This Week in The Journal

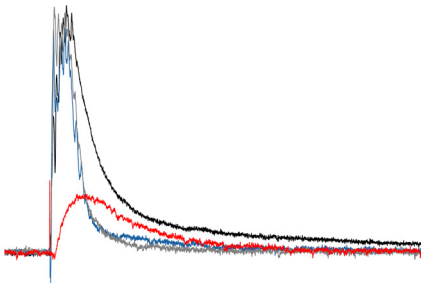
Cellular/Molecular

Extrasynaptic GABA Receptors Modulate Phasic Inhibition

Murray B. Herd, Adam R. Brown, Jeremy J. Lambert, and Delia Belelli

(see pages 14850–14868)

GABAergic neurons in the thalamic reticular nucleus (nRT) inhibit thalamocortical relay neurons by acting on synaptic $\alpha1\beta2\gamma2$ $GABA_A$ receptors ($GABA_A$Rs) and extrasynaptic $\alpha4\beta2\delta$ $GABA_A$Rs. Activation of synaptic $GABA_A$Rs produces phasic inhibition of thalamocortical neurons, whereas activation of extrasynaptic $GABA_A$Rs underlies tonic inhibition. To investigate how these receptors interact, Herd et al. recorded from synaptically coupled pairs of nRT neurons and thalamocortical neurons of the ventrobasal complex (VB) in mouse brain slices. Surprisingly, knocking out $\alpha4$ subunits and thus extrasynaptic $GABA_A$Rs not only reduced tonic inhibitory currents in VB neurons, but also reduced the duration of phasic inhibition evoked by spike bursts in nRT neurons. Furthermore, a selective agonist of δ-subunit-containing (extrasynaptic) $GABA_A$Rs prolonged inhibition evoked by nRT bursts, and stimulation of nRT evoked IPSCs even in VB neurons that lacked $\alpha1$ subunits and thus the predominant synaptic GABA receptor. Together, these data indicate that extrasynaptic receptors not only mediate tonic inhibition of VB neurons, but also contribute to phasic inhibition evoked by nRT bursts.



IPSCs evoked by nRT stimulation were of shorter duration in VB neurons lacking extrasynaptic $GABA_A$Rs (blue) than in wild-type neurons (black). IPSCs persisted in neurons lacking synaptic $GABA_A$Rs (red). See the article by Herd et al. for details.

Development/Plasticity/Repair

Adult-Born Neurons Are Unresponsive to $GABA_B$ Agonist

Matthew T. Valley, Lansdale G. Henderson, Samuel A. Inverso, and Pierre-Marie Lledo

(see pages 14660–14665)

Neurons are continuously generated in the subventricular zone of adult mammals. Newborn neurons travel along the rostral migratory stream (RMS) to the olfactory bulb, where most differentiate into granule cells (GCs) that provide inhibitory input to mitral cells. Newborn GCs contribute to olfactory learning and discrimination, and it has been hypothesized that newborn GCs have functional properties that earlier-born GCs lack. To investigate this possibility, Valley et al. injected channelrhodopsin-expressing virus into mouse RMS, selectively infecting newborn GCs en route to the olfactory bulb. They then compared postsynaptic responses evoked by optical stimulation of newborn GCs to responses evoked by electrical stimulation, which activates GCs of all ages. Notably, $GABA_B$ receptor ($GABA_B$R) agonists, which reduced IPSCs evoked by electrical stimulation by suppressing GABA release from GCs, did not affect IPSCs evoked by photoactivation of adult-born GCs. This reduced responsiveness to $GABA_B$R agonist was associated with altered patterns of $GABA_B$R expression, supporting the hypothesis that adult-born GCs are fundamentally different than earlier born neurons.

Systems/Circuits

Hippocampal CA2 Directly Projects to Entorhinal Cortex

David C. Rowland, Aldis P. Weible, Ian R. Wickersham, Haiyan Wu, Mark Mayford, et al.

(see pages 14889–14898)

Neurons in layer II (LII) of the entorhinal cortex (EC) provide the main input to the hippocampal formation, projecting to the dentate gyrus, which in turn projects to CA3; CA3 projects to CA1, which projects to deep layers of EC. Transmission of information through this circuit is involved in constructing spatial maps and episodic memories. To identify inputs to EC LII, Rowland et al. used a recombinant rabies virus in which the glycoprotein required for transsynaptic infection was deleted, the protein required to infect neurons was replaced by one that recognizes an avian receptor, and a fluorescent protein was inserted. This virus was injected into transgenic mice in which the deleted glycoprotein and the avian receptor were expressed exclusively in medial EC LII neurons. The virus therefore selectively infected these neurons and their presynaptic partners. In addition to labeling known inputs, this technique revealed direct projections from CA2 to EC. This suggests that CA2 has unique roles in hippocampal processing.

Neurobiology of Disease

miR-26b Induces Pathologies Found in Alzheimer's Disease

Sabrina Absalon, Dawn M. Kochanek, Venkatesan Raghavan, and Anna M. Krichevsky

(see pages 14645–14659)

Although accumulation of toxic β-amyloid peptides is the chief defining feature of Alzheimer's disease (AD), many other pathologies are present, including accumulation of abnormally phosphorylated tau protein, cell cycle re-entry, and apoptosis. Absalon et al. propose that these other pathologies stem from increased levels of microRNA miR-26b, which they detected in temporal cortex in early stages of AD. Increasing miR-26b levels in cultured rat cortical neurons decreased levels of retinoblastoma protein (Rb) and p27, which normally prevent cell cycle entry by preventing transcription of cell cycle proteins. Consequently, increasing miR-26b levels also increased expression of cell cycle proteins, ultimately resulting in apoptosis. Additionally, because p27 forms a complex that localizes cyclin-dependent kinase 5 (Cdk5) to the nucleus, decreasing p27 allowed Cdk5 to exit the nucleus and phosphorylate cytoplasmic targets, including AD-associated sites on tau. Cell cycle entry, nuclear exit of Cdk5, and apoptosis also occur when neurons are treated with H_2O_2, but intriguingly, inhibiting miR-26b increased neuronal survival after H_2O_2 treatment.