This Week in The Journal

● Cellular/Molecular

Hypothalamic Degeneration and HAP1

Lack of Huntingtin-Associated Protein-1 Causes Neuronal Death Resembling Hypothalamic Degeneration in Huntington's Disease

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(see pages 6956 – 6964)

Huntington's disease (HD) is marked by a polyglutamine expansion in the disease protein huntingtin (Htt), significant neurodegeneration in several brain areas including the hypothalamus, and an eventual loss of body weight, or "wasting." Mutant Htt with its polyglutamine expansion can associate with several proteins to form cytosolic protein aggregates. One of these is huntingtin-associated protein-1 (HAP1). A recently defined role for HAP1 in trafficking of epidermal growth factor receptor (EGFR) may provide clues to the pathology of HD. This week Li et al. report hypothalamic neurodegeneration in mutant HAP1(−/−) mice. The HAP1 knockout mice also did not gain weight after birth, dying only a few days apparently because of the loss of feeding behavior. Terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling and electron microscopy revealed cell death throughout the hypothalamus. HD mice also had degenerating neurons in the hypothalamus. The authors suggest that loss of HAP1 function in HD arises from binding to mutant Htt, and that a loss of proper EGFR signaling may underlie the behavioral phenotype seen in HD mice, and perhaps patients. HAP1 may play an important part in hypothalamic regulation of feeding behavior, the details of which may one day point to therapeutic targets for HD in humans.

▲ Development/Plasticity/Repair

A BDNF Polymorphism and Human Hippocampal Memory

Brain-Derived Neurotrophic Factor $val^{66}met$ Polymorphism Affects Human Memory-Related Hippocampal Activity and Predicts Memory Performance

Ahmad R. Hariri, Terry E. Goldberg, Venkata S. Mattay, Bhaskar S. Kolachana, Joseph H. Callicott, Michael F. Egan, and Daniel R. Weinberger

(see pages 6690 – 6694)

Brain-derived neurotrophic factor (BDNF) is known to affect hippocampal plasticity and hippocampal-dependent memory. A recently described common single nucleotide polymorphism in the gene $val^{66}met$ affects intracellular trafficking and regulated secretion from neurons, but not the function of the mature protein. Human carriers of the met allele have impaired hippocampal function and episodic memory, suggesting that this genetic variant may contribute directly to human diversity in memory performance. However, a direct link between the met allele and memory-related hippocampal behavior had yet to be demonstrated. Now Hariri et al. have used blood oxygenation level-dependent functional magnetic resonance imaging to examine regional hippocampal activity during an episodic memory test in human subjects with both genotypes. As expected, the results revealed better memory recognition performance in val homozygotes. This group also exhibited greater memory-related hippocampal activity during encoding and retrieval than subjects with the met allele. The results confirm that the BDNF polymorphism affects memory formation in humans as well as animals. It still remains to be seen, however, whether the effect arises from an acute insufficiency in regulated BDNF release during hippocampal activity or from a longer-range effect of the reduced growth factor on the formation of hippocampal neuronal circuits.

■ Behavioral/Systems/Cognitive

Cellular Responses to Contrast in Visual Cortex

Response to Contrast of Electrophysiologically Defined Cell Classes in Primary Visual Cortex

Diego Contreras and Larry Palmer

(see pages 6936 – 6945)

One approach to the diversity of cell types in the cortex is to group them according to their electrophysiological responses. However, it is not always clear whether these experimentally derived classification schemes accurately predict or correspond to *in vivo* responses to natural stimuli. In this week's *Journal*, Contreras and Palmer examine how electrophysiological cell classes in area V1 of the cat visual cortex generate membrane depolarization and spike trains in response to a sensory input, in this case, contrast. They grouped each neuron as regular spiking (RS), fast spiking (FS), fast rhythmic bursting (FRB), or low-threshold spiking (LTS). Next, they created a contrast response function (CRF) for the membrane potential and spike rate response of each neuron. Neurons were also classified functionally as "simple" or "complex" as originally described by Hubel and Wiesel 40 years ago. There was no obvious correspondence between electrophysiological class and functional type, except that LTS cells were exclusively complex. However, the present work revealed that although classes of neurons differed in their firing rates in response to contrast, membrane potential changes were similar. In all cases, the firing behavior of a neuron seemed to depend on the relationship between membrane potential response and spike rate, providing a link, albeit a complex one, between electrophysiological cell class and response to natural stimuli.