This Week in The Journal

How Relaxin-3 Increases Eating

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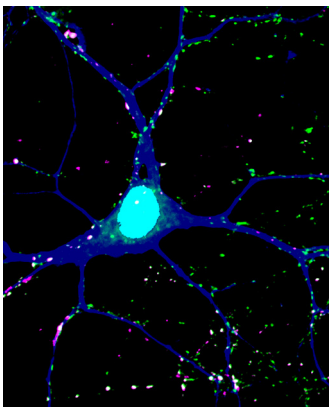
(see pages 5362–5375)

Relaxin-3, a neuropeptide expressed primarily in neurons in the pontine nucleus incertus, regulates arousal, stress responses, and feeding by activating relaxin-family peptide receptor 3 (RXFP3). This $G_{i/o}$-coupled receptor is expressed in many brain areas, including the hypothalamus. Injection of relaxin-3 into the hypothalamic paraventricular nucleus (PVN) of rats increases food intake and weight gain, with larger effects in females than in males. Furthermore, repeated periods of food restriction followed by stress and access to highly palatable food increases relaxin-3 expression and binge-like eating selectively in female rats, and the excessive eating is blocked by an RXFP3 antagonist (Calvez et al., 2016, Br J Pharmacol 174:1049). Previous work by Kania et al. suggested that relaxin-3 promotes eating by inhibiting PVN neurons that produce the anorexigenic hormones oxytocin and arginine-vasopressin (AVP). That work was done exclusively in males, however, and how RXFP3 activation caused neuronal hyperpolarization remained unresolved. In their current work, these authors compared relaxin-3 expression, projection patterns, and effects on PVN neurons in male and female rats.

Application of relaxin-3 or an exogenous RXFP3 agonist produced hyperpolarizing outward currents in nearly all magnocellular PVN neurons, including both oxytocin- and AVP-expressing neurons, in hypothalamic slices from male and female rats. The amplitude of these currents was similar in the two sexes. The agonist did not induce outward currents at the potassium reversal potential, but it induced inward current at this potential in ~40% of neurons in both sexes. Notably, the agonist-induced current was blocked by cadmium, which blocks calcium currents, as well as by a blocker of potassium M-type currents. Furthermore, KCNQ2, a potassium channel that mediates M-currents, was expressed along with RXFP3 in many magnocellular neurons. Consistent with previous work, relaxin-3-expressing axons were dense around PVN, but sparse within the nucleus itself. This pattern was similar in males and females, but the fiber density was higher in females.

These data suggest that relaxin-3 inhibits oxytocin- and AVP-expressing PVN neurons by activating M-currents. This effect might depend on calcium influx, at least in some cells. The effects of relaxin-3 are similar in males and females, but PVN receives denser innervation from relaxin-3-expressing fibers in females. This might help explain why females are more sensitive than males to stress-induced feeding.



Ectopic expression of Kirrel3 in CA1 pyramidal neurons induces formation of synapses (white) with dentate granule cell axons. See Taylor, Martin, et al. for details.

Role of Kirrel3 in Synapse Formation

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(see pages 5376–5388)

For neural circuits to function properly, growing axons must bypass many neurons they encounter and form synapses only with appropriate targets. This is achieved through cell-type-specific expression of synaptic adhesion molecules: an axon expressing one type of synaptic adhesion molecule will form synaptic adhesions only with dendrites that express the proper partner molecule. Synaptic adhesion molecules do not just mediate cell recognition, however: some also initiate synapse formation by recruiting components of vesicle release machinery and postsynaptic receptor complexes.

Mutations in several synaptic adhesion molecules are linked to autism spectrum disorders and intellectual disability. At least 17 variations in Kirrel3 have been identified in people with such conditions, for example. Furthermore, knockout of Kirrel3 produces autism-related phenotypes in mice. Because Kirrel3 knockout selectively disrupts the formation of synapses between dentate granule cell axons and GABAergic interneurons in hippocampal area CA3, hyperexcitability of CA3 pyramidal cells may account for the behavioral phenotypes.

To investigate how Kirrel3 influences synapse formation, Taylor, Martin, et al. expressed Kirrel3 in dissociated hippocampal neurons, including CA1 pyramidal neurons that do not normally express this protein. Transfected neurons were then cocultured with nontransfected neurons, allowing wild-type granule cell axons to contact both wild-type and Kirrel3-expressing pyramidal cells. Ectopic expression of Kirrel3 significantly increased the number of presynaptic terminals formed on CA1 pyramidal cells by dentate granule cell axons, but it did not increase the number of contacts between axons and dendrites or the number of presynaptic boutons formed by other pyramidal neurons. Expression of Kirrel3 in CA1 neurons did not increase synaptic input from dentate granule cells in which Kirrel3 had been knocked out, however. Importantly, when Kirrel3 variants linked to neurodevelopmental disorders were expressed in pyramidal cells, four of six failed to induce synapse formation, even though two of these retained the ability to mediate cell adhesion. A fifth variant impaired, but did not prevent synapse induction, and the sixth did not significantly alter synapse formation.

These results indicate that interactions between presynaptic and postsynaptic Kirrel3 induces synapse formation between neurons not only by forming transsynaptic adhesions, but also by recruiting other synaptic components. Future work should determine which of these components interact with the intracellular domain of Kirrel3.

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