Dopamine 2016
Vienna, 5–8 September 2016

MEETING ABSTRACT

A18.10

Contribution of synchronized GABAergic neurons to dopaminergic neuron firing and bursting
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In the ventral tegmental area (VTA), interactions between dopamine (DA) and γ-aminobutyric acid (GABA) neurons are critical for regulating DA neuron activity, and thus DA efflux throughout the brain. We explored how time-patterned activity of the inhibitory network modulates the dynamics of DA neuron firing. For this purposes, we developed a local circuit model of the VTA, which is based on feed-forward inhibition and recreates canonical features of the VTA neurons. In particular, the DA neuron fires at relatively low firing rates spontaneously and when driven by tonic AMPA receptor activation and increases the frequency to the levels observed in bursts following application of NMDA or pauses in GABA receptor stimulation (by disinhibition). Our simulations challenge the classical view that GABA neurons exclusively reduce DA neuron firing and bursting. We found that a synchronous GABAergic input enables an increase in DA neuron firing and bursting. Distinct from previous mechanisms, the increases were not based on a lowered firing rate of GABA neurons or weaker hyperpolarization by the GABA receptor synaptic current. A mechanism of GABA-mediated increases in firing is based on a dynamic reduction of a long-lasting hyperpolarization due to the SK-type Ca2+-dependent K+ current. Our model suggests that GABA-mediated hyperpolarization replaces the hyperpolarization produced by the SK current; however, the pulsatile pattern of this inhibitory input allows the DA neuron to fire during the pauses. Furthermore, we found that DA neuron bursting and transient DA release can be produced in the absence of bursty glutamatergic input, if the neuron receives transiently synchronized GABA input. This suggests that rewarding stimuli need not be encoded in increases in the afferent excitatory drive directly to DA neurons. The presented data add to a number of studies that explored how synchronous activity of GABA interneurons alters the computational properties of neural networks. The biological relevance of our modeling prediction was validated by calculating shuffle-corrected cross-correlograms between pairs of simultaneously recorded putative VTA GABA neurons. We observed a large number of pairs (76 of 197) that exhibit millisecond-timescale synchrony, which is, according to our modeling results, more than necessary to achieve an increase in DA neuron burstiness. Our results provide a mechanistic understanding of the diverse mechanisms whereby GABA neurons regulate DA neuron burst firing.

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This work was supported by NIAAA (grant R01A022821), ANR-13-NEUC-0003-01, IdEx ANR-11-0001-02 PSL and LabEx ANR-10-LABX-0087 (France), Russian Foundation for Basic Research (grant 14-02-00916-a).