

This Week in The Journal

● Cellular/Molecular

Channel Subunits Are Heterogeneously Expressed in the AIS

Andrea Lorincz and Zoltan Nusser

(see pages 14329–14340)

An action potential's threshold and shape are governed by the distribution and subunit composition of voltage-gated sodium and potassium channels in the axon. To learn how differences in subunit expression might contribute to the exact site of action potential initiation, Lorincz and Nusser examined the distribution of four potassium and sodium channel subunits (Nav1.1, Nav1.6, Kv1.1, and Kv1.2) in the axon initial segment (AIS) of neurons in several regions of adult rat brain. The expression pattern was surprisingly heterogeneous across cell types and brain regions. For example, only inhibitory interneurons expressed Nav1.1, and in some neurons, it was expressed along the entire AIS, whereas in others it was restricted to the proximal AIS. Likewise, expression of other subunits was uniform or graded depending on cell type. In Purkinje cells—in which action potential generation occurs in the first node of Ranvier rather than the AIS—neither potassium channel subunit was expressed in the AIS.

▲ Development/Plasticity/Repair

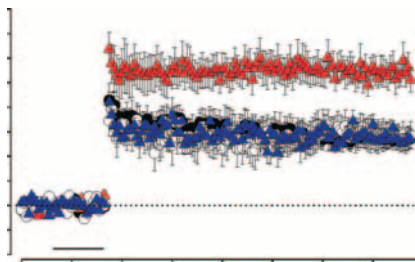
Amyloid- β Enhances Memory

Daniela Puzzo, Lucia Privitera, Elena Leznik, Mauro Fa', Agnieszka Staniszewski, Agostino Palmeri, and Ottavio Arancio

(see pages 14537–14545)

Amyloid- β ($A\beta$) is generally considered a toxic agent in Alzheimer's disease, but it is also released during synaptic transmission in healthy brains. Whether $A\beta$ has a positive function—or is simply an unwanted byproduct created when amyloid precursor protein is cleaved to produce more essential fragments—remains a matter of debate. Evidence from transgenic mice suggests the former: knock-out of enzymes required for $A\beta$ production impairs memory and long-term potentiation

(LTP). More evidence for a positive role of $A\beta$ is presented by Puzzo et al. They found that picomolar (near physiological) amounts of monomeric and oligomeric $A\beta_{42}$ enhanced LTP in mouse hippocampal slices and strengthened reference and contextual fear memory *in vivo*. In contrast, nanomolar concentrations reduced LTP. The enhancement of LTP appeared to occur presynaptically, likely by increasing calcium accumulation, and it required activation of $\alpha 7$ nicotinic acetylcholine receptors. Whether monomeric $A\beta$, oligomeric $A\beta$, or both was responsible for the enhancement is unknown.



$A\beta_{42}$ (200 pM; applied during time indicated by horizontal bar) enhanced LTP in slices from wild-type mice (red), but not from $\alpha 7$ -knock-out mice (blue). White, Untreated wild type; black, untreated knock-out.

■ Behavioral/Systems/Cognitive

BOLD Signals Do Not Always Reflect Neural Activity

Anna Devor, Elizabeth M. C. Hillman, Peifang Tian, Christian Waeber, Ivan C. Teng, Lana Ruvinskaya, Mark H. Shalinsky, Haihao Zhu, Robert H. Haslinger, Suresh N. Narayanan, Istvan Ulbert, Andrew K. Dunn, Eng H. Lo, Bruce R. Rosen, Anders M. Dale, David Kleinfeld, and David A. Boas

(see pages 14347–14357)

Each year, thousands of publications present functional magnetic resonance imaging (fMRI) data that suggest that a particular brain region is active during a particular cognitive task. Casual readers of such papers might forget that this technique does not actually measure neural activity, but rather blood oxygenation level-dependent (BOLD) contrasts. Syn-

aptic transmission requires large energy expenditures, and increased energy metabolism has been hypothesized to act directly on blood vessels to increase blood flow and alter BOLD signals. This week, however, Devor et al. report that this hypothesis is not always correct. As expected, stimulating the forepaw of rats increased blood oxygenation, vessel diameter, glucose uptake, spiking, and synaptic release in the contralateral primary somatosensory cortex. In the ipsilateral cortex, however, neural activity and glucose uptake increased, but blood oxygenation and blood flow did not. These results indicate that blood flow is not directly tied to metabolism, and BOLD signals do not always reflect neural activity.

◆ Neurobiology of Disease

REST and miRNAs Provide Double Negative Feedback

Amy N. Packer, Yi Xing, Scott Q. Harper, Lesley Jones, and Beverly L. Davidson

(see pages 14341–14346)

RE1-silencing transcription factor (REST) inhibits expression of neuronal genes in non-neural cells. Huntingtin sequesters REST in the cytoplasm of neurons, precluding transcriptional repression and allowing neuronal specification. Mutations in huntingtin disrupt its interactions with REST, enabling repression of neuronal genes and contributing to Huntington's disease (HD). Among the genes inhibited by REST are several miRNAs—small, noncoding RNAs that inhibit translation by binding to complementary sequences in regulatory regions of mRNA. Packer et al. found that the levels of several miRNAs decreased as HD progressed. Of these, miR-9 and miR-9* had upstream regulatory regions that enabled repression by REST. Interestingly, regulatory regions of REST and its cofactor CoREST have complementary sequences targeted by miR-9 and miR-9*, and miR-9 reduced expression of REST, while miR-9* targeted CoREST. These molecules apparently form a double negative feedback loop, which is likely important for precise regulation of cell fate commitment.