This Week in The Journal

Cellular/Molecular

New Roles for ASICs
Acid-Sensing Ion Channel 1 Is Localized in Brain Regions with High Synaptic Density and Contributes to Fear Conditioning
John A. Wemmie, Candice C. Askwith, Ejvis Lamani, Martin D. Cassell, John H. Freeman Jr, and Michael J. Welsh (see pages 5496–5502)

Protons have long been known to evoke excitatory responses in central and sensory neurons. The discovery several years ago of a family of acid-sensing ion channels (ASICs) confirmed the idea that protons open specific channels. With an activation range around neutral pH, these proton sensors are well positioned to sense the pain of ischemia and injury in various peripheral tissues. In the CNS, ASICs likely act as neuronal modulators. Some have postulated that their localization in areas of intense synaptic activity allows them to detect the slightly elevated concentration of protons released from synaptic vesicles. Others have suggested roles in cerebral ischemia and long-term potentiation. In this week’s Journal, Wemmie et al. examined the distribution of ASIC1a in the CNS. They found a remarkably wide expression pattern in areas ranging from the whisker barrel cortex to the striatum, all centers of strong excitatory input. Expression was particularly intense in the amygdala. Following this lead, the group examined a possible behavioral role for ASIC1a there; knock-out mice displayed a deficit in cue and context fear conditioning. Although the expression pattern and channel physiology of ASICs are now fairly well understood, their possible cellular and behavioral roles have only begun to emerge.

Development/Plasticity/Repair

Endogenous Glucocorticoids in Cerebral Immunity
Glucocorticoids Play a Fundamental Role in Protecting the Brain during Innate Immune Response
Sylvain Nadeau and Serge Rivest (see pages 5536–5544)

Neuroendocrine hormones are controlled by highly regulated feedback loops. Thus it is not surprising that either too much or too little of a hormone can be detrimental to brain function. In the case of glucocorticoids (GCs), endogenous GCs regulate the immune response, yet stress-induced GCs can lead to neuronal cell death. Exogenous glucocorticoids are widely used to reduce autoimmune CNS diseases such as multiple sclerosis. GCs inhibit transcription of immune-related genes, including proinflammatory signal cascades such as those involving microglial-derived tumor necrosis factor α (TNF-α). In this issue, Kimpo and Rivest report that endogenous glucocorticoids are essential to prevent an overly exuberant reaction to antigens. For their experiments, they used single intrastriatal injections of the Escherichia coli cell-wall component lipopolysaccharide (LPS). The neuroinflammation induced by LPS was enhanced and accompanied by prominent cell death after inhibition of GCs with RU486, a GC receptor antagonist. Inhibition of TNF-α abolished the neurotoxic effect of RU486, and TNF-α infusion mimicked the damage. Because inhibition of GCs prolonged the inflammatory response, the authors suggest that endogenous GCs control the balance between the short-term positive effects of these cytokines on regeneration and the toxic effects of runaway activation of neuroinflammatory cytokines.

Behavioral/Systems/Cognitive

Spike Timing in the Songbird
Propagation of Correlated Activity through Multiple Stages of a Neural Circuit
Rhea R. Kimpo, Frederic E. Theunissen, and Allison J. Doupe (see pages 5750–5761)

Action potentials within individual neurons in a single brain region can be highly correlated. Such spike timing should be more effective in activating downstream centers in a neural circuit. However, the variability in synaptic transmission predicts that correlated spiking will degrade as the signal is transmitted across multiple synaptic connections. The degradation could in theory be prevented by factors such as high synaptic efficacy or a large pool of synchronized neurons that drive the circuit. In this issue, Kimpo et al. make use of the vocal control circuit in the songbird to examine correlated spiking across multiple brain nuclei. They report that correlated spiking was preserved across the entire circuit involving nuclei separated by three or more synapses. The authors suggest that the high degree of interconnections between these nuclei counterbalance the effect of unreliability of individual synapses. They suggest that the similar architecture in mammalian basal ganglia–cortical circuits may indicate that correlated spiking is a general property of such motor learning pathways.

Models of possible connectivity patterns in the song system of the zebra finch. Each row of circles denotes neurons within a song nucleus, and each row represents a different song nucleus. The activity of neurons 1 and 2 is more likely to be correlated in b or c than in a. This image is taken from Figure 8 of this article.