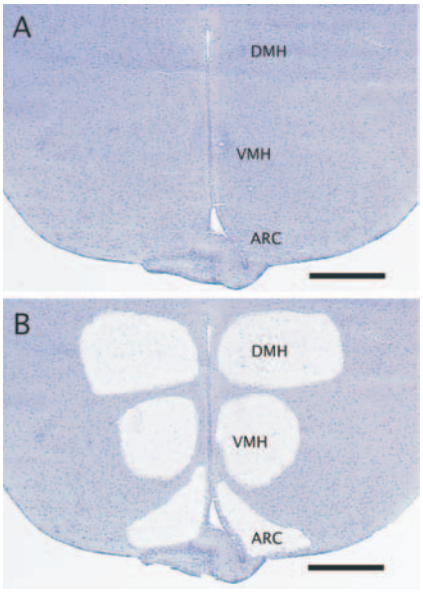
This Week in The Journal

● Cellular/Molecular

On the Trail of Hypothalamic Marker Genes

Jeremy P. Segal, Nancy R. Stallings, Charlotte E. Lee, Liping Zhao, Nicholas Socci, Agnes Viale, Thomas M. Harris, Marcelo B. Soares, Geoffrey Childs, Joel K. Elmquist, Keith L. Parker, and Jeffrey M. Friedman
(see pages 4181–4188)

It has been known for more than half a century that lesions of the ventromedial hypothalamus (VMH) produce hyperphagia and obesity, whereas lateral hypothalamic lesions produce hypophagia and weight loss. However, the complexity of hypothalamic circuits has made cellular and molecular analysis difficult. Several hypothalamic nuclei express specific neuropeptides that allow for cell-type-specific identification, such as orexin in the lateral hypothalamus, oxytocin in the paraventricular nucleus, and proopiomelanocortin in the arcuate nucleus (ARC). However, to date there are no such markers for classes of VMH neurons. Thus Segal et al. set out to identify marker genes using laser-capture microdissection. They identified nine VMH marker genes, several of which were confirmed by *in situ* hybridization, including *pituitary adenylate cyclase activating peptide*, *cerebellin 1*, and a novel expressed sequence tag. One of the nine genes, the transcription factor *steroidogenic factor-1* (*SF-1*), may regulate gene expression in the VMH, because four of the eight VMH marker genes were reduced in SF-1 $^{-/-}$ mice.



Nissl-stained sections of the mouse hypothalamus before (***A***) and after (***B***) excision of specific nuclei [dorsomedial hypothalamus (DMH), VMH, and ARC] by laser-capture microdissection. See the article by Segal et al. for details.

▲ Development/Plasticity/Repair

Branching out with Cul3 in the Fly

Sijun Zhu, Rosanne Perez, Marc Pan, and Tzumin Lee
(see pages 4189–4197)

This week, Zhu et al. identify a seemingly unlikely gene as involved in the development of axons and dendrites. The authors used MARCM (mosaic analysis with a repressible cell marker) technology in developing mushroom body neurons of the *Drosophila* protocerebrum. This approach allows morphological analysis of labeled homozygous mutant neurons within mosaic fly brains. After a chemical mutagenesis screen, the authors identified the *Cullin3* (*Cul3*) gene based on a homozygous lethal phenotype. MARCM analysis of *Cul3* mutant neurons in mosaic fly brains revealed abnormalities in axonal arborization and dendritic elongation. Axons that usually had multiple arbors were stunted, whereas axons that did not normally arborize were seemingly unaffected. Cul3 is a scaffolding protein for E3 ubiquitin ligase complexes that target substrates for degradation. How does that affect axons and dendrites, you ask? Well the cell biology is still not clear, but the authors suggest that Cul3-enhanced turnover of substrates in axonal and dendritic tips likely explains the phenotype.

■ Behavioral/Systems/Cognitive

A One-Sided Fear

Hugh T. Blair, Virginia K. Huynh, Vanessa T. Vaz, John Van, Reekesh R. Patel, Amit K. Hiteshi, Jennie E. Lee, and Jason W. Tarpley
(see pages 4198–4205)

Rodents "freeze" when a neural conditioned stimulus (CS), such as a tone, is paired with an aversive unconditioned stimulus (US), such as an eyelid shock. This pavlovian fear conditioning requires the amygdala, particularly the lateral nucleus of the amygdala (LA), where the CS–US association may be stored. Bilateral amygdala lesions cause severe impairment of fear conditioning, but the left and right amygdala can independently cause mild impairment. Blair et al. now report that the amygdala fear circuitry can be exclusively one-sided, depending on the site of the US. They selectively inactivated either the right or left LA with muscimol infusion. Both acquisition and expression of fear conditioning required only the amygdala that was contralateral to the side of the eyelid shock. In the case of unilateral eyelid shock, it appears that nociceptive pathways drive the contralateral amygdala, suggesting that the fear conditioning circuitry is lateralized depending on the source of the threat.

♦ Neurobiology of Disease

ER-to-Mitochondria Calcium Transfer

Frédéric Darios, Marie-Paule Muriel, Myriam Escobar Khondiker, Alexis Brice, and Merle Ruberg
(see pages 4159–4168)

Calcium accumulation in mitochondria can lead to a death spiral involving mitochondrial dysfunction, cytochrome *c* release, caspase activation, and apoptosis. In the case of excitotoxicity, transmembrane calcium influx appears to enter mitochondria directly. However, in ceramide- or staurosporine-induced cell death, calcium is transferred from the endoplasmic reticulum (ER) to mitochondria. The mysterious (and lethal) calcium transfer requires close apposition of the organelles as well as proapoptotic Bcl-2 family members. This week, Darios et al. show in ceramide-treated cultured neurons and pheochromocytoma PC12 cells that this transfer also depends on cyclin-dependent kinase 5 (CDK5). Calcium levels decreased in the ER as they increased in mitochondria, an effect that was blocked by CDK5 inhibitors. The substrate for the kinase was the microtubule-binding protein tau, specifically the threonine 231 residue. Phosphorylation results in release of tau from microtubules, allowing organelles to cluster and make contact in a sort of traffic jam around the centrosome. The end result is calcium transfer and cell death.