This Week in The Journal

● Cellular/Molecular

PARP-1 and Ischemic Preconditioning

Ischemic Preconditioning by Caspase Cleavage of Poly(ADP-Ribose) Polymerase-1

Philippe Garnier, Weihai Ying, and Raymond A. Swanson
(see pages 7967–7973)

Ischemic preconditioning is a surprising phenomenon in which mild ischemia actually confers short-term protection against more severe cerebral ischemia. An understanding of the molecular events that underlie preconditioning has obvious clinical implications. In this issue, Garnier et al. explore the seemingly paradoxical role of poly(ADP-ribose) polymerase (PARP-1), the normal function of which is to facilitate DNA repair. However, PARP-1 becomes highly activated during ischemia and promotes cell death. PARP-1 can be irreversibly cleaved and inactivated by caspases that are themselves activated during ischemia. Thus the authors hypothesized that caspase cleavage of PARP-1 could cause preconditioning by decreasing the available PARP-1. Consistent with this idea, mouse cortical cultures were less sensitive to injury by a PARP-1-activating agent after a preconditioning stimulus. In addition, the caspase inhibitor Ac-Asp-Glu-Val-Asp-aldehyde (DEVD-CHO) decreased cleavage of PARP-1 and reduced the protection conferred by preconditioning. The data suggest that a delicate balancing act between two cell death pathways contributes to ischemic preconditioning: caspase activation (probably caspase-3), sufficient to cleave PARP-1 but not to cause cell death itself, reduces the cell death attributable to PARP-1.

▲ Development/Plasticity/Repair

Crossing the Midline with Slit2

Slit2 Guides Both Precrossing and Postcrossing Callosal Axons at the Midline *In Vivo*

Tianzhi Shu, Vasi Sundaresan, Margaret M. McCarthy, and Linda J. Richards
(see pages 8176 – 8184)

Commissural axons that cross the corpus callosum must follow a circuitous path involving several turns, and they cannot turn back. Guidance of callosal axons is known to involve bilateral glial structures ("glial wedges") that express the repellant molecule Slit2. In mice lacking Slit2, callosal axons reach the midline but are unable to cross. Instead, they defasciculate and grow into confused, swirling masses called Probst bundles, suggesting that Slit helps guide axons before they cross the midline. However, in the spinal cord, Slit guides axons only after they cross the midline, preventing them from recrossing as they grow along their rostral path next to the floorplate. Shu et al. used a clever approach to investigate the precrossing and postcrossing actions of Slit. The authors injected Slit2 antisense oligonucleotides in one cortical hemisphere *in utero* to deplete the molecule unilaterally. They also blocked Slit2 function by injecting the soluble ectodomain from its receptor, Robo1/2, which is expressed on callosal axons. Finally, they examined the action of Slit *in vitro* using explant cocultures of hemisected cortical slices and glial wedges. Analysis of the path of callosal axons suggested that Slit2 and the glial wedge are important for axon guidance on both sides of the cortical midline.

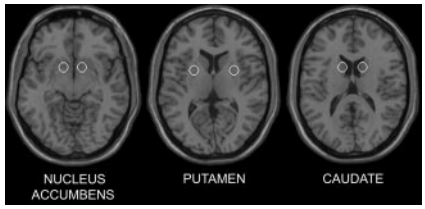
■ Behavioral/Systems/Cognitive

A Human Response to the Unexpected

Human Striatal Response to Salient Nonrewarding Stimuli

Caroline F. Zink, Giuseppe Pagnoni, Megan E. Martin, Mukeshwar Dhamala, and Gregory S. Berns
(see pages 8092– 8097)

How many times has your concentration been rudely interrupted by a sudden movement in the corner of your eye? A study this week by Zink et al. using functional magnetic resonance imaging (fMRI) shows that the human striatum, in addition to processing rewarding stimuli, appears to respond to such salient distractors, which can hardly be considered rewarding. Adult subjects completed a visual task during which distractors flickered in their peripheral vision, drawing their attention away. The particular structures within the striatum responded to different stimuli: the nucleus accumbens had a stronger fMRI signal to increasingly salient (i.e., less frequent) distractors, whereas the caudate responded only to behaviorally relevant cues (i.e., those that required a response from the subject). The results suggest that the striatum responds to the unexpected and arousing as well as to rewarding stimuli. Because fMRI signals are indirect measures of neuronal activity, more study will be necessary to define the cellular mechanisms of saliency responses within the striatum.



The regions of interest (ROIs) in the striatum of human subjects as shown on axial sections of structural template MRI.