Endocannabinoid Signaling Differs in Males and Females

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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 signaling by metabotropic glutamate receptors. This signaling pathway triggers 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.

PCs normally exhibit spontaneous spiking that depends partly on inwardly rectifying K+ (KIR) and big-conductance, Ca2+-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.