This Week in The Journal

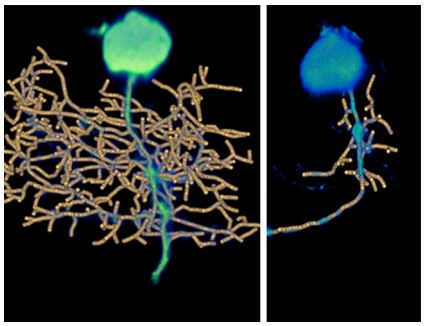
Development/Plasticity/Repair

Adf-1 May Pause FasII Transcription to Allow Dendrite Growth

Christina Timmerman, Somu Suppiah, Baraka V. Gurudatta, Jingping Yang, Christopher Banerjee, et al.

(see pages 11916–11931)

Memory formation requires changes in gene expression, which is achieved by activating various transcription factors, many of which also have roles in synaptic development. One such transcription factor is Adf-1 in *Drosophila*. Timmerman et al. found that reducing Adf-1 expression led to decreased growth and branching of motor neuron dendrites. Removing a putative phosphorylation site in Adf-1 likewise reduced dendritic growth and branching and prevented activity-induced increases in these features. Interestingly, Adf-1 binding sites were often found in promoters at which RNA polymerase II pauses for a long time after initiating transcription and at which histone modification patterns indicated low transcriptional activity, suggesting a role for Adf-1 in transcriptional pausing. Consistent with this hypothesis, inhibiting Adf-1 increased expression of one of its targets, FasII, a neural cell adhesion molecule implicated in dendritic growth and memory formation, and overexpressing FasII recapitulated the reduction of dendritic growth and branching that occurred when Adf-1 expression was decreased.



Mutating a putative phosphorylation site in Adf-1 (right) decreased dendritic length and branching in a *Drosophila* motor neuron, relative to control (left). See the article by Timmerman et al. for details.

Systems/Circuits

AgRP Stimulates Hepatic Triglyceride Production

James P. Warne, Jillian M. Varonin, Sofie S. Nielsen, Louise E. Olofsson, Christopher B. Kaelin, et al.

(see pages 11972–11985)

Energy homeostasis is maintained by a complex network of hormones that carry status information between the gut, brain, and other organs to regulate nutrient intake, storage, and usage. Leptin, which is produced by adipocytes, is a key component of this network. Leptin inhibits production of agouti-related protein (AgRP), a powerful inducer of food intake, by hypothalamic neurons. Between meals, leptin levels drop, allowing AgRP production to rise, thus promoting food consumption. Warne et al. demonstrate that AgRP also stimulates hepatic production of triglycerides, which are required to make ketone bodies—an important energy source during fasting. Expression of mRNA encoding DGAT2, an enzyme involved in triglyceride synthesis, progressively increased in mouse liver during fasting, while plasma leptin levels dropped. Injecting leptin or knocking out AgRP prevented increases in hepatic *Dgat2* mRNA and triglyceride levels, suggesting disinhibition of AgRP production underlies these effects. The effects of AgRP appeared to be mediated by suppression of hepatic norepinephrine release, which normally lowers *Dgat2* mRNA levels.

Behavioral/Cognitive

Stress Inhibits Dopamine Clearance in Nucleus Accumbens

Evan N. Graf, Robert A. Wheeler, David A. Baker, Amanda L. Ebben, Jonathan E. Hill, et al.

(see pages 11800–11810)

Cocaine addicts are more likely to seek cocaine when under stress. The cellular and molecular underpinnings of this stress-induced relapse are unclear. Relapse is studied in rats by first training them to self-administer cocaine by pressing a lever, extinguishing lever pressing by administering saline instead of cocaine, then testing the ability of experimental manipulations to induce reinstatement of lever pressing. Although neither acute stress nor lever-independent administration of low cocaine doses induce reinstatement, Graf et al. found that reinstatement occurred when these two treatments were combined. Reinstatement required release of endogenous corticosterone from the adrenal glands or injection of exogenous corticosterone into the nucleus accumbens (NAc). Reinstatement also required dopamine release in the NAc, but corticosterone did not stimulate such release. Instead corticosterone potentiated cocaine-induced increases in dopamine levels, most likely by inhibiting dopamine clearance by members of the so-called uptake$_2$ family of monoamine transporters. Indeed, another inhibitor of these transporters replicated the effects of corticosterone, potentiating cocaine-induced reinstatement of cocaine seeking.

Neurobiology of Disease

Chromatin Structure Regulates Transcription of GAD1

Rahul Bharadwaj, Yan Jiang, Wenjie Mao, Mira Jakovcevski, Aslihan Dincer, et al.

(see pages 11839–11851)

Gene transcription requires binding of RNA polymerase to a promoter, which can be facilitated by binding of transcription factors to enhancer regions. Enhancers are sometimes located far from promoters, however; in these cases, the enhancer is functional only when the 3D structure of the DNA strand brings the enhancer close to the promoter. Thus, regulation of chromatin 3D structure can control whether transcription factors activate particular genes. Using the chromosome conformation capture technique to map interactions between noncontiguous regulatory elements, Bharadwaj et al. discovered interactions between the transcription start site of *GAD1*, which encodes the GABA-synthesizing enzyme GAD67, and a sequence ~50 kB upstream that had several characteristics of enhancers. The interaction, likely made possible by chromosomal loop formation, occurred in human prefrontal cortex, but not skin fibroblasts, and in mouse brain it occurred selectively in GABAergic neurons. Interestingly, the interaction was reduced in prefrontal cortex from schizophrenic patients, suggesting that alteration of 3D chromatin structure contributes to reduced GAD67 expression in this disease.