EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 7
150-155
Year: 2016

NON-CLASSICAL ESTROGEN/XENOESTROGEN RECEPTOR SIGNALLING IN MODULATION OF NEURONAL FUNCTION

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Article Received on 26/04/2016 **Article Revised on 16/05/2016** **Article Accepted on 05/06/2016**

ABSTRACT
Significance of fast signalling membrane-linked nonclassical estrogen receptors has emerged in recent years to understand biological consequences of exposure to many environmental estrogenic substances. Any menace from fast signalling receptor function should primarily affect excitable tissue functions eg.the nervous system. Both peripheral and higher functions may be subject to infringement. Architecture of estrogen receptors; their interaction with ligands and dynamics are all very complex, associated with peculiar variation of outcomes as per the contexts. Receptor molecules, their association molecules, signaling cascades and second messengers exhibit differences based on contexts. The challenge for progress of physiological and pharmacological understanding of biologic involvement of estrogens in health and disease of organs and human being demands the defining of patterns amidst the chaos. This is timey attempt to review the context, as environmental estrogens acquire greater place among ubiquitous pollutants.

KEYWORDS: Membrane estrogen receptors; Endocrine disruptors and nervous function; Nervous estrogenic action.

INTRODUCTION

Environmental xenoestrogens modify developmental process of organisms and contribute to increased incidence of some cancers. Given the usual exposure levels, these effects do not convince of genomic mechanisms of xenoestrogen effects. This has led to discovery of cell membrane located receptors, distinct from nuclear steroid receptors. Context dependency is distinctive feature of receptor physiology and pharmacology of steroid hormones, including estrogen. Neither complete nor crucial aspects of structure and function of such receptors are revealed using agonist and antagonist manipulation. These aspects appear to be dependent on interaction of the receptors with associated partnering proteins, which differ among different cells and tissues.

Membrane Estrogen Receptor

Membrane estrogen receptors are mobile proteins in clusters. These are unevenly scattered and therefore, other signalling molecules influence their interactions and activation events. Response of such receptors commences at cell membrane, carried inwards and may even reach the nucleus.[1] When genes coding estrogen receptor are transfected in to different cell types, the generated receptor molecules exhibit changed preference for ligands. Their responses to estrogen, in context of different cell types, differ both in case of genomic and non genomic or non classical schemes.[2] Pocket of proteins associating receptor that bind the ligands, may change under influence of local environmental components, including other proteins and lipids.

Estrogen Receptor Ligands

Estrogenic ligands may signal by binding to certain region on receptors of other well defined mediators (viz. adrenaline, serotonin, GABA etc), or estrogen receptors may signal sharing activation of protein kinases, also influenced via other receptors.[3,4] Estrogen may bind and induce allosteric change in enzymes, causing their activation. In this respect, protein kinases, ATPase, glyceraldehyde-3-phosphate dehydrogenase are identified as estrogen receptors. The estrogen receptors may be interacting with such enzymes directly or indirectly via adaptor molecule.[5] Membrane of some cells have receptor to bind the estrogen binding globulin of plasma. When membrane bound, such protein can stabilize or DOCK membrane estrogen receptor and participate in mediating membrane action of estrogen. Other unique membrane associated proteins are described to bind estrogen with physiologic consequences.[6,7]

The interaction of estrogen receptors with receptors and effectors of peptide hormones and growth factors, further increases complexity of single protein mediated estrogen signalling.

Estrogen receptor seems like an organization centre for interaction or co-modulator of other functional proteins. An attempt to knock out signalling at one receptor site may affect signalling through other mechanisms. Thus blockade of estrogen-induced MAPK activation accompanies block of mRNA expression for prolactin. Anti sense technique suppressing formation of estrogen receptors may suppress other receptor types.[8] Estrogen receptor systems thus represent context modified systems.

Membrane estrogen receptors in nervous tissue

Estradiol binding proteins in cell membrane of various neurons include estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), G-protein coupled estrogen receptor (GPR 30), estrogen receptor X (ER-X) and a receptor that may be activated by STX (an estrogen like agent). The membrane associated ERα and ERβ rely on metabotropic glutamate receptors to activate cell signalling events. Assembly of signalling complexes of these receptors is served by GPR-30 as scaffolding protein. GPR-30 has typical G-Protein-Coupled-Receptor trans-membrane part that can activate protein kinases and modulate calcium signalling. STX-stimulated estrogen binding protein is probably also a GPR, found in hypothalamic neurons and involved in homeostatic regulation. ER-X is functionally coupled to MAP Kinase.[9]

Estrogen/ Xenoestrogen actions and Hormesis

When more than one estrogen receptors are present in same tissue of cell population mediating genomic or non-classical responses, ERα generally dominates response. ERβ or GPR-30 if working with ERα, bear antagonistic influence on the response/function.[10]

Estrogens can activate several pathways simultaneously. Signalling by different estrogens however proceeds through specific pathways at different speeds. Different concentrations and combinations also cause such difference.[11] Multiple pathways, in time and dose-dependent manner, contribute to a composite effect on shared target. Time course of non-classical responses to different estrogen/xenoestrogen is different and the dose-response relationship is non-monotonous (the monotonous response rises with increasing dose and finally plateaus at maximum). Successive increasing doses therefore, do not yield unidirectional change in response. They may be irregular or opposite and even revert. By analogy to electrical circuits, the multiple signalling pathways evoked may be seen as linked not in "series" but in "parallel". There are other reasons to cause non-monotonous dose-responses. The different receptor targets may contribute opposing effects to one another. The estrogen activation of phospho-Erk would be opposed by estrogen activation of phosphatases. Opposite effect profile with increasing dose is termed Hormesis.[12]

The effects of estrogens/xenoestrogens are indeed studied on top of the physiological signalling of endogenous estrogen. Bisphenol A (BPA) and other xenoestrogens therefore, cause concentration-dependent enhancement or inhibition of specific signalling events.[13,14] In general, the lowest xenoestrogen concentrations enhance the activity induced by physiological estrogen and the highest cause inhibition. There can be instances however, when xenoestrogen enhances the hormonal endpoint at every concentration or inhibits at every concentration. Impact may fluctuate back and forth, between inhibition and enhancement, in case of agents with extreme non-monotonic response curves.[15] Estrogen receptors liganded by a given estrogen create specific shape changes in the receptor. As a result different constellation of interaction surfaces bind other proteins. The partner proteins may be activated or recruit additional proteins, toward the functional response.[16] Differences of lipid content and availability of other signalling molecules and scaffolding proteins in the receptor environment influence responses for different rates and directions. Multiple signalling pathways are at naturally different phases of travel and subject to feedback or feed forward regulatory mechanisms. There can be a crossover to parallel paths. Various regulatory mechanisms in different cell populations at any point of time affect respective expression level of membrane estrogen receptors.[17] Protein content and osmolarity of the milieu critically influences regulation and signalling in cells.[18] All these contribute to different response levels for dose at different time points.

Affinity and activation of Non-Classical Estrogen Receptors

Multiple mechanisms of mediation of non-classical estrogen effects, through estrogen receptor types in different systems are reported.[19,20] Rapid estrogenic responses usually initiate second messenger triggered signal cascades arising from plasma membrane. Such mechanisms are reported for every class of steroid hormones and related compounds.[21] Broad tissue distribution of multiple subtypes of ERs, working via multiple pathways can explain xenoestrogen effects and can guide ways of preventing and treating their adverse health effects.

There are fine differences in amino acids which line the ligand binding pockets of the estrogen receptor protein. ERα and ERβ receptor subtypes therefore, show different selectivity for the ligands. The phyto-estrogens exhibit low but selective binding to ERβ. BPA has higher affinity for binding to GPR 30 than for binding to ERα or ERβ. The ability of ERα and ERβ to bind co-activator proteins differs according to the xenoestrogen ligands. In presence of xenoestrogen, ERβ activation exhibits higher

ability of recruiting co-activators than does ERα. There is consequent enhancement of some responses.[22] Tissue-dependent complex agonist, antagonist behaviour of certain xenoestrogen may be due to differences in recruiting ability for co-activator proteins of ERα and ERβ depending on the ligand. Xenoestrogen Bisphenol A induced rapid, dose dependant and irreversible inhibition of monosynaptic and polysynaptic spinal reflexes. These effects were preventable by tamoxifen pretreatment, indicating ER-alpha mediation. 17-beta estradiol was devoid of any effect on synaptic transmission, their by proving distinctive BPA specific mechanism. Transmission inhibitory effect involved BPA enhancement of nitric oxide formation. Nitric oxide may directly, or via GABAergic link, may bring about observed depression of mono and polysynaptic reflexes.[23]

Regulation of localization of receptors is significant determinant of specificity or kind of signalling. Artificial alteration of localization of ER profoundly affects choice of signalling pathways. Plasma membrane localizing ability of ERα and ERβ differs cell types with differences in signalling. The kinetic properties of signals generated via ERα or ERβ differ, resulting in different downstream consequences.[24] Physiological estrogen is mostly bound to globulin and only small circulating fraction may enter cell. Membrane resident ERα receptors are dominant determinants of most non-classical responses on account of ready accessibility to ligands. In estrogen free-state, ERα predominates at neuronal membrane and MAPK activation mediated by ER-alpha is much faster than by ERβ. After estrogen binds ERβ in cytoplasm or nucleus they move transiently and rapidly to cell membrane domain. Such translocation brings active ERβ in proximity to downstream rapid signal transduction molecules.

Estrogen entry dependent ERβ activity then appears to counter ERα signalling. When higher estrogen milieu results in significant intracellular entry of estrogen, BPA exhibits higher affinity to bind available ERβ than ERα.[25] ERα selective effects are however exhibited by BPA at lower concentrations.[26]

Non-Classical Estrogen receptors: Cellular physiology

Estrogen ERα is co-localized with caveolin$_1$, a scaffolding protein. The mitochondria always have ERβ even in cells not exhibiting any membrane estrogen receptors. Mitochondrial ERβ does not translocate upon binding estrogen. Importance of scaffolding proteins is apparent in regard to ER translocation and consequent signalling. ERβ may mediate some or all estrogen effects on mitochondrial function.[27]

Both ERα and ERβ are expressed throughout brain and contribute to neuronal effects of estrogen. PI_3 Kinase/ ErK (extracellular regulated Kinase) pathway is shared by both ERα and ERβ. Temporal (time-dependent) coding for induction of the cascade by ERα and ERβ is different, however.[28] An estrogen sensitive protein (different from known kinds of estrogen receptor), is born on mitochondrial membrane, termed estrogen related receptor, ERR. It does not bind 17β-estradiol but interacts with several other estrogen receptor agonists and antagonists.[29] BPA induced inhibition of mono and polysynaptic spinal reflexes, also was not replicated by 17-beta estradiol, in our study.[23] ERRs mediate activation/ inhibition of mitochondrial calcium uni-porters on exposure to pharmacological concentrations of estrogen agonists and antagonists. The agonists activate while antagonists inhibit Ca^{2+} uniporter activity. Ca^{2+} uptake by mitochondria plays a key role in the control of cellular calcium homeostasis.[30] In experiments on frog sciatic nerve, BPA induced inhibition of combined action potential also involved calcium dependant mechanism.[31] The cytoplasmic Ca^{2+} buffering actions of mitochondria are enhanced by estrogen agonists, which, is considered neuro-protective.[32]

Cross talks between conventional membrane estrogen receptors with the G-protein coupled receptor is important to stimulation of signalling responses. ERs interact with GPRs in cell membrane and indirectly influence G-protein coupling.

Conventional estrogen receptors ERα and ERβ are not protein Kinases. They lack properties of adaptor or scaffolding components of protein Kinase signalling cascade. Interaction of ERs with adaptor proteins is necessary to mediate rapid activation of MAPK pathway by estrogen. Estrogen stimulation of MAPK (Erk) activation through phosphorylation and activation of C-ras, Src, raf and recruitment of adaptors Shc and Grb_2 at the cell membrane is thought to involve different estrogen receptor, ER-X.

Rapid activation of PKC and PKA by estrogen depends on G-protein Gαq coupled activation of phospholipase C. Impermeable estrogen-BSA complex also has such effect, so the effect is surface mediated. Antagonist tamoxifen also has such effect, which shows that ERs are not mediating the effect. Activation of ErK and C-fos is not blocked by tamoxifen, which suggest these estrogen effects are not mediated by conventional ERs.[33]

Modulation of Neuronal Function

Estrogen modulation of neuronal activity involves alterations of ion channel opening, G-protein signalling and activation of trophic factor like signal transduction pathways.[34]

G-protein stimulation is implied in alteration of ion channel opening and second messenger signalling by estrogen for modulation of neuronal activity.[35] The classical membrane receptor mediating the estrogen effect is ERα.[36] One of the hypotheses is that ERα and ERβ might directly bind G-proteins, but this cannot

explain variety of signalling cascades activated by estradiol.[37]

Estrogen binding to ER, trans-activates metabotropic glutamate receptors (mGluR), independently of glutamate. Conformational change of mGluR activates G-protein to initiate second messenger signalling. Direct interaction of ERs with mGluR is also detected. The expression of mGluR is restricted to nervous tissue. Interestingly different regions in brain have different types of mGluR interacting with ER, despite the fact that same messenger system is activated as consequence. Interaction of ER with mGluR is dependent on Caveolin proteins.[38]

G-protein coupled estrogen receptor GPR-30 differs in structure from classical ERs, however has similar ligand binding affinities in the receptor pocket, broadly. BPA exhibits 8 to 50 times higher binding affinity to GPR-30 in various contexts, compared to its affinity for classical ERs. Several of intracellular signalling pathways activated by estrogen in GPR-30 bearing cells are reported. Most xenoestrogens act both on classical and GPR-30 estrogen receptors to produce effects.[39] Estrogen stimulation of GPR-30 triggers production of cAMP.[40] There is intracellular Ca^{2+} release also[41], and there is activation of inositol triphosphate Kinase (IP_3K).[42] Estrogen increases protein Kinase activity through classical ER which modulates the GPR30 coupling to effector system stated above, throughout the CNS.

In dorsal root ganglia neurons, GPR30 expression is universal across all populations of neurons. Potential overlap of GPR30 expression is particularly very high with ERβ expression. The neurons that express ERα have majority of those co-expressing GPR30, but such dual ERα/ GPR30 expressing neurons constitute higher percentage in male. ERα is known to inhibit calcium influx in DRG neurons by trans-activating mGluR and subsequent G-protein coupled signalling. Such mechanism in nociceptive neurons would inhibit nociceptive input. There are indications that ERβ partially contributes pro-nociceptive estrogen effect.[43] GPR30 agonist G1 is also found to dose-dependently depolarize cultured spinal cord neurons.[44] GPR30 agonist G1 however, like ERα agonist, attenuates calcium influx in DRG neurons-induced by ATP and such inhibitory effect of estrogen is blocked by GPR30 antagonist G15.[45] Inhibition of ATP-induced calcium influx by estrogen was found mediated through ERα and GPR30 receptors, which probably involves intracellular cAMP-PKA-ErK1/2 pathway. Some of these mechanisms corroborate with reported BPA induced depression of compound action potential in frog sciatic nerve, by involving calcium dependant events.[31] The role of ERβ in brain is significant and often seen as counter balancing ERα activity.[46] Prolonged estrogen exposure is understood to down regulate neuronal ERα but upregulates ERβ, exhibiting a kind of adaptation.

ERβ activation is understood to inhibit Capsaicin-induced TRP-vanilloid$_1$ ($TRPV_1$) receptor activation which is involved in desensitization of neurons to pain through sustained elevation of intracellular calcium ion.[47] Nitric oxide (NO) also is known to inhibit voltage activated calcium ion currents in Capsaicin sensitive afferent neurons.[48] This effect of NO is inhibitory to nociception. Although all DRG neurons express NO-synthase, the expression is more in thoracic and declines progressively in rostral and caudal parts of spinal cord. In periphery NO exerts sensitization of afferent nerve fibers.[49] Estrogen increases NO production and effects of estrogen on neuronal NOS (n-NOS) are region dependent. Estrogen alters the NOS expression by activation of ERβ and is partially mediated through NO-signalling.[50] BPA induced inhibition of mono and polysynaptic reflexes studied by us suggested involvement of distinctive ER-alpha receptor type (unaffected by estradiol, linking to nitric oxide formation.[23] There could be role of interlinked GABAergic mechanisms as well.[51]

Among the classical estrogen receptors, ERα represents the faster activated membrane receptor, while the ERβ responses have necessarily to be delayed on account of the need to first translocate to the membrane. Rapid desensitization is distinct feature of G-protein coupled receptor and hence they are more suited to play modulatory roles. Cross talk of ERα receptor with GPR30 receptor would boost response at the start. Later desensitization in GPR30 receptor will result in impediment of response requiring ERα-GPR30 cross talk. These possibilities are analogous to the modulatory pre-synaptic auto-receptors neurotransmitter systems. Ab-noxious or nociceptive stimuli may be less perceived by interference in neuronal signal. In long run, such signals, when sustained, also serve as mechanism for desensitization of nociceptive perception. An interference with signalling would result in failure of desensitization and exaggerated nociception. This is the case in post traumatic neuralgia and such other conditions.

Epilogue

The context dependent signalling of non-classical estrogen receptors may exhibit both co-operation and counter-balancing relationship among various known receptor types. Overtly, the ERα in outer membrane, appeals as primary in non-classical estrogen and xenoestrogen signalling. The more inwardly placed receptor sub-types might come into play roles for homeostasis. The scope for them to synergistically serve physiologic and toxic excegency also requires exploration. Stimulant functional effects of estrogen frequently reveal co-operation among ERα and GPR30 receptors. The clinical consequences of long term exposures to xenoestrogen and resultant disruption in estrogen receptor neurophysiology will bear such consideration.

Conflict of interest

There is no conflict of interest.

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