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CALCIUM REGULATION OF HCN CHANNELS SUPPORTS PERSISTENT ACTIVITY IN A MULTISCALE MODEL OF NEOCORTEX

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Abstract—Neuronal persistent activity has been primarily assessed in terms of electrical mechanisms, without attention to the complex array of molecular events that also control cell excitability. We developed a multiscale neocortical model proceeding from the molecular to the network level to assess the contributions of calcium (Ca^{2+}) regulation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in providing additional and complementary support of continuing activation in the network. The network contained 776 compartmental neurons arranged in the cortical layers, connected using synapses containing AMPA/NMDA/$GABA_A$/$GABA_B$ receptors. Metabotropic glutamate receptors (mGluR) produced inositol triphosphate (IP_3) which caused the release of Ca^{2+} from endoplasmic reticulum (ER) stores, with reuptake by sarco/ER Ca^{2+}-ATP-ase pumps (SERCA), and influence on HCN channels. Stimulus-induced depolarization led to Ca^{2+} influx via NMDA and voltage-gated Ca^{2+} channels (VGCCs). After a delay, mGluR activation led to ER Ca^{2+} release via IP_3 receptors. These factors increased HCN channel conductance and produced firing lasting for ~1 min. The model displayed inter-scale synergies among synaptic weights, excitation/inhibition balance, firing rates, membrane depolarization, Ca^{2+} levels, regulation of HCN channels, and induction of persistent activity. The interaction between inhibition and Ca^{2+} at the HCN channel nexus determined a limited range of inhibition strengths for which intracellular Ca^{2+} could prepare population-specific persistent activity. Interactions between metabotropic and ionotropic inputs to the neuron demonstrated how multiple pathways could contribute in a complementary manner to persistent activity. Such redundancy and complementarity via multiple pathways is a critical feature of biological systems. Mediation of activation at different time scales, and through different pathways, would be expected to protect against disruption, in this case providing stability for persistent activity.

Key words: hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, I_h, persistent activity, neocortex, computer simulation, multiscale modeling.

INTRODUCTION

Computational models of functional neural activity patterns in neuronal networks have traditionally focused primarily on the role of electrical activity in shaping these patterns, neglecting the rich chemical complexity that complements electrical signaling in neurons. Persistent neuronal activity, lasting several seconds, has been proposed to underlie several functions in the central nervous system including short-term working memory (Goldman-Rakic, 1995; Braver et al., 1997; Kane and Engle, 2002) and motor preparatory set (Ames et al., 2014). Additional functions probably also depend on similar mechanisms subserved by the "UP state," identified originally in sleep and in slice but now also demonstrated in the visual cortex (Cossart et al., 2003) and other brain areas (Major and Tank, 2004; Poskanzer and Yuste, 2011; Oikonomou et al., 2014; Zhou et al., 2015). Computational models of network persistent activity that have been proposed largely rely on continued interactions of neurons maintaining activity in one another through

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Abbreviations: Ca^{2+}, calcium; E cell, excitatory cell; E2/3 or E2, excitatory cell of layer 2/3, similarly E5, E6; E/I balance, excitation/inhibition balance; ER, endoplasmic reticulum; FRD, firing-rate distinction; FS cell, fast-spiking soma-targeting interneuron; HCN channel, hyperpolarization-activated cyclic nucleotide-gated channel (with I_h current); IP_3, inositol triphosphate; IP_3R, IP_3 receptor; I cell, inhibitory cell; I2L, LTS inhibitory cell of layer 2/3 (similarly I5L, etc.); I2, FS inhibitory cell of layer 2/3 (similarly I5, etc.); LTS cell, low-threshold spiking dendrite-targeting interneuron; mGluR, metabotropic glutamate receptor; PYR, neocortical pyramidal neuron; RxD, reaction-diffusion; SERCA, sarco/ER Ca^{2+}-ATP-ase pumps; VGCC, voltage-gated calcium channel.

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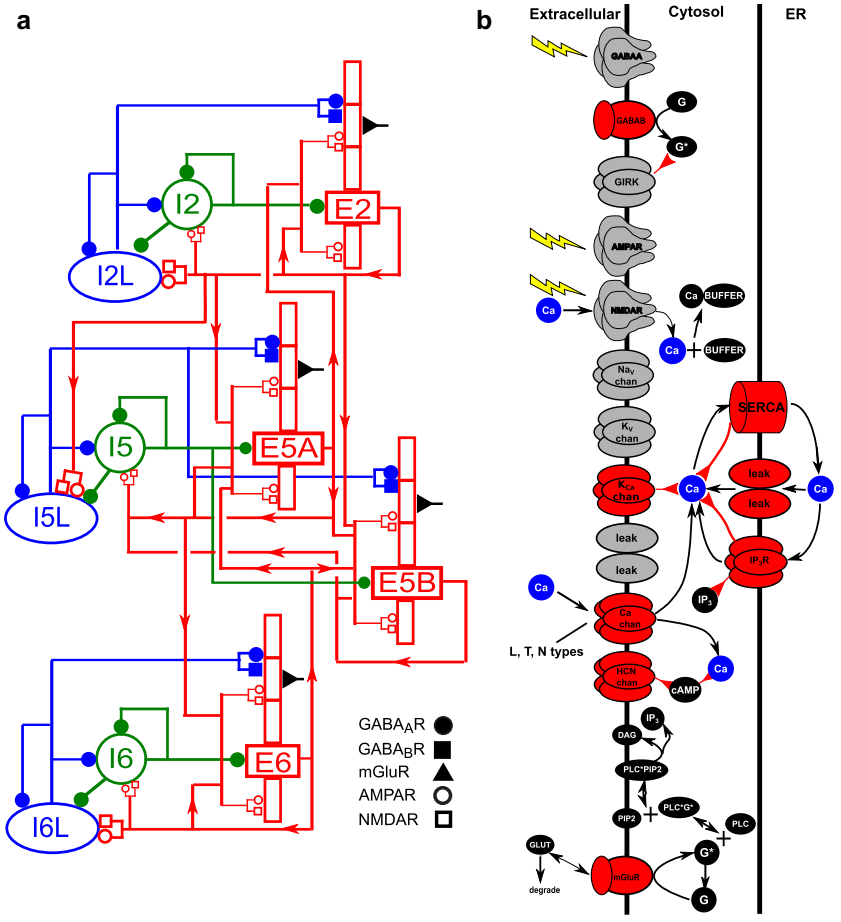

Fig. 1. Model schematics. (A) Schematic of neocortical network architecture. Red rectangles represent populations of 5-compartment excitatory cells (largest rectangle represents soma, three apical-dendrite compartments point upward, basal dendrite compartment points downward); green circles represent fast-spiking interneurons; blue ellipses represent low-threshold firing interneurons. Lines (with arrows) indicate connections between the populations. E cells synapse with AMPAR/NMDARs; I cells synapse with $GABA_A$ R/$GABA_B$Rs. Filled circles represent $GABA_A$R/$GABA_B$Rs. Open circles and rectangles represent AMPAR/NMDARs. (B) Schematic of chemical signaling in pyramidal cells showing fluxes (black arrows) and second- (and third- etc.) messenger modulation (red back-beginning arrows). We distinguish membrane-associated ionotropic and metabotropic receptors and ion channels involved in reaction schemes in red (in reality, it is likely that almost every membrane-bound protein is modulated). External events are represented by yellow lightning bolts – there is no extracellular diffusion; the only extracellular reaction is glutamate binding, unbinding and degradation on mGluR1 after an event. Ca^{2+} is shown redundantly in blue – note that there is only one Ca^{2+} pool for extracellular, 1 pool for cytoplasmic, and 1 pool for ER. (PLC: phospholipase C, DAg: diacyl-glycerol, cAMP: cyclic adenosine monophosphate; PIP_2: phosphatidylinositol 4,5-bisphosphate). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mutual synaptic activation (Lisman et al., 1998; Wang, 1999; Wang, 2001; Lim and Goldman, 2013, 2014).

A separate class of studies has focused on modulation of the single neuron via chemical signaling sequences (Egorov et al., 2002; Loewenstein and Sompolinsky, 2003; Fall et al., 2005; Fall and Rinzel, 2006; Fransén et al., 2006; Ramakrishnan and Bhalla, 2008; Sidiropoulou and Poirazi, 2012; Honnuraiah and Narayanan, 2013; Ashhad et al., 2015; Tiganj et al., 2015). Many of these have demonstrated that calcium (Ca^{2+}) signaling pathways underlie a large repertoire of cell dynamics that complements electrical signaling – interactions of chemophysiology and electrophysiology. Ca^{2+} pathways can enable persistent activity at the single-cell level through effects on hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (with I_h current) (Destexhe et al., 1996; Winograd et al., 2008). This molecular/cellular mechanism has also been proposed as one underpinning for working memory (Thuault et al., 2013). HCN channels are an important control point (Burdakov, 2005) in other respects as well, regulating somatic and dendritic responsivity and having effects on network oscillations (Kocsis and Li, 2004; Neymotin et al., 2013).

These network and molecular views of persistent activity and memory are entirely complementary. Indeed, it would be remarkable if multiple scales and multiple mechanisms were not involved in such a basic phenomenology (Lytton et al., 2014). In this paper, we combine these observations through a multiscale computer model of the neocortex that ranges in scale from intracellular Ca^{2+} dynamics, up through cellular electrochemical coupling and on to network activity. Intracellular species simulated include Ca^{2+}, inositol triphosphate (IP_3), Ca^{2+} buffers, and cAMP.

Both single cells and the network produced persistent activity following excitatory stimulation. Metabotropically, the stimulus triggered an intracellular signaling cascade