This Week in The Journal

Regulating Surface Levels of α7 Nicotinic Receptors

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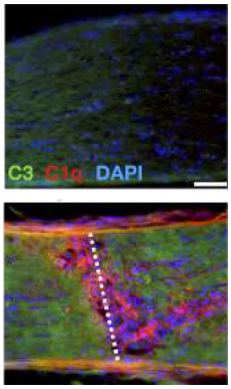
(see pages 8461–8474)

Acetylcholine has many functions in the CNS, including the regulation of attention, synaptic plasticity, and memory consolidation. Many of these effects are mediated by nicotinic acetylcholine receptors (nAChRs), including those composed of $\alpha 7$ subunits that are highly expressed in hippocampal and cortical neurons. Because $\alpha 7$-nAChRs are ligand-gated ion channels that are highly permeable to calcium, their expression levels and permeability must be tightly regulated to ensure optimal function without predisposing neurons to calcium overload. Numerous proteins work together to achieve this regulation, including Ly6h, a membrane-tethered protein that forms stable complexes with $\alpha 7$ subunits. Ly6h limits delivery of $\alpha 7$-nAChRs to the plasma membrane and suppresses agonist-induced currents in receptors that reach the cell surface.

Wu et al. have identified two proteins that regulate this regulator. The first is NACHO, a chaperone protein previously shown to guide assembly of nAChRs in the endoplasmic reticulum. Consistent with previous work, knocking down NACHO reduced acetylcholine-induced calcium influx in cultured hippocampal neurons, whereas knocking down Ly6h increased calcium influx and surface expression of $\alpha 7$-nAChRs. In addition, introduction of Ly6h reduced surface expression of $\alpha 7$-nAChRs and acetylcholine-induced calcium influx in HEK cells, whereas expressing NACHO increased surface expression and enhanced calcium influx. Importantly, coexpression of NACHO reduced binding between Ly6h and $\alpha 7$ and led to intermediate levels of $\alpha 7$-nAChR surface expression and acetylcholine-induced calcium influx, suggesting that NACHO suppresses the effects of Ly6h.

Previous work has shown that β-amyloid (Aβ) peptides, which accumulate in Alzheimer's disease (AD) bind to $\alpha 7$-nAChRs and increase their expression levels. Wu et al. found that exogenous Aβ reduced Ly6h levels in hippocampal neurons, and this effect depended on activation of $\alpha 7$-nAChRs. Notably, levels of Ly6h were lower in cortical tissue from people with AD than in control subjects.

These results suggest that NACHO reduces and Aβ increases the ability of Ly6h to promote delivery of $\alpha 7$-nAChRs. The effects of Aβ on Ly6h may explain why cholinergic signaling is impaired in AD. Intriguingly, downregulation of Ly6h by Aβ might also lead to hyperphosphorylation of the microtubule-associated protein tau, a major pathological hallmark of AD. Indeed, knockdown of Ly6h led to dramatic increases in tau phosphorylation. Therefore, Ly6h might be a valuable target for AD therapy.



After optic nerve crush (bottom), the expression of C1q (red) and C3 (green) increases near the injury site (dashed line). See Peterson et al. for details.

A Role for Complement System in Optic Nerve Regeneration

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(see pages 8508–8531)

The complement system is a group of >40 proteins that work together to identify tissue injury and activate immune responses. In the classical activation pathway, a protein complex containing complement C1q becomes activated when it binds to pathogen-associated molecules or antigen-bound antibodies. Activated C1 complex then initiates a cascade of cleavage events that activates other complement proteins, including C3. Cleavage of C3 produces diffusible C3a, which attracts immune cells to the injury site, and membrane-bound C3b, which tags cells for phagocytosis and helps activate additional complement proteins.

Like other elements of the immune system, the complement system can have both positive and negative effects in the injured nervous system. Although tagging cellular debris for phagocytosis facilitates removal of obstacles to axon growth, excessive stimulation of immune cells can lead to cell death. Moreover, previous studies have demonstrated that beneficial or detrimental effects may predominate depending on the type and location of injury. Peterson et al. provide further evidence that the effects of the complement system on axon regeneration are context dependent.

After optic nerve crush, levels of C1q and C3 increased in the optic nerve, with peak elevation occurring near the injury site. The density of myeloid cells (microglia and/or monocytes) expressing the C3b receptor CR3 also increased. These CR3-expressing cells exhibited signs of phagocytic activity, including internalization of myelin basic protein (MBP), leading to a reduction in MBP levels over time. Notably, axon regeneration was greatest in regions densely populated by CR3-expressing cells and devoid of MBP. Despite this, knocking out C1q, C3, or CR3 had no effect on optic nerve regeneration in the absence of other treatments. When regeneration was stimulated by inducing inflammation or preventing zinc accumulation in the retina, however, knocking out any of these proteins reduced regeneration. Knocking out C1q also suppressed the phagocytic response of CR3-expressing cells, and knocking out CR3 reduced MBP clearance.

These results suggest that the complement system can contribute to regeneration of optic nerve fibers, likely by promoting clearance of myelin debris. But activating the complement system is insufficient to induce regeneration in the absence of other proregenerative treatments. This demonstrates the importance of taking a multipronged approach to induce regeneration in the CNS.

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