Frontiers in Neuroendocrinology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review article

Gonadal hormone modulation of intracellular calcium as a mechanism of neuroprotection

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ARTICLE INFO

Article history:
Received 1 November 2015
Received in revised form 22 February 2016
Accepted 26 February 2016
Available online xxxx

Keywords:
Calcium
Sex differences
Development
Estradiol
Testosterone

ABSTRACT

Hormones have wide-ranging effects throughout the nervous system, including the ability interact with and modulate many aspects of intracellular calcium regulation and calcium signaling. Indeed, these interactions specifically may help to explain the often opposing or paradoxical effects of hormones, such as their ability to both promote and prevent neuronal cell death during development, as well as reduce or exacerbate damage following an insult or injury in adulthood. Here, we review the basic mechanisms underlying intracellular calcium regulation—perhaps the most dynamic and flexible of all signaling molecules—and discuss how gonadal hormones might manipulate these mechanisms to coordinate diverse cellular responses and achieve disparate outcomes. Additional future research that specifically addresses questions of sex and hormone effects on calcium signaling at different ages will be critical to understanding hormone-mediated neuroprotection.

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http://dx.doi.org/10.1016/j.yfrne.2016.02.003
0091-3022/

1. Introduction

Gonadal steroid hormones such as testosterone and estradiol have profound effects throughout the nervous system; perhaps most striking is their control of sexually dimorphic cell death. For example, males have more motoneurons in the spinal nucleus of the bulbocavernosus (SNB) than females, due to neuroprotection afforded by the androgen, testosterone (Breedlove and Arnold, 1983; Nordeen et al., 1985). Since neonatal males produce testosterone from their testes, more SNB neurons are protected from death and males end up with a larger SNB than females. Paradoxically, though, hormones are not always neuroprotective – the same hormone can increase or decrease the amount of neuronal cell death depending on the brain area. The estrogenic metabolite of testosterone, estradiol, protects neurons in the sexually dimorphic nucleus of the preoptic area (SDN), leaving this nucleus volumetrically larger in males than females (Davis et al., 1995; Arai et al., 1996). In the nearby anteroventral periventricular nucleus (AVPV), on the other hand, the presence of estradiol increases cell death, producing a smaller nucleus in males (Sumida et al., 1993; Arai et al., 1994; Zup et al., 2003; Waters and Simerly, 2009). Therefore, gonadal hormones themselves do not possess intrinsic protective or toxic properties, but instead must interact with different intracellular signaling molecules and pathways to appropriately "organize" the nervous system in a sex specific manner. The resulting sexually dimorphic nervous system then serves as a substrate for adult hormones to activate functions and behaviors appropriate for that sex (reviewed in Zup and Forger, 2002a). For example, estradiol acts on the large AVPV present in adult females to coordinate ovulation (Gu and Simerly, 1997), a function obviously only required for females. In addition to shaping adult physiology and behavior, developmental hormones can also affect cell death processes in adulthood, as early hormone exposure can alter neuronal survival in disease states or following injury. We suggest that a large number of these dynamic and varied effects of hormones can actually be explained by their interaction with a single signaling mechanism: calcium.

Perhaps the first question to be addressed is, why calcium? Why is this divalent cation at the heart of hormonal effects and sex differences in neuronal survival? Calcium is the most abundant intracellular signaling molecule in mammalian cells and is elegantly coordinated: simultaneously simple and complex. The concentration of extracellular free calcium is in the millimolar range with intracellular calcium levels hovering around 100 nM, thereby creating a striking 10,000-fold concentration gradient larger than that of any other ion such as Na^+ or K^+ (reviewed in Carafoli, 2002; Brini et al., 2014; De Loof, 2015). When excited, a neuron experiences a massive surge of calcium that enters the cell via neurotransmitter receptors and calcium channels from the external milieu, and is also released from internal storage sites. Therefore, a sudden and dramatic increase in free cytosolic calcium is a robust on/off indicator of neuronal function.

The high levels of intracellular calcium present after neuronal firing are, however, toxic. Individual neurons must employ a range of strategies to keep a tight rein on this potentially lethal ion, such as regulating the rate of calcium influx from outside the cell, sequestering calcium within organelles, and adjusting the number and activity of calcium sensing molecules such as calbindin and calmodulin. The physical location of these different mechanisms within a neuronal network and within a single neuron, along with differences in the timing and coordination of these mechanisms, allows for a complex array of possible neuronal responses to that "simple" signal of cytosolic calcium influx. This complexity allows calcium to act as an effective and flexible signaling molecule, one that hormones can harness to activate a variety of second messenger systems and changes in gene transcription, and ultimately drive differences in both excitation and cell death.

2. Mechanisms of intracellular calcium regulation

Changes in intracellular calcium convey different information depending on localization within the cell and the timing of calcium release: from milliseconds (*e.g.* inducing the fusion of presynaptic vesicles to the axonal membrane) to seconds (*e.g.* activating second messenger cascades) to minutes (*e.g.* modulating endoplasmic reticulum and mitochondrial function or facilitating gene transcription). Therefore, the information carried by the calcium signal depends on where, when, and how the calcium enters and exits the cytosol. Excellent reviews provide in-depth explanations of these mechanisms (*e.g.* Miller, 1988; Carafoli, 2002; Clapham, 2007); here, we will briefly cover them (Fig. 1) to facilitate discussion of the developmental and hormonal influences that fine-tune these processes, including regulation of extracellular calcium, intracellular calcium and the coordination of these at the mitochondria to alter apoptosis.

2.1. Calcium from the external milieu

Most often, calcium enters neuronal somata and dendrites due to presynaptic neurotransmitter release and a subsequent change in membrane potential; it is this influx that can act as an acute and binary signal of neuronal activity. While the specific mechanism of calcium influx can vary, in general, there are two key avenues for calcium entry from the external milieu: through voltage-dependent calcium channels (VDCC), especially after excitatory events (via glutamate or excitatory GABA), and through the NMDA glutamate receptor itself.

2.1.1. Voltage-dependent calcium channels

Any depolarizing event allows calcium into the neuron due to the opening of voltage-dependent calcium channels (VDCCs) in

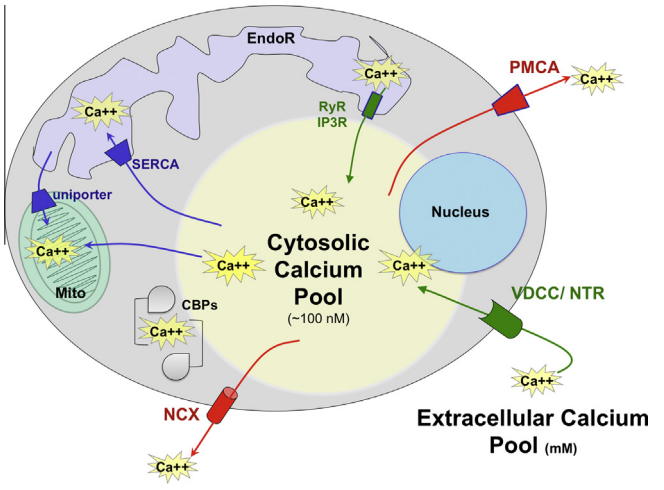

Fig. 1. Mechanisms of calcium influx and homeostasis. Free calcium can enter the cytosol though VDCCs or from internal stores via the ryanodine receptor or IP3 receptor. Homeostatic levels are regained by pumping calcium out to the extracellular space via NCX or PMCA, or into internal stores via SERCA. Calcium can also be inactivated or corralled into microdomains by calcium binding proteins. Abbreviations: EndoR, endoplasmic reticulum; Ca++, calcium; SERCA, sarco/endoplasmic reticulum calcium ATPase; mPTP, mitochondrial permeability transition pore; mito, mitochondrion; NCX, sodium calcium exchanger; VDCC, voltage-dependent calcium channel; NTR, neurotransmitter receptor; CBPs, calcium binding proteins; PMCA, plasma membrane calcium ATPase; RyR, ryanodine receptor; IP3R, IP3 receptor.

Please cite this article in press as: Zup, S.L., Madden, A.M.K. Gonadal hormone modulation of intracellular calcium as a mechanism of neuroprotection. Front. Neuroendocrinol. (2016), http://dx.doi.org/10.1016/j.yfrne.2016.02.003