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Review

Disinhibition in learning and memory circuits: New vistas for somatostatin interneurons and long-term synaptic plasticity

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A B S T R A C T

Neural circuit functions involve finely controlled excitation/inhibition interactions that allow complex neuronal computations and support high order brain functions such as learning and memory. Disinhibition, defined as a transient brake on inhibition that favors excitation, recently appeared to be a conserved circuit mechanism implicated in various functions such as sensory processing, learning and memory. Although vasoactive intestinal polypeptide (VIP) interneurons are considered to be the main disinhibitory cells, recent studies highlighted a pivotal role of somatostatin (SOM) interneurons in inhibiting GABAergic interneurons and promoting principal cell activation. Interestingly, long-term potentiation of excitatory input synapses onto hippocampal SOM interneurons is proposed as a lasting mechanism for regulation of disinhibition of principal neurons. Such regulation of network metaplasticity may be important for hippocampal-dependent learning and memory.

1. Introduction

Cortical neuronal networks are highly organized brain structures that comprise a majority of glutamatergic excitatory pyramidal cells (PC) and a 15–20% fraction of GABAergic cells. These inhibitory interneurons finely tune and regulate neuronal interaction between PCs, allowing the emergence of complex cognitive functions. In these networks, both PCs and interneurons receive a high level of inhibition, giving to GABAergic cells the ability to control principal neurons both by direct inhibitory and disynaptic disinhibitory mechanisms. Disinhibition is defined as transient and selective brakes on inhibition that favors excitation (Letzkus et al., 2015). Compared to principal neurons, inhibitory interneurons are very diverse, endowed with distinct morphologies, patterns of connectivity, physiological properties and molecular pattern of protein expression, making for many different subtypes. This high level of heterogeneity has pushed investigations to unravel complementary functional roles of distinct interneuron classes (Kepecs and Fishell, 2014).

Two major non-overlapping GABAergic cell subtypes express parvalbumin (PV) and SOM, and provide powerful inhibition onto PC perisomatic and dendritic compartments, respectively. Another interneuron class expresses VIP and appears to be specialized in inhibiting other inhibitory interneurons, conferring them a major role in disinhibition of PCs (Acsady et al., 1996; Gulyas et al., 1996; Francavilla et al., 2015). However, a growing body of evidence indicates that other subtypes of interneurons are endowed with such properties, especially SOM interneurons. Indeed, due to their dendritic-targeting inhibition and to their facilitating synaptic dynamics, SOM interneurons are well suited to fulfill PC disinhibition. Moreover, SOM interneurons display a broad range of synaptic plasticity (Pelletier and Lacaille, 2008; Kullmann et al., 2012) that was recently suggested to provide a mechanism for regulation of disinhibition (Vasuta et al., 2015).

Here we describe works that illustrate the classical model of disinhibition by VIP interneurons, while highlighting other recent studies which propose an alternative view in which SOM interneurons activity and synaptic plasticity play a more central role in modulation of principal cells disinhibition in the neocortex, amygdala and hippocampus.

2. Neocortex

In neocortical networks, PCs receive a dense and powerful inhibitory innervation from both translaminar and intralaminar interneurons. The latter provides what has been termed a “blanket inhibition” and refers to a dense and unspecific inhibition of local PCs by SOM, PV and Chandelier interneurons (Karnani et al., 2014). PV, SOM and VIP cells are the three largest and non-overlapping classes of molecularly distinct interneurons in neocortex (Kepecs and Fishell, 2014). The pattern of interneuron interconnectivity is fairly well known and standard across different neocortical regions, both in layer 2/3 and 5: PV cells preferentially inhibit one another, SOM cells avoid one another but inhibit all other types of interneurons, and VIP cells preferentially inhibit SOM interneurons (Fig. 1A) (Lee et al., 2013; Pfeffer et al., 2013;

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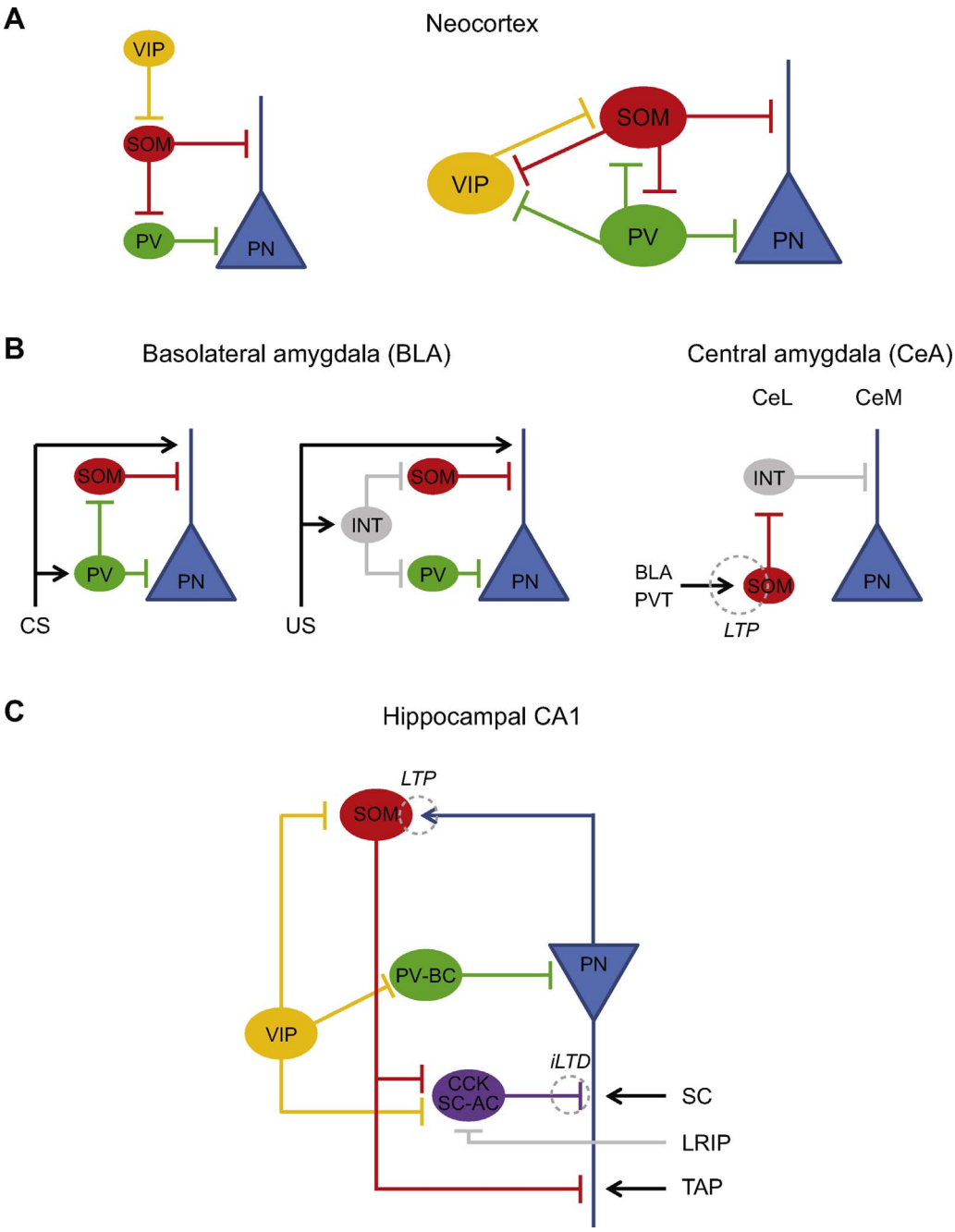

Fig. 1. Interneuron connectivity patterns for disinhibition and sites of long-term synaptic plasticity in these disinhibitory circuits.
(A-C) Diagrams illustrating patterns of connectivity among cooperative interneurons in neocortex (A), amygdala (B) and CA1 hippocampus (C).
(A) Left: classical model of interneuron for disinhibition (based on Lee et al., 2013; Pfeffer et al., 2013; Kepecs and Fishell, 2014; Zhang et al., 2014). Right: emergent new model based on interneuron cooperativity rather than on hierarchical connectivity (modified from Karnani et al., 2016b).
(B) Disinhibition in basolateral amygdala (BLA; left and middle) and central amygdala (CeA; right) during fear learning. Left: a conditioned stimulus (CS) recruits PV interneurons which mediate principal neuron perisomatic inhibition and dendritic disinhibition through inhibition of SOM interneurons. Middle: the unconditioned stimulus (US) recruits unidentified interneurons which strongly inhibit SOM and PV interneurons and trigger disinhibition of the entire somatodendritic domain of projection cells in BLA, enhancing associative learning (modified from Letzkus et al., 2015). Right: during fear learning in CeA, projection neurons in BLA and the paraventricular nucleus of the thalamus (PVT) recruit SOM interneurons which inhibit non-SOM interneurons of lateral central amygdala (CeL), resulting in disinhibition of principal neurons of medial central amygdala (CeM) and allowing gating and expression of fear. Interestingly, this model involves long-term potentiation (LTP) of excitatory inputs from BLA neurons onto SOM interneurons in the CeL, providing a mechanism for modulation of synaptic disinhibition.
(C) Disinhibition and input selection of Schaffer collaterals (SC) over temporo-ammonic pathway (TAP) in hippocampal pyramidal cells (based on Leao et al., 2012; Basu et al., 2013; Vasuta et al., 2015; Basu et al., 2016). During SC activity, Schaffer collateral associated cells (SC-ACs) and/or CCK interneurons in stratum radiatum are inhibited by VIP interneurons, SOM cells and long-range inhibitory projections (LRIP) from entorhinal cortex resulting in SC input selection. In addition, SOM interneuron inhibition provides a bidirectional mechanism for input selection of SC over TA. Synaptic plasticity in this circuit regulates disinhibition via long-term depression of inhibition (iLTD) by SC-AC/CCK interneurons and LTP of excitatory inputs from pyramidal cells onto SOM interneurons.

Pi et al., 2013).

This pattern of connectivity places VIP interneurons at the heart of a disinhibitory system in which they allow excitatory activity to propagate through inhibition of SOM interneurons. For example, activation of VIP interneurons in the primary visual cortex (V1) inhibits SOM interneurons and increases local PC responses to visual stimulations (Fu et al., 2014; Zhang et al., 2014), thus opening transient “holes” in the blanket of inhibition (Karnani et al., 2016a). This disinhibitory pattern by VIP interneurons which promote PC activity and sensory integration is also found in auditory cortex (Pi et al., 2013; Kuchibhotla et al., 2017), in somatosensory cortex (Gentet et al., 2012; Lee et al., 2013; Wall et al., 2016; Munoz et al., 2017) and improve short-term memory in dorso-medial prefrontal cortex (Kamigaki and Dan, 2017).

However, other studies recently demonstrated that VIP interneurons and PC coactivity in V1 does not necessary support visual processing. For example, sound presentation increased PC activity during cross-modal sensory processing in V1, while VIP cells are inhibited by non-VIP interneurons in layer 1 activated by glutamatergic neurons in the primary auditory cortex (Ibrahim et al., 2016). Also, during locomotion-driven visual processing, PC, VIP and SOM neurons can be coactive (Karnani et al., 2016b; Pakan et al., 2016). This indicates that disinhibition of PC by VIP interneurons, but also direct inhibition and disinhibition by other interneuron subtypes, notably SOM cells, can occur jointly during visual processing (Fig. 1A).

Indeed, several studies in V1 recently pointed out that SOM interneurons make more synapses onto other interneurons such as VIP (Karnani et al., 2016b) and PV (Cottam et al., 2013) than onto PCs, which can modulate and even counterbalance disinhibition of PCs by