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Review

Estrogen and the regulation of mitochondrial structure and function in the brain

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ABSTRACT

The mitochondrion is the unquestionable cellular compartment that actively preserves most of the cell functions, such as lipid metabolism, ion homeostasis, energy and ROS production, steroid biosynthesis, and control of apoptotic signaling. Thus, this cell organelle depicts a major drop-in centre for regulatory processes within a cell irrespective of the organ or tissue. However, brain tissue is unique in spite of everything due to its extremely high energy demand and sensitivity to oxidative stress. This makes brain cells, in particular neurons, considerably vulnerable against toxins and challenges that attack the mitochondrial structural organization and energetic performance. Estrogens are known to regulate a multitude of cellular functions in neural cells under physiological conditions but also play a protective role under neuropathological circumstances. In recent years, it became evident that estrogens affect distinct cellular processes by interfering with the bioenergetic mitochondrial compartment. According to the general view, estrogens indirectly regulate the mitochondrion through the control of genomic transcription of mitochondrial-located proteins and modulation of cytoplasmic signaling cascades that act upon mitochondrial physiology. More recent but still arguable data suggest that estrogens might directly signal to the mitochondrion either through classical steroid receptors or novel types of receptors/proteins associated with the mitochondrial compartment. This would allow estrogens to more rapidly modulate the function of a mitochondrion than hitherto discussed. Assuming that this novel perception of steroid action is correct, estrogen might influence the energetic control centre through long-lasting nuclear-associated processes and rapid mitochondria-intrinsic temporary mechanisms. In this article, we would like to particularly accentuate the novel conceptual approach of this duality comprising that estrogens govern the mitochondrial structural integrity and functional capacity by different cellular signaling routes.

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Contents

Abbreviations: ARKO, aromatase-knockout mice; CamK, calcium-dependent calmodulin kinase; cAMP, cyclic adenosine monophosphate; CGSD, combined glucose-serum deprivation; CNS, central nervous system; COX, cytochrome c oxidase; CREB, cAMP response element-binding protein; D1, dopamine D1 receptor; Dyn, dynamin-related protein; ER, estrogen receptor; Fis, fission protein; GFAP, glial fibrillary acidic protein (astroglial marker); GPR30, G-protein coupled receptor 30; ICI, ICI 182,780; IHC, immunohistochemistry; ko, knockout; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; Mfn, mitofusin; MNAR, modulator of nongenomic activity of ER; MRC, mitochondrial respiratory chain; mtDNA, mitochondrial DNA; ncDNA, nuclear DNA; NRF, nuclear respiratory factor; OVX, ovariectomized; PELP1, prolin-, glutamic acid-, leucine-rich protein1; PGC, peroxisome proliferator-activated receptor; PI3K, phosphatidylinositol kinase; PKA, protein kinase A; PKC, protein kinase C; ROS, radical oxygen species; SERM, selective estrogen receptor modulator; Src, sarcoma; Tfam, mitochondrial transcription factor A; UCP1, uncoupling protein from brown adipose tissue mitochondria.

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1. Estrogen and cell function and signaling

The steroid hormone 17β-estradiol or derivatives either reaching the brain via peripheral circulation or formed/metabolized intrinsically within the brain by neurons and astroglia represent well-known regulative factors in the CNS. During development, distinct aspects of neuronal differentiation, synapse and neural network formation are under the control of estrogen irrespective of the gender [1–3]. In addition, sex-specific aspects of CNS maturation are largely due to the presence or absence of estrogens during specific time windows of brain development [4,5]. Later in life, estrogens are decisive for the control of the hypothalamic-pituitary axis and reproduction [6]. Besides these well-described effects, estrogens are directly implicated in the control of motor and cognitive behavior often associated with synaptic remodeling of brain structures such as the nigro-striatal complex and hippocampus, respectively [3,7–10]. Finally and in the focus of actual research, this gonadal steroid fulfils the criteria of a neuroprotective agent in the brain either under acute toxic and hypoxic challenges such as stroke or classical neurodegenerative conditions including Parkinson's and Alzheimer's disease as well as multiple sclerosis [11–15]. Thus, this steroid hormone is eligible and undisputed for playing a neurodevelopmental, neuroplastic, and neuroprotective role in the CNS.

To ensure this multifaceted role, the brain, i.e. neurons, astrocytes, and oligodendrocytes, is equipped with all known estrogen receptors (ER) and has even the ability to synthesize de novo estrogen by expressing all relevant metabolizing enzymes and in particular the key enzyme aromatase [16–20]. Although not object of this article, we want to emphasize at this stage that the presence of classical nuclear ERs and estrogen-synthesizing enzymes is not ubiquitously distributed in the CNS but rather highly regulated in an age-, brain region-, sex-, and damage-specific way. This allows estrogens to act in a precisely controlled fashion depending on the susceptibility of target cells and tissues. In order to refine effects of estrogen on the cellular level, we would like to briefly summarize the state of the art of estrogen signaling, since this will be of importance for the understanding of estrogen action upon mitochondria. In the past years, tremendous advances have been made in elucidating the cellular mechanisms by which estrogen mediates its effects on the cellular and molecular level. Yet, classical genomic signaling involving the two known ERs in mammals, ER-α and ER-β, is the major route of intracellular estrogen action and is responsible for long-term steroid effects in the range of hours–days. Besides, a number of non-classical but receptor-dependent pathways of estrogen-mediated effects have been discovered covering typically rapid and short-term effects in the range of seconds–minutes–hours. These involve binding to membrane-bound receptors/proteins such as G-protein-coupled receptor 30 (GPR 30) [21,22], caveolin-associated proteins [23], various neurotransmitter receptors [24,25], the sigma-1 receptor system [26], cytoplasmic coupling to and activation of a plethora of different intracellular signal transduction pathways including cAMP/PKA/CREB, PI3-kinase, CaMK, MAPK/Src-kinase, the scaffolding protein MNAR/PELP1, p21-activated kinase, and Ca^{2+}-signaling [26–32], interactions with growth factor signaling cascades [33] as well as non-classical probably receptor-independent action including the role as radical scavenger [34] and interactions with ion channels [35,36]. Although much effort has been put into this research field, only spares information is available concerning the different molecular mechanism which defines the selective coupling to these different signal pathways.

2. Mitochondrial estrogen signaling and mitochondrial estrogen receptors

The multitude of ERs and signaling systems and the only partially availability of highly specific pharmacological inhibitors makes it at the moment very difficult to attribute estrogen effects to a respective signaling pathway. With respect to the mitochondrial complex, there is also information showing that the mitochondrion itself represents a target for estrogen. The major routes of direct and indirect estrogen interactions with the mitochondrial complex are highlighted in Fig. 1. Although it is now firmly established that estrogen and its receptors exist outside the nucleus, one has to say however with certain constraints that the data concerning direct estrogen- or ER and mitochondria interactions are still preliminary and need further verification. This applies particularly to the physiological processes which might be subsequently regulated intrinsically to this cell compartment. Most of these studies originally derived from other tissues and organ systems such as the uterus, cardiovascular system, bone- and cancer tissue but have now also found their counterpart in the CNS [37–39]. Mitochondria typically integrate a number of signaling cascades through different intracellular routes activated by a variety of molecules. Here, we attempt to focus where possible on intra-mitochondrial processes and interactions. Briefly, we would like to summarize the supportive evidence that ERs are part of the mitochondrial complex which was subject of several excellent recent reviews [38,39]. Estrogen receptor-α and ER-β have been first described in the rabbit reproductive tract [40]. The existence of mitochondrial ERs in the matrix was further corroborated in MCF-7 cells by Chen and coworkers using subcellular fractionation together with biochemical and immunochemical standard approaches [39]. These findings were then successively approved in the CNS, where brain endothelial cells were shown to contain intra-mitochondrial ER-α [41] and mitochondrial ER-β was detected in the forebrain and hippocampus using ultrastructural analysis [42,43]. Thus, it seems safe to conclude that both types of classical ERs are present in the mitochondrion. Interestingly, mitochondrial variants of the classical nuclear ERs have been reported which reveal differences in their expression profiles during aging [44]. The presence of the ER-β1 subunit but not of others in the mitochondria of different cell types suggests the implication of a selective mitochondrial import mechanism, i.e. the mitochondrial targeting polypeptide signal, encoded within the ER-β1 [45]. Up to now, the majority of data indicate that ER-β is more frequently present in the mitochondrion of neural cells compared to ER-α. Several important questions arise from these observations are whether (i) ERs in the mitochondrion are stationary or freely moving, (ii) ERs shifting between different cellular compartments including the mitochondrion and, if so, how they are im-/exported, (iii) ERs require dimerization to achieve their full activity in this cell compartment as known for the nucleus, and (iv) estrogen receptor response elements are known for mitochondrial-encoded genes or, alternatively, other ER-mediated intra-mitochondrial actions exist.

Besides classical ER-mediated action inside the mitochondrion, one has additionally to consider other mitochondrial proteins/structures as interaction partners and receptor structures for activated ERs or estrogen itself. Grossmann et al. reported in 1989 immunoreactive estrogen-binding sites within the mitochondrial matrix in pancreatic acinar cells [46]. A decade later, it was demonstrated that radioactive-labeled estrogen coupled to bovine serum albumin binds directly to and inhibits the subunit (oligomycin sensitivity-conferring protein, OSCP) of the proton FOF1 mitochondrial ATPase/ATP synthase in brain tissue which is