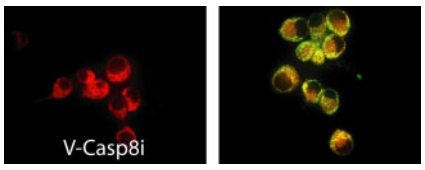
This Week in The Journal

● Cellular/Molecular

Perfecting siRNA Targeting

Thomas J. Davidson, Sivan Harel, Valerie A. Arboleda, Giselle F. Prunell, Michael L. Shelanski, Lloyd A. Greene, and Carol M. Troy
(see pages 10040–10046)

The discovery of RNA interference created new opportunities for experimental manipulation of gene expression. As for any reagent with an intracellular target, a practical issue is how to deliver these sequence-specific double-stranded RNAs into cells. This week Davidson et al. linked synthetic small interfering RNA (siRNA) to the vector peptide Penetratin1 (Pen1). Pen1 is a 16 aa peptide from the third helix of the *Antennapedia* homeodomain protein. The disulfide linkage is cleaved in the reducing environment of the cytoplasm, thus releasing the siRNA. This method allowed rapid uptake into cultured neurons with resulting efficient reduction of targeted proteins within 6 hr. In the authors' case, the targeted proteins were Cu–Zn superoxide dismutase 1 and several caspases. The reduction in protein expression preceded targeted RNA degradation, suggesting that early translational repression is responsible for the reduction in protein. This method offers promise as a nontoxic and low-cost means to reduce expression of targeted proteins in neurons.



Immunostaining of cultured hippocampal neurons for caspase-8 (green) and caspase-9 (red) after treatment with a caspase-8-specific Pen1 siRNA (V-Casp8i; left). An untreated control is shown to the right. See the article by Davidson et al. for details.

▲ Development/Plasticity/Repair

A BDNF Polymorphism and Cortical Size in Normal Humans

Lukas Pezawas, Beth A. Verchinski, Venkata S. Mattay, Joseph H. Callicott, Bhaskar S. Kolachana, Richard E. Straub, Michael F. Egan, Andreas Meyer-Lindenberg, and Daniel R. Weinberger
(see pages 10099–10102)

Brain-derived neurotrophic factor (BDNF) contributes to synaptic plasticity and memory formation by several mechanisms. The human val66met polymorphism in the *BDNF* gene affects its targeting and secretion and thus provides a natural probe of deficits in neurotrophin function. Subjects with met alleles show reduced episodic memory and reduced hippocampal activity during memory tasks. Now Pezawas et al. report that in subjects with even one met allele, form follows function. They drew from an initial pool of 214 subjects that were screened with multiple magnetic resonance imaging scans and then genotyped. Subjects with a met allele had small but significant volume decreases in the hippocampus and also in the dorsolateral prefrontal cortex, two structures linked to memory. The changes were independent of age and sex. The authors suggest that BDNF not only influences fast-acting synaptic mechanisms but also shapes circuit development in a way that can be seen at the macroscopic level.

■ Behavioral/Systems/Cognitive

Associating Action with Reward in the GPe

David Arkadir, Genela Morris, Eilon Vaadia, and Hagai Bergman
(see pages 10047–10056)

The basal ganglia is involved not only in movements but also in the predicted outcome of an action. To chart the convergence of reward- and movement-related activity in the globus pallidus (GPe), Arkadir et al. recorded extracellular unit responses in the GPe during a visuomotor task. Monkeys pressed a button to a visual stimulus indicating the desired direction of movement and the probability of a water reward. The GPe was long considered to be a purely motor area. Indeed, one-third of the units responded only to the direction of movement, and a tiny fraction responded to reward only. However the largest fraction responded to both. In the latter group, responses were time dependent, with activity modulated early in trials by both direction of movement and reward prediction and later by the direction of movement only. The authors suggest that GPe neurons may integrate activity of different neuronal circuits.

♦ Neurobiology of Disease

Nicotine Withdrawal and the β4 AChR Subunit

Ramiro Salas, Fredalina Pieri, and Mariella De Biasi
(see pages 10035–10039)

Sadly, quitting smoking is no easy task. This week, Salas et al. report that nicotinic acetylcholine receptors containing β4 subunits are one of the molecular culprits that makes it hard to quit. In mice, withdrawal causes increased grooming, scratching, shaking, and even hyperalgesia. To examine withdrawal, the authors first delivered nicotine via a transplanted minipump for 13 d, presumably easier than asking the mice to chew nicotine gum. The authors then induced withdrawal by injecting a nicotinic receptor antagonist. Wild-type and β2 subunit-deficient mice displayed withdrawal symptoms, whereas β4 knock-out mice were less affected. Chronic nicotine treatment causes upregulation of nicotinic receptors, an effect thought to contribute to addiction. However the increase in β2-containing receptors did not correlate with signs of withdrawal. The authors suggest that the nicotinic receptors associated with negative reinforcement (withdrawal) may be different from those associated with positive reinforcement, which occurs during the early stages of addiction.