers reduced free Ca and its regulation of HCN, thereby reducing FRD. 3. ER Ca stores modulated network excitability: both IP3R and SERCA density correlated positively with FRD, since both allow mGLUR stimulation to retrieve more ER Ca. The model showed a complex interplay among synaptic weights, excitation/inhibition network balance, altered firing rates and depolarization, changes in calcium levels, altered regulation of HCN, and FRD. These interlocking cascades of effects demonstrated that a regime of inhibition allowed the intracellular calcium levels that effected persistent activity in a population-specific manner. An important consequence of the interplay of factors was the existence of more than one pathway that could bring about persistent activity, demonstrated with both AMPA/NMDA and mGLUR stimulation. The existence of multiple pathways is a critical feature of biological systems, which are remarkably resistant to disruption -- several electrochemical interactions could lead to the persistent activity associated with working memory.