This Week in The Journal

● Cellular/Molecular

PGC-1α May Suppress Eating while Increasing Metabolism

Janna Blechman, Liat Amir-Zilberstein, Amos Gutnick, Shifra Ben-Dor, and Gil Levkowitz

(see pages 14835–14840)

Many hormones, neurotransmitters, tissues, and brain regions cooperate to balance energy expenditure and intake. When energy supplies are high, e.g., after meals, glucose and fat storage are stimulated, metabolism increases, and eating is suppressed. Between meals, stored fat and glucose are released, and as energy stores are depleted, metabolism slows and food seeking is stimulated. Elucidating the signaling pathways underlying energy homeostasis and its disruption may reveal new ways to reduce obesity. One possible target is the transcriptional coactivator PGC-1α, which regulates cellular metabolism by stimulating mitochondrial biogenesis and oxidative metabolism. Studies by Blechman et al. suggest that PGC-1α also reduces eating by regulating expression of the appetite-suppressing peptide oxytocin. Zebrafish PGC-1α binds to the oxytocin promoter in neurons of the neurosecretory preoptic area, and both PGC-1α binding and oxytocin mRNA levels were higher in well fed than in fasted fish. PGC-1α knockdown reduced oxytocin mRNA levels, whereas overexpressing PGC-1α increased oxytocin mRNA.

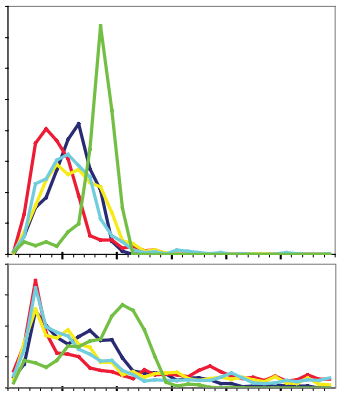
▲ Development/Plasticity/Repair

BrdU Impairs Neuronal Survival and Migration

Alvaro Duque and Pasko Rakic

(see pages 15205–15217)

Cells treated with tritiated thymidine ([^{3}H]dT) or bromodeoxyuridine (BrdU) incorporate these molecules during DNA synthesis, allowing the progeny of dividing cells to be tracked. These techniques have been invaluable in developmental neuroscience, revealing, for example, the inside-out pattern of cortical development and the existence of adult neurogenesis. But the value and prevalence of these techniques often eclipse their toxicity. Because it requires less time, penetrates deeper, allows double-labeling, and is not radioactive, BrdU is generally preferred to [^{3}H]dT; nonetheless, BrdU alters DNA stability, increases double-strand breaks, causes mutations, and can lead to developmental defects. To examine the relative toxicity of BrdU and [^{3}H]dT, Duque and Rakic labeled neuronal progenitors in embryonic monkeys and examined cortical neurons 6 months later. Their analyses suggested that fewer BrdU-labeled cells survived, and these neurons were more widely dispersed across cortical layers than [^{3}H]dT-labeled neurons, suggesting that BrdU impairs neuronal migration as well as survival.



The distribution of labeled neurons across layers from pia (left) to white matter (right) shows that in all cortical regions examined (different color traces), the number of labeled neurons was greater in [^{3}H]dT-treated (top panel) than in BrdU-treated (bottom panel) animals. Furthermore, BrdU-labeled neurons were more widely distributed. See the article by Duque and Rakic for details.

■ Behavioral/Systems/Cognitive

Adult-Born Neurons Encode Components of Memory

Maithe Arruda-Carvalho, Masanori Sakaguchi, Katherine G. Akers, Sheena A. Josselyn, and Paul W. Frankland

(see pages 15113–15127)

Neurons are generated throughout adulthood in the subgranular zone of the dentate gyrus, from which they migrate into the granule cell layer, mature, and become integrated into neural circuits. Adult-born neurons are activated during memory formation and retrieval, but whether they are essential components of memory traces is ambiguous. To investigate this question, Arruda-Carvalho et al. created transgenic mice that expressed both tamoxifen-inducible Cre recombinase under the control of the nestin promoter (which is active in neuronal progenitors) and Cre-inducible diphtheria toxin receptor (DTR). Inducing Cre expression caused expression of DTRs in a limited population of neuronal precursors and their progeny, and these DTR-expressing cells survived until they were selectively killed with diphtheria toxin. Killing adult-generated neurons before mice performed hippocampal-dependent learning tasks had no effect on either learning or recall, but killing neurons after learning altered memory performance. Interestingly, memory was not completely abolished: rather, the ability to distinguish between similar cues was impaired.

♦ Neurobiology of Disease

DHA-Derived Lipid Attenuates Pain Responses

Chul-Kyu Park, Ning Lu, Zhen-Zhong Xu, Tong Liu, Charles N. Serhan, et al.

(see pages 15072–15085)

Upon tissue damage, cells release inflammatory cytokines that promote efflux of proteins and leukocytes from the bloodstream. These stimulate repair processes and phagocytose damaged cells, respectively. Inflammation is actively terminated by anti-inflammatory agents, many of which are derived from polyunsaturated fatty acids such as docosahexaenoic acid (DHA). These lipid mediators act via G-protein-coupled receptors to resolve inflammation by inhibiting cytokine release and leukocyte infiltration. Dysfunction of inflammatory and anti-inflammatory processes leads to chronic inflammation, which contributes to many neuropathological conditions; stimulating inflammation-resolving pathways may mitigate such diseases. Indeed, neuroprotectin D1 (NPD1), a DHA-derived anti-inflammatory lipid produced by neural tissue, appears to be protective in models of stroke, retinal injury, and Alzheimer's disease. Park et al. show that NPD1 may also reduce chronic inflammatory pain by inhibiting long-term potentiation of nociceptive inputs onto spinal neurons. This effect likely was mediated by interfering with signaling downstream of tumor necrosis factor α and TRPV1 channels.