Investigative Ophthalmology & Visual Science

Estrogen Potentiates Inositol 1, 4, 5–Trisphosphate Receptor–Mediated Calcium Signaling in Rod Bipolar Cells

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Commercial Relationships: P. Koulen, None; **C. Madry**, None; **E. Nixon**, None; **N. McClung**, None; **J.W. Simpkins**, None; **M. Singh**, None.
Support: UNTHSC Intramural Research Program and NIH grants AG22550 and EY14227

Abstract

Purpose: Homeostasis and control of the intracellular calcium concentration are critical for multiple physiological and functional processes in neurons as well as for neuronal viability. Inositol–1, 4, 5–trisphosphate(IP3) receptors (IP3Rs) are major intracellular calcium channels releasing calcium from intracellular stores, such as the endoplasmic reticulum, and contribute to calcium–mediated neuronal functions. IP3Rs are gated by their ligand IP3 and are subject to modulation by a plethora of intracellular signaling substances including the cytosolic calcium concentration itself. Besides their well–documented function in non–excitable cells, endogenously produced steroid hormones have been shown to modulate normal neuronal function as well as to contribute to neuroprotection. In the present study, we investigated the effect of estrogen / 17 ß–estradiol (E2) on IP3Rs and subsequently on homeostasis and control of the intracellular calcium concentration in rod bipolar cells of the mouse retina. Besides identifying mechanisms of action underlying neuronal calcium signaling in the retina, the study determined potential novel therapeutic strategies for treating retinal neurodegenerative diseases.

Methods: Rod bipolar cells were exposed to E2 and the expression and distribution of IP3Rs, estrogen receptors and related signaling molecules was determined with immunochemistry. Functional effects of E2 exposure were analyzed with optical imaging of intracellular Ca2+ concentrations in acutely isolated rod bipolar cells and single channel electrophysiology of IP3Rs.

Results: Estrogen receptors and IP3Rs were colocalized intracellularly in rod bipolar cells. E2 treatment of rod bipolar cells led to a robust phosphorylation of IP3Rs and in parallel a significantly potentiated IP3R channel activity. In isolated rod bipolar cells, IP3R–mediated intracellular Ca2+ signals were detected after E2 treatment that showed a significant correlation with the E2–mediated changes in the biophysical properties of IP3Rs.

Conclusions: Data from the present study suggest that steroid hormones control the intracellular calcium concentration in retinal neurons through activation of kinases that target IP3Rs. Furthermore, steroid hormones appear capable of influencing the gain and sensitivity of calcium signaling pathways indicating potential roles in retina neuroprotection.
Supported by a grant from The UNT Health Science Center Intramural Research Program (MS, PK), and NIH grants AG22550 (JWS, MS, PK), and EY14227 (PK).

Keywords: retina • retina: proximal (bipolar, amacrine, and ganglion cells) • neuroprotection