This Week in The Journal

5-HT Enhances Depolarization by Reducing Ca^{2+} Influx

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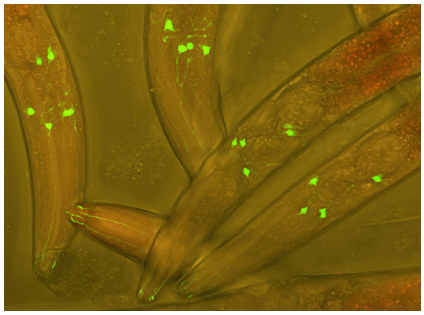
(see pages 2069–2080)

Animals adjust their responses to stimuli depending on context. For instance, signs of danger might delay approach to food unless an animal is extremely hungry. The ability to vary behavioral responses depends on neuromodulators that alter neuronal excitability and synaptic communication. In *Caenorhabditis elegans*, for example, serotonergic signaling elicited by the presence of food potentiates aversive responses to the odorant 1-octanol. This effect is mediated in part by serotonergic modulation of ASH nociceptors, which trigger reverse locomotion. Specifically, serotonin (5-HT) increases 1-octanol-evoked depolarization and reduces 1-octanol-evoked calcium transients in ASH neurons (Zahratka et al. 2015 J Neurophysiol 113:1041).

Although enhancement of ASH depolarization can explain serotonergic potentiation of aversion, the simultaneous decrease in ASH calcium transients is perplexing. These transients are mediated primarily by L-type voltage-sensitive calcium channels (L-VSCCs), and should therefore increase with increased depolarization. Williams et al. now explain this counterintuitive finding. They report that direct depolarization of ASH with potassium, like 1-octanol, elicited L-VSCC-dependent calcium transients, and that serotonin blunted this effect by acting on SER-5 receptors. SER-5 receptors are coupled to $G\alpha_q$, and as is typical of $G\alpha_q$ signaling, activation of SER-5 led to release of calcium from intracellular stores. Downstream activation of the calcium-dependent phosphatase calcineurin acted to reduce calcium transients elicited by subsequent application of 1-octanol. Moreover, blocking L-VSCCs potentiated 1-octanol-evoked depolarization of ASH. Finally, the voltage- and calcium-activated potassium channel SLO-1 was required for serotonin to potentiate aversive responses.

Together, these results suggest that 1-octanol-mediated depolarization of ASH neurons leads to influx of calcium through L-VSCCs, and this limits depolarization by opening SLO-1 potassium channels. In the presence of food, serotonin binds to SER-5 receptors, leading to release of calcium from internal stores, downstream activation of calcineurin, and reduction of calcium influx—possibly via dephosphorylation of L-VSCCs, as occurs in some mammalian neurons. Regardless, calcium reduction leads to closure of SLO-1 channels, reducing their hyperpolarizing effect and thus enhancing depolarization. Besides elucidating the mechanisms through which serotonin enhances aversive responses in *C. elegans*, these results demonstrate that calcium levels are not always an accurate measure of neuronal depolarization—an important caveat for those using calcium indicators to measure neuronal activity.



C. elegans are transparent, allowing visualization of neurons that express fluorescent proteins, such as genetically encoded calcium indicators. Changes in calcium levels are not necessarily accurate reflections of depolarization, however. See Williams et al. for details. Image by Heiti Paves. CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=16624959.

Role of eIF4E Phosphorylation in Depression

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(see pages 2118–2133)

By regulating translation, cells can rapidly synthesize proteins when and where they are needed. Translational regulation occurs primarily at the initiation step, where eukaryotic initiation factors (eIFs) bring mRNA and ribosomal subunits together. In most cases, mRNA is brought into the initiation complex by eIF4E, which binds to the 5′ cap. Sequestration of eIF4E by eIF4E-binding proteins inhibits this step, thus limiting translation of many mRNAs. Growth factors and other signals promote phosphorylation of eIF4E-binding proteins, causing them to release eIF4E, which then promotes translation of eIF4E-dependent proteins.

Direct phosphorylation of eIF4E is another potential mechanism of translational control. A single residue on eIF4E (Ser209) is phosphorylated by Mnk kinases, which are activated downstream of MAPK and ERK kinases. These kinases are activated by many signaling molecules and are important for synaptic plasticity. Intriguingly, phosphorylation of eIF4E is stimulated by fluoxetine, a common antidepressant that inhibits serotonin reuptake. How eIF4E phosphorylation affects translation, particularly in neurons, is poorly understood, however.

To address this question, Amorim et al. used knock-in (4Eki) mice in which mutation of Ser209 precluded phosphorylation. Remarkably, 4Eki mice exhibited behaviors that model depression and anxiety: compared with wild-type, they spent more time immobile in forced-swim and tail-suspension tests, and they spent less time in the center of an open field and in the open arms of an elevated plus maze. Moreover, fluoxetine treatment failed to decrease immobility time in 4Eki mice, like it does in wild-type. These behavioral effects likely stemmed from altered translational profiles. Although global translation levels were unchanged, translation of numerous mRNAs was reduced in 4Eki mice, whereas translation of some mRNAs increased. Transcripts lacking sequences that allow eIF4E-independent translation were particularly subject to downregulation. Notably, several genes involved in serotonergic signaling and inflammation were upregulated in 4Eki mice. Some of these transcripts harbored sequences in their 3′ untranslated regions that inhibit translation through interaction with eIF4E.

These data suggest phosphorylation of eIF4E facilitates its role in translation, promoting expression of specific proteins. Loss of this regulation might be important in the etiology of depression, particularly forms that do not respond to antidepressant treatment. Thus, these results might prompt the discovery of new treatments for depression.

This Week in The Journal was written by Teresa Esch, Ph.D.