This Week in The Journal

Endocannabinoid Signaling Differs in Males and Females

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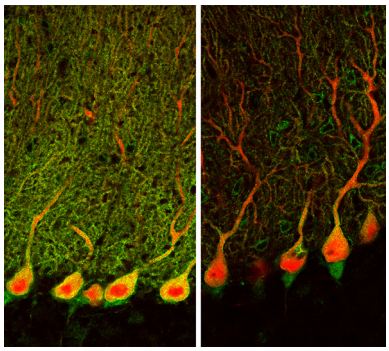
(see pages 11252–11265)

Although estrogen is typically considered a female gonadal hormone, it is also produced in the brain of both males and females. Estrogen—particularly 17β-estradiol—increases EPSC amplitudes in some hippocampal pyramidal neurons, enhances long-term potentiation, increases dendritic spine density, and enhances memory performance in both male and female rats. These effects are mediated by estrogen receptors (ERs) that can act as transcription factors or activate other signaling pathways. Notably, ERs can initiate signaling by metabotropic glutamate receptors (mGluRs) independently of glutamate (for review, see Sellers et al., 2015, Front Neuroendocrinol 36:72).

While many neurophysiological effects of estradiol are similar in males and females, some effects are sex-specific. For example, estradiol suppresses inhibition of 50–60% of hippocampal pyramidal neurons in female, but not male, rats. This effect is mediated by ERα, requires activation of mGluRs and presynaptic endocannabinoid receptors, and stems from reduced probability of GABA release. Having further investigated the molecular pathways underlying estradiol-induced suppression of inhibition, Tabatadze et al. report that it requires activation of mGluR1, downstream activation of phospholipase C and inositol triphosphate receptors (IP3Rs), and resulting increases in Ca^{2+}. This signaling pathway triggers production of the endocannabinoid anandamide in some cells. Inhibiting anandamide breakdown was previously shown to occlude estradiol-mediated suppression of inhibition, supporting the hypothesis that this pathway is responsible for estradiol's effect.

Interestingly, although mGluR1 agonists induced similar increases in IP3 levels in males and females, and although estradiol-mediated suppression of inhibition was wholly mediated by mGluR1, estradiol induced a greater elevation of IP3 in females. This suggests that estradiol potentiates mGluR1-mediated signaling selectively in females. Consistent with this, estradiol promoted formation of protein complexes containing ERα, mGluR1a, and IP3R in females, but not in males. In addition, inhibiting anandamide breakdown in the absence of exogenous estradiol reduced IPSCs in ~55% of female neurons, but not in males, suggesting that GABA release is tonically inhibited by anandamide only in female rats.

These results emphasize that sex differences in neurophysiology extend beyond differential effects of sex hormones. Such differences may contribute to sex differences in stress responses and other endocannabinoid-regulated behavior.



Compared to wild-type cerebellum (left), BK channel expression (green) is reduced in 5-week-old ATXN[82Q] cerebellum (right). Calbindin expression (red) suggests PC dendrites have not significantly atrophied at this age. See Dell'Orco et al. for details.

Atrophy May Compensate for Channel Loss

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(see pages 11292–11307)

The electrical properties of neurons are determined by the complement of ion channels they express. Homeostatic processes are thought to coordinate channel expression levels to ensure that the electrical properties remain stable over time, but these processes are sometimes unable to offset disruptions in channel expression or function. This is clear from the existence of several neurological conditions—including some forms of epilepsy and ataxia—linked to mutations in channel proteins.

Spinocerebellar ataxia type 1 (SCA1) is a neurodegenerative disease caused by mutation of the gene encoding ataxin-1 (*ATXN1*). Although *ATXN1* is widely expressed, the mutated form most strongly affects cerebellar Purkinje cells (PCs), which atrophy early in the disease and eventually die. Because ATXN1 is a transcriptional regulator, the loss of PCs in SCA1 may result from altered expression of genes required for PC function. Dell'Orco et al. reveal that these genes include voltage-sensitive K+ channels.

PCs normally exhibit spontaneous spiking that depends partly on inwardly rectifying K^+ (KIR) and big-conductance, Ca^{2+}-activated K+ (BK) channels. Although apparently normal spontaneous activity was present in 2-week-old mice expressing human SCA1-linked ataxin-1 (ATXN[82Q]), spontaneous activity was absent in mutant PCs by 5 weeks. This loss of activity was attributable to reduced expression of BK and two KIR channels. Because of this reduction, the amplitude of the spike afterhyperpolarization (AHP) was reduced in ATXN[82Q] PCs, making the cells unable to sustain repetitive spiking.

Surprisingly, although BK channel expression further declined in ATXN[82Q] PCs by 15 weeks, the AHP returned to wild-type amplitudes and spontaneous spiking reemerged. Because PC dendrites had begun to atrophy at this time, the authors hypothesized that the atrophy restored BK channel density to near-normal levels despite reduced overall expression. Indeed, levels of BK channels relative to an indicator of dendritic arbor size was similar in wild-type and ATXN[82Q] cerebella. Furthermore, increasing BK channel expression in ATXN[82Q] cerebella reduced dendritic loss while rescuing AHP amplitude and spontaneous spiking.

The authors suggest that dendritic atrophy is a homeostatic response to compensate for reduced K^+ channel density and thus reinitiate spontaneous spiking. While this compensation does not appear to prevent loss of motor function, it may extend the period of normal functioning. Smaller-scale changes in dendritic arbor size might be used to regulate neuronal electrical properties in the normal brain.

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