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Behavioral state-dependent modulation of distinct interneuron subtypes and consequences for circuit function

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Multiple neuromodulators regulate neuronal response properties and synaptic connections in order to adjust circuit function. Inhibitory interneurons are a diverse group of cells that are differentially modulated depending on neuronal subtype and play key roles in regulating local circuit activity. Importantly, new tools to target specific subtypes are greatly improving our understanding of interneuron circuits and their modulation. Indeed, recent work has demonstrated that during different behavioral states interneuron activity changes in a subtype specific manner in both neocortex and hippocampus. Furthermore, in neocortex, modulation of specific interneuron microcircuits results in pyramidal cell disinhibition with important consequences for synaptic plasticity and animal behavior. Thus, neuromodulators tune the output of different interneuron subtypes to provide neural circuits with great flexibility.

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Introduction

Inhibitory interneurons are key participants in the generation of normal neural activity in the cerebral cortex and hippocampus, acting to gate the flow of information and coordinate local networks [1,2]. They are highly diverse and the many different subtypes undoubtedly play specific roles in circuit function. With the development of transgenic mouse lines to manipulate distinct interneuron cohorts, a sophisticated understanding of how distinct modes of inhibition shape neural activity is beginning to emerge [3]. Importantly, all neurons are under the influence of a diverse set of neuromodulatory systems, which are activated during different behavioral states [4,5]. These modulators adjust intrinsic membrane properties and synaptic connections in a cell type specific manner to alter how neural circuits respond to and process information. Thus, neural circuits are flexible and how they function depends on behavioral context. Here, we review recent progress toward understanding how distinct cortical interneuron subtypes are modulated during different behavioral states. Furthermore, we review the likely circuit and neuromodulatory mechanisms responsible.

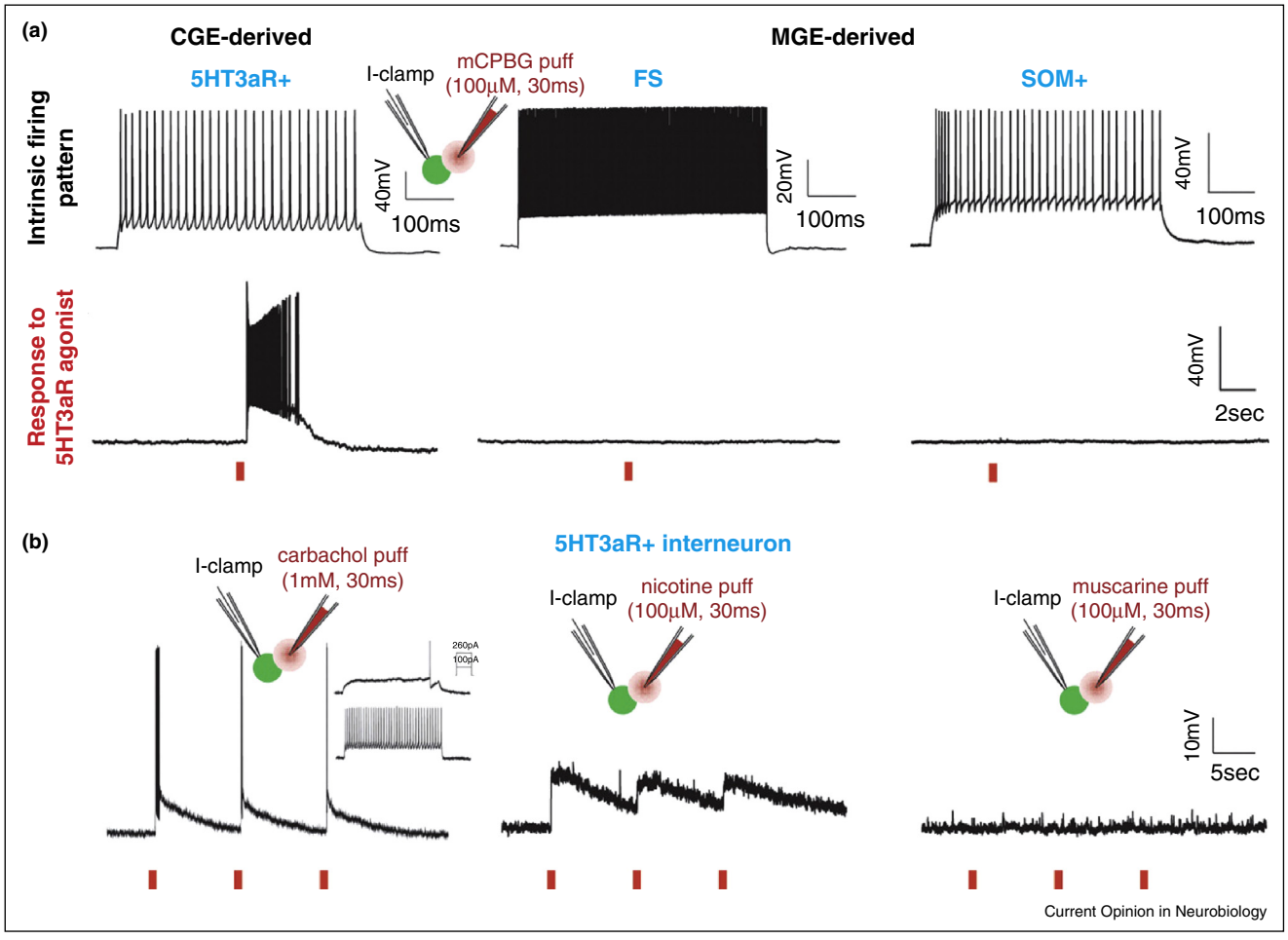
Inhibitory interneurons are diverse but a subset have shared neuromodulatory response properties

Interneurons can be classified according to many features including electrophysiological characteristics, morphology, and molecular expression profile (for recent reviews see [6,7]). Different subtypes display distinct axonal branching patterns and innervate specific membrane compartments to control synaptic integration along the somato-dentritic axis [2]. Importantly, different interneuron cohorts can be identified by the differential expression of calcium-binding proteins such as parvalbumin (PV) or neuropeptides such as somatostatin (SOM) or vasointestinal peptide (VIP) [6,8,9]. Multiple transgenic mouse lines take advantage of this to selectively label or optogenetically manipulate different interneuron groups [10]. PV+ interneurons include those with a fast spiking (FS) phenotype that provide perisomatic inhibition; SOM+ interneurons are non-FS and include those that target apical dendrites; and VIP+ interneurons are all non-FS but diverse morphologically. Although useful for distinguishing broad categories, multiple subtypes are represented among the PV, SOM, and VIP expressing groups. For example, FS/PV+ interneurons include not only perisomatic basket cells but also axon targeting chandelier cells [11] and dendrite targeting bistratified cells [12], and VIP+ interneurons represent multiple subtypes [9,13–15].

Not surprisingly, these diverse subtypes exhibit a wide range of responses to different neuromodulatory inputs, presenting a very difficult combinatorial problem. For example, basket cells can be distinguished by differential expression of PV or cholecystokinin (CCK) and these two types respond very differently to modulators such as acetylcholine, serotonin, or cannabinoids [16–19]. However, recent work on the developmental

lineage of interneurons has provided a useful organizational framework for understanding their diversity and some aspects of their modulation. During embryogenesis the majority of neocortical and hippocampal interneurons are derived from the medial and caudal ganglionic eminences (MGE and CGE) [13,15,20]. In the cortex, the MGE produces PV+ and SOM+ interneurons, while the rest (including CCK+ and VIP+ interneurons and neurogliaform cells) are generated by the CGE. This is similar in the hippocampus, however the MGE also generates a large set of PV−/SOM− interneurons that includes ivy cells and a subset of neurogliaform cells [15,21]. Importantly, it was recently discovered that interneuron subtypes produced by the CGE, but not the MGE, all functionally express the ionotropic serotonin receptor 5HT3a (5HT3aR) [14••,22] (Figure 1a). Interestingly, hippocampal interneuron subtypes that appear anatomically similar, such as neurogliaform cells and oriens-lacunosum molecular projecting interneurons, can be generated from both the CGE and MGE [21,23], and differentially express 5HT3aRs depending on their origin [23]. Furthermore, in the cortex, 5HT3aR+ interneurons might also be selectively excited by activation of ionotropic nicotinic acetylcholine receptors (nAChRs) [14••] (Figure 1b), in agreement with previous work demonstrating nicotinic excitation of VIP+ and CCK+ interneurons (CGE-derived) but not those that are PV+ or SOM+ or are fast spiking (MGE-derived) [24,25]. Thus, in spite of an incredible diversity of CGE-derived interneuron subtypes [13,15], they share a set of common neuromodulatory response properties. However, it should be noted that in the hippocampus both 5HT3aR+ and 5HT3aR−/SOM+ interneurons are excited by nAChR agonists [23]. The functional significance of multiple subtypes all expressing 5HT3aRs or nAChRs is currently unknown.

Figure 1



CGE-derived interneurons are modulated by ionotropic serotonin and nicotinic acetylcholine receptors. **(a)** Puffing *m*-chlorophenyl-biguanide (mCPBG) on the soma of 5HT3aR expressing interneurons but not SOM+ or FS interneurons results in depolarization and action potential firing. *Top*, intrinsic firing properties of the three interneuron types are different. *Bottom*, responses to a single 30 ms puff of 100 μM mCPBG. **(b)** 5HT3aR-expressing interneurons also respond to cholinergic input via nicotinic but not muscarinic acetylcholine receptors.Modified with permission from [14••].