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Review

Regulation of Parvalbumin Basket cell plasticity in rule learning

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ABSTRACT

Local inhibitory Parvalbumin (PV)-expressing Basket cell networks shift to one of two possible opposite configurations depending on whether behavioral learning involves acquisition of new information or consolidation of validated rules. This reflects the existence of PV Basket cell subpopulations with distinct schedules of neurogenesis, output target neurons and roles in learning. Plasticity of hippocampal early-born PV neurons is recruited in rule consolidation, whereas plasticity of late-born PV neurons is recruited in new information acquisition. This involves regulation of early-born PV neuron plasticity specifically through excitation, and of late-born PV neuron plasticity specifically through inhibition. Therefore, opposite learning requirements are implemented by distinct local networks involving PV Basket cell subpopulations specifically regulated through inhibition or excitation.

1. PV Basket cell plasticity upon learning

Reinforced trial-and-error learning protocols provide experimental settings to investigate how plasticity is adjusted during learning. Effective acquisition and combination of potentially task-relevant information is essential during early phases of trial-and-error learning, whereas reliable application of validated routines dominates when prediction errors get vanishingly small [1]. At the circuit level, these contrasting requirements are reflected by shifts in the configuration of local PV-expressing Basket cell networks, which exhibit pronounced plasticity induced by experience [2]. Thus, PV network configurations enriched in neurons expressing low levels of the cytosolic calcium-binding protein PV and of the key GABA-synthesizing enzyme GAD67, and exhibiting high inhibitory connectivity onto them are induced locally early during trial-and-error incremental learning. Such “low-PV configurations” promote acquisition and retention of new memories and structural synaptic plasticity [2]. By contrast, configurations enriched in neurons expressing high levels of PV and GAD67, and exhibiting high excitatory connectivity onto them are induced towards completion of trial-and-error learning protocols. Such “high-PV configurations” interfere with the acquisition of new memories and structural synaptic plasticity [2]. The opposite configurations might emerge through learning-specific mechanisms sequentially shifting whole local PV neuron ensembles towards distinct network states. Alternatively, the opposite configurations might be induced through task-selective regulation of PV neuron subpopulations.

2. PV Basket cell functions

PV-positive Basket cells are widely distributed GABAergic inhibitory interneurons that provide local feedforward and feedback inhibition through perisomatic boutons onto principal excitatory neurons [3–5]. In addition, PV Basket cells inhibit each other reciprocally through perisomatic innervation and are dynamically coupled electrically through gap junctions [3,5]. Accordingly, PV Basket cells filter activation of principal neurons, and networks of PV Basket cells have major roles in regulating local ensemble activities, including theta and gamma oscillations [5,6–9]. Synaptic regulation of PV Basket cells has been implicated in adult learning, and the maturation state of PV Basket cells has been implicated in critical period-type plasticity [8,10–13]. The mechanisms through which PV neuron networks contribute to such a diverse range of functions have remained poorly understood.

The functions of GABAergic interneurons have been traditionally classified based on anatomical connectivities and physiological properties [4]. More recently, it became apparent that interneuron subtypes have distinct roles during behavior and in learning by gating distinct information flows to principal neurons [7,9,14]. These observations have led to new classifications of GABAergic neuron subtypes based on their specific circuit functions during behavior, complementing the original classifications based on anatomy and physiology [15].

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Although PV Basket cells all share characteristic physiological and anatomical features, distinctions among them have been reported [16–18]. One way through which neuronal subpopulations can be specified while maintaining their defining functional properties is through the acquisition of sub-features during distinct developmental time windows of neurogenesis. For example, GABAergic interneurons differing in their schedule of neurogenesis tend to settle at different cortical layers in the adult [19,20]. PV Basket cells are generated in medial ganglionic eminence (MGE) during a protracted period of neurogenesis from embryonic day (E) 9.5 to E15.5 [21]. Accordingly, PV neurons generated at different times within this period might differ in connectivity/PV/GAD67 expression and/or in how they are regulated during experience-related plasticity (Fig. 1).

3. Subpopulations of PV Basket cells defined by time schedule of neurogenesis

To investigate whether PV Basket cells might differ systematically as a function of when they are generated during neurogenesis, we labeled proliferating cells with BrdU and analyzed BrdU/PV double-positive cells in hippocampal CA3 and CA1, primary somatosensory whisker cortex, and dorsal striatum of adult mice. Hippocampal PV neurons generated at E9.5 or E11.5 were predominantly high- and intermediate-high PV, whereas neurons generated at E13.5 or E15.5 were predominantly intermediate-low- and low-PV [22].

To determine whether the relationship between developmental time of neurogenesis and PV-excitatory/inhibitory values reflected intrinsic properties of PV neurons, we carried out donor-host graft experiments in embryonic mice. Donor PV neurons were dissected from the MGE of E13.5 PV-Cre:Rosa-flex-tdTomato embryos in which PV-expressing neurons are fated to express tdTomato and introduced into E11.5 non-transgenic host MGE. In the adult, donor PV neurons exhibited predominantly low-PV neuron values and low excitatory-to-inhibitory synaptic puncta ratios characteristic of their birthdate in the donor embryo. In complementary experiments tdTomato-positive E11.5 donor PV neurons transplanted into an E13.5 host exhibited high- and intermediate-high PV neurons values characteristic of their birthdate in donor E11.5 embryo. We concluded that PV and excitation/inhibition connectivity profiles of early- and late-born PV neurons in the adult reflect distinct intrinsic properties of these neurons determined at the time of neurogenesis [22].

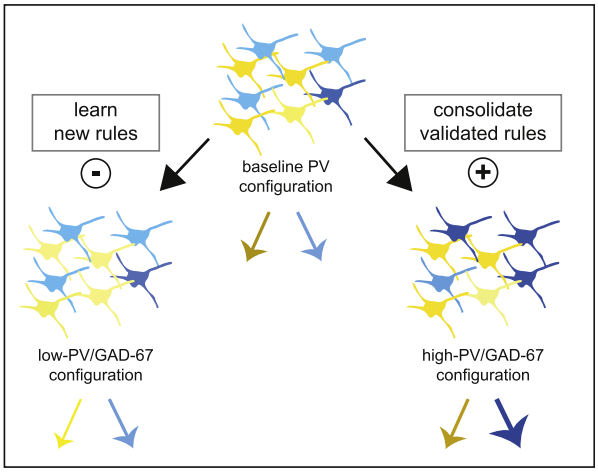

Fig. 1. Regulation of PV Basket cell subpopulation plasticity upon rule learning. A local PV Basket cell network is indicated by eight cell bodies and proximal dendrites. PV expression levels are indicated by a color code (low-PV: pale yellow; intermediate-low PV: yellow; intermediate-high PV: pale blue; high-PV: dark blue). Arrows under PV networks indicate separate outputs for early-born PV (blue) and late-born PV (yellow). Early-PV outputs strengthen for rule consolidation (regulation through excitation; plus-sign); late-PV outputs weaken for learning of new rules (regulation through inhibition; minus sign).

4. Rule learning involves plasticity in either early- or late-born PV neurons

To determine how PV neurons generated at early and late embryonic developmental time points are affected by learning, we subjected BrdU-labeled mice to either contextual fear conditioning (cFC) or environmental enrichment (EE). cFC had a major impact on PV value distributions in hippocampal CA3 and CA1 cells labeled at E9.5 or E11.5, whereas cells labeled at E13.5 or E15.5 were not noticeably affected. By contrast, EE affected PV value distributions of hippocampal CA3 and CA1 cells labeled at E13.5 or E15.5, but not of cells labeled at E9.5 or E11.5. Furthermore, Mef2a levels [23] decreased specifically in early-born PV neurons in parallel with increased excitatory puncta densities, whereas upon EE Mef2a levels increased specifically in late-born PV neurons in parallel with increased inhibitory puncta densities. In water maze learning hippocampal CA3 and CA1 PV neurons first shift to a low-PV network configuration (days2–6) and then to a high-PV network configuration (>day7) [2]. Late-born PV neurons were selectively regulated during early phases of maze learning, when they reversibly shifted to low-PV/high-Mef2a values. By contrast, early-born PV neurons were selectively regulated during late phases of maze learning, when they shifted to high-PV/low-Mef2a values.

In stark contrast to hippocampal CA3 and CA1, the PV cell network in hippocampal dentate gyrus (DG) shifted to a low-PV configuration upon cFC and at the end of MWM learning, and to a high-PV configuration upon EE and during MWM learning. Notably, however, only early-born cells shifted PV levels upon cFC or at the end of MWM learning, although in DG the shift was towards low-PV values. Likewise, upon EE or early in MWM learning only late-born cells shifted their PV levels, but the shift in DG was towards high-PV values. Furthermore, in DG cFC specifically induced a reduction in excitatory synaptic puncta onto early-born PV cells, and EE specifically induced a reduction in inhibitory synaptic puncta onto late-born PV cells. Therefore, both in CA3/CA1 and in DG early-born PV neuron cell-plasticity specifically involved changes in excitatory connectivity onto PV neurons, whereas late-born cell-plasticity specifically involved changes in inhibitory connectivity onto PV neurons [22].

5. Subpopulation cell-plasticity specifically regulated through excitation or inhibition

To investigate whether early-born PV neurons specifically respond to changes in synaptic excitation, we treated adult mice pharmacogenetically with the competitive inhibitor of NMDA receptors AP5. The NMDA inhibitor induced lower contents of high-PV and higher contents of low-PV neurons in hippocampal CA3. Notably, AP5 specifically affected PV levels in early-born neurons, whereas late-born neurons were not affected. To further investigate specific regulation of PV subpopulation cell-plasticity by excitation or inhibition we induced PV shifts using a pharmacogenetic approach [24] *in vivo*. While pharmacogenetic activation of PV neurons induced a high-PV shift and pharmacogenetic inhibition induced a low-PV shift, only early-born neurons exhibited a corresponding shift in Mef2a levels and excitatory synaptic puncta densities upon pharmacogenetic activation. Likewise, only late-born cells exhibited a corresponding Mef2a/inhibitory

connectivity shift upon pharmacogenetic inhibition. These results provided evidence that persistent direct non-synaptic excitation or inhibition of PV neurons can shift PV expression values in all PV cells, but only early-born neurons exhibit Mef2a/connectivity plasticity upon excitation and only late-born neurons exhibit Mef2a/connectivity plasticity upon inhibition [22].

We next investigated whether interventions that re-induce critical period-like plasticity by enhancing inhibition in the adult selectively target subpopulations of PV neurons. Dissolving perineuronal nets by locally applying Chondroitinase ABC (ChABC) induced a robust low-PV shift in hippocampal CA3 in the adult. Notably, ChABC specifically affected PV levels in late-born cells, whereas early-born cells were not affected. Consistent with specific regulation of late-born PV neurons through inhibition, the low-PV shift upon ChABC was accompanied by a specific increase in inhibitory puncta densities onto late-born cells, whereas excitatory puncta were not affected. In further experiments, local delivery of the GABA-A receptor agonist Diazepam induced higher contents of low-PV neurons in hippocampal CA3, and this specifically involved PV levels in late-born PV neurons, whereas early-born neurons were not affected.

6. Early- and late-born PV Basket cells target distinct principal neurons subpopulations

The consistent experience-related plasticity regulation of the two subpopulations of PV Basket cells raised the issue of whether these might also exhibit distinct output targets related to behavioral function [15,17]. While PV Basket cells exhibit high probabilities of connectivity to local principal neurons, early-born PV neurons are more abundant in deep cortical layers of neocortex, whereas late-born neurons are more abundant in upper layers [20], suggesting that early- and late-born PV neurons might directly control different ensembles of excitatory cortical neurons. Indeed, we found that early-born PV neurons preferentially target deep cells in the pyramidal layer of hippocampal CA1, whereas late-born PV neurons preferentially target superficial cells [22]. While the functional implications of the selective output connectivity of PV neuron subpopulations remain to be determined, our findings would be consistent with the notion that the distinct excitation/inhibition input ratios onto early- and late-born PV neurons and the specific regulation upon learning might reflect information flow through functionally distinct microcircuits (e.g. [25]).

7. Plasticity regulation through excitation or inhibition in learning

Our findings suggest that PV neuron regulation specifically through excitation provides a mechanism to match implementation of validated rules in learning to early-born PV neuron cell plasticity. Likewise, regulation of PV neurons specifically through inhibition matches enhanced plasticity and learning to late-born PV neuron cell plasticity. This might involve specific learning-related gating mechanisms as revealed in recent studies of Pavlovian conditioning (e.g. [26]). Concerning the mechanisms underlying specific regulation of PV Basket cell subpopulations through excitation or inhibition, our findings suggest that early- and late-born PV neurons exhibit distinct cellular regulatory networks. Distinct intracellular signaling features [27] in early- and late-born PV neurons might be sufficient to ensure control of early-born PV neurons selectively through excitation and of late-born PV neurons selectively through inhibition.

8. Distinct functional roles of PV Basket cell subpopulations

Our results establish late-born PV Basket cells as the subpopulation that specifically accounts for positive regulation of plasticity during learning, upon EE, and during critical period-like plasticity. Enhancing inhibitory connectivity and reducing PV and GAD-67 levels in late-born PV neurons might enhance further learning by reducing the impact of PV-mediated inhibition of principal neuron subpopulations [28,29] under acquisition regimes involving local circuit disinhibition. By contrast, early-born PV Basket cells appear to account for characteristic features of mature fast-spiking PV neuron networks such as narrow synchronization windows and learning-related theta-gamma entrainment [3]. Consistent with this notion, high PV and GAD-67 levels enhance fast and high frequency firing properties of PV neuron networks important for gamma band network activity [6–8,30,31]. Enhanced functionality of early-born PV neuron networks upon validated learning might promote consolidation of strong memories within and between brain systems, e.g. through enhanced gamma-phase coupling [32].

In summary, and reflecting specific regulation through inhibition or excitation, late-born PV neuron network plasticity might promote learning through reduced functional recruitment of PV neurons, whereas early-born PV neuron network plasticity might promote consolidation of validated learning through enhanced PV neuron function and network coherence [22]. Deficits in the strength of inhibitory transmission might impair late-born PV neuron plasticity in mental retardation and autism [33–35], whereas deficits in the strength of excitatory transmission might account for greatly reduced gamma band activity and impaired prefrontal working memory support as found in schizophrenia [36].

Conflict of interest

None.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.02.023.

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