Role of VTA GABAergic neurons in high-frequency firing of dopaminergic neuron

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Dopaminergic (DA) neurons play a key role in reinforcement learning and motivation system. In particular, their activity encodes reward value [1]. DA neurons show three types of behavior: a tonic mode (spontaneous spiking) providing a background level of DA concentration; a phasic (high frequency) bursts corresponding to positive rewards; and a silent state (spiking is almost absent) in the case of a negative reward value. *In vitro* DA neurons are active spontaneously and their high frequency activity may be evoked by bath application of NMDA agonists (see, for example, [2]). *In vivo* tonic DA neuron firing is a result of balanced the NMDA and GABA inputs [3,4]. To evoke high frequency bursts, one may to disinhibit DA neurons (to suppress GABA neurons activity) or to increase the glutamatergic inputs. On the other hand there is a body of evidence that GABA neurons may play a more complex role in DA firing beyond only tonic inhibition and disinhibition processes. In particular, we have shown that simultaneous activation of GABA and AMPA receptors may change the DA neuron excitability type (from type I to II) allowing for DA neuron synchrony and increased DA release [5]. Furthermore recent data suggest "paradoxical" excitations of the DA neurons by GABA inputs [6-8] and their definitive role in producing bursts as opposed to elevated tonic frequencies [7,8]. We hypothesize that one of the possible mechanisms explaining such "paradoxical" effects on DA neurons activity is based on the short time synchronization of GABA networks. The VTA interneurons may be synchronized by multiple mechanisms: e.g. glutamatergic inputs from the PFC, phasic activation of nicotinic acetylcholine receptors among others. In this case the synchronized population of GABA neurons generates a strong nearly periodic input pulse train "forcing" synchronization of DA neurons on the frequency of GABAergic neurons [9,10]. In summary our computational work points out how structured GABA input to the DA neurons may lead to increased burst firing in sculpt the ensuing DA release.

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