# This Week in The Journal

## γ-Protocadherins Limit Postnatal Culling of Interneurons

Candace H. Carriere, Wendy Xueyi Wang, Anson D. Sing, Adam Fekete, Brian E. Jones, et al.

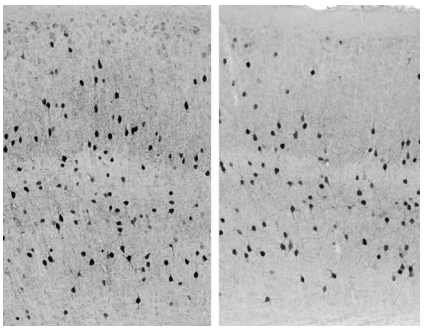
(see pages 8652–8668)

During nervous system development, an overabundance of neurons is produced, and excess neurons are eventually eliminated via programmed cell death, presumably to optimize target innervation and create an appropriate balance of excitatory and inhibitory neurons. In the CNS, activity levels are a crucial determinant of neuronal survival; but a group of homophilic cell adhesion molecules called γ-protocadherins promotes survival of some spinal cord and retinal neurons. Carriere, Wang, Sing, et al. and Mancia Leon et al. (2020, eLife 9:474) show that γ-protocadherins also support survival of inhibitory neurons throughout the mouse brain.

Deletion of the γ-cluster of protocadherin genes (*Pcdhgs*) in newborn GABAergic neurons led to an overall reduction in brain volume at postnatal day 28 (P28), with the greatest reduction in structures that normally have numerous GABAergic neurons, including the globus pallidus, bed nucleus of the stria terminalis, and superior colliculus. Furthermore, the number of parvalbumin-expressing ($PV^+$) interneurons was reduced by ~35–60% in the globus pallidus, basolateral amygdala, cerebral cortex, and molecular layer of the cerebellar cortex. Consistent with the widespread loss of inhibitory interneurons, mutant mice exhibited spontaneous seizures.

GABAergic interneurons migrate into the cerebral cortex circa embryonic day 14, and in wild-type mice 20–40% of them undergo apoptosis postnatally. The number of migrating GABAergic interneurons and the number of interneurons populating the cerebral cortex at P5 were similar in *Pcdhg*-deficient and control mice, but the number of apoptotic neurons was greater in mutants on P7, and more interneurons were lost between P8 and P14 in mutant mice than in controls. If *Pcdhg* was deleted at P12, however, the number of interneurons surviving at P28 was similar in mutants and controls. Finally, activation of the kinase AKT, which promotes neuron survival, was lower, whereas nuclear levels of the pro-apoptotic transcription factor FoxO3A were higher in *Pcdhg*-deficient GABAergic neurons than in controls.

These results suggest that γ-protocadherins expressed in GABAergic interneurons promote neuronal survival selectively during the postnatal period of programmed cell death by activating AKT, which inhibits nuclear translocation of FoxO3A. The molecular pathways through which γ-protocadherins regulate AKT activation and the extent to which they are related to neuronal activity levels should be addressed in future studies.



The number of $PV^+$ interneurons (black) is lower in cortex of mice lacking *Pcdhg* in GABAergic cells (right) than in controls (left). See Carriere, Wang, Sing, et al. for details.

## Novelty Aids Learning by Cutting Quinone Reductase 2 Levels

Nathaniel L. Gould, Vijendra Sharma, Mohammad Hleihil, Sailendrakumar Kolatt Chandran, Orit David, et al.

(see pages 8698–8714)

Novel experiences promote the formation of rich episodic memories, including the remembrance of less salient stimuli that might otherwise be forgotten. This effect is mediated partly by novelty-induced dopamine release from locus coeruleus projections to the hippocampus. Dopamine affects synaptic plasticity and learning via several mechanisms, including changes in gene expression. Gould et al. now describe a novel pathway through which dopamine enhances hippocampus-dependent learning: by regulating levels of the reducing enzyme quinone reductase 2 (QR2) in inhibitory interneurons.

Previous work by the authors indicated that exposure to a novel taste increased expression of microRNA miR-182 in the insular cortex, that this led to a reduction in QR2 mRNA, and that knocking down QR2 enhanced memory for the taste. Given that miR-182 expression increases in the hippocampus after novel experiences, the authors hypothesized that QR2 also plays a role in hippocampus-dependent learning. Consistent with this hypothesis, QR2 expression was reduced in hippocampal area CA1 3 h after trace fear conditioning and knocking down or inhibiting QR2 enhanced memory. Importantly, simply placing mice in a novel cage for 15 min increased hippocampal expression of miR-182 and reduced expression of QR2, and these effects were prevented by silencing the locus coeruleus or blocking $D_1$ dopamine receptors in the hippocampus.

Because baseline QR2 levels were higher in inhibitory neurons than in excitatory neurons in CA1 and because novelty exposure reduced these levels, the authors knocked down QR2 selectively in inhibitory neurons. This enhanced performance on a novel object recognition task, whereas knocking down QR2 selectively in excitatory neurons had no effect. Additional experiments indicated that inhibiting QR2 reduced oxidation of Kv2.1 potassium channels and hyperpolarized the resting membrane potential, increased the rheobase, and decreased the firing rate of hippocampal inhibitory neurons.

These results suggest that novelty-induced release of dopamine from locus coeruleus axons leads to activation of hippocampal $D_1$ dopamine receptors, increased expression of miR-182, and downstream degradation of QR2 mRNA. This reduces the excitability of inhibitory neurons, possibly in part by altering the oxidation state of ion channels. The resulting loss of inhibition may increase the likelihood of spiking in pyramidal cells, which may promote synaptic plasticity and the formation of new memories.

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