This Week in The Journal

Presynaptic Calcium Channels in Homeostatic Plasticity

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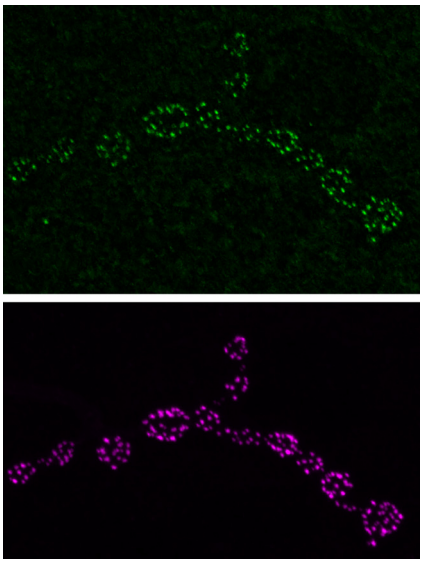
(see pages 2416–2429)

Neurons maintain optimal activity levels by engaging homeostatic plasticity mechanisms that produce changes in intrinsic excitability, neurotransmitter-receptor expression, and presynaptic vesicle release. At neuromuscular junctions (NMJs) of larval *Drosophila*, reducing muscle activation by blocking glutamate receptors leads to a compensatory increase in vesicle release from motor neurons, a phenomenon called presynaptic homeostatic potentiation (PHP). Conversely, increasing the amount of glutamate in each synaptic vesicle leads to reduced vesicle release, called presynaptic homeostatic depression (PHD). These changes in vesicle release result from changes in spike-triggered calcium influx and, for PHP, the size of the readily releasable pool of vesicles.

Experiments using fluorescently tagged Cacophony (Cac), the voltage-gated calcium channel involved in synaptic vesicle release in *Drosophila*, suggested that PHP- and PHD-associated changes in calcium influx result from changes in the number of Cac channels present in the presynaptic membrane. But in these studies, a single Cac isoform was overexpressed using the transcriptional activator GAL4, so the channel was produced at abnormally high levels and its transcriptional regulation and protein–protein interactions were likely disrupted.

To measure endogenous Cac levels without these confounds, Gratz et al. used CRISPR to add a fluorescent tag to the native Cac gene. This revealed that the number of channels varies considerably across the hundreds of active zones formed by single motor axons. The number of channels was strongly correlated with the probability of vesicle release, as measured by the postsynaptic response. Consistent with previous work, inducing PHP by knocking out a glutamate receptor subunit caused Cac levels to increase in presynaptic active zones. Blocking glutamate receptors also increased Cac levels; this occurred within minutes, and the increase at each site was proportional to the initial Cac level. In contrast, inducing PHD by overexpressing a vesicular glutamate transporter in motor neurons did not affect Cac levels in presynaptic active zones.

These results suggest that PHP-associated increases in spike-induced calcium influx are mediated at least partly by increases in the number of Cac channels present at active zones, whereas PHD-associated decreases in calcium influx are not accompanied by changes in Cac levels. Instead, decreases in calcium influx might result from changes in the functional properties of Cac channels.



Fluorescently tagged Cac (top) aligns with the active-zone protein Bruchpilot (bottom) at NMJs of *Drosophila* larvae. See Gratz et al. for details.

The Genetics of Impulsivity

Sandra Sanchez-Roige, Pierre Fontanillas, Sarah L. Elson, Joshua C. Gray, Harriet de Wit, et al.

(see pages 2562–2572)

To prosper, people must often consider the pros and cons of various options, choose actions with tolerable risks, and delay actions until an appropriate time. The tendency not to deliberate or delay action is called impulsivity. Because impulsivity is thought to contribute to various psychiatric conditions, including substance-use disorders, researchers have sought to identify the genetic bases of this trait. Difficulties have emerged, however, because impulsivity is a complex construct with multiple subcomponents that probably are shaped by different sets of genes. Furthermore, various assessments define different subcomponents of impulsivity. For example, one commonly used questionnaire, the UPPSP, defines four subcomponents—lack of premeditation, lack of perseverance, urgency (inability to refrain from acting under strong positive or negative emotions), and sensation seeking (the desire to engage in new or exciting activities)—whereas another common assessment, BIS-11, includes three—attentional, motor, and nonplanning subcomponents.

Sanchez-Roige et al. used genome-wide association studies in >22,000 people to find genetic variants associated with drug use and/or with the subcomponents of impulsivity measured by UPPSP and BIS-11. They found that genetic variation accounted for 5–11% of the variability in impulsivity and drug use across individuals. Moreover, sensation-seeking, premeditation, urgency, motor, and nonplanning subcomponents of impulsivity were genetically correlated with lifetime cannabis, tobacco, and/or alcohol use. The analyses also revealed high genetic correlation among attentional, motor, and nonplanning aspects of impulsivity. But of the UPPSP subcomponents, only urgency and premeditation showed significant genetic correlation; sensation seeking was not genetically correlated with any other aspect of impulsivity.

Two single-nucleotide polymorphisms (SNPs) were significantly associated with impulsivity: a SNP at *CACNA1I*, which encodes a subunit of T-type voltage-dependent calcium channels, was associated with negative urgency, and a SNP in *CADM2*, which encodes a synaptic cell adhesion molecule, was associated with sensation-seeking. Notably, variation in *CADM2* was also associated with drug experimentation.

These results suggest that sensation-seeking is somewhat different from other aspects of impulsivity and that variations in *CADM2* contribute to this trait, as well as to drug use. This is consistent with previous results that linked *CADM2* to risk-taking and drug use. Studies in animals might clarify how *CADM2* affects these behaviors.

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