Bioenergetics: Open Access
ISSN: 2167-7662

Mao, Bioenergetics 2014, 3:2
DOI: 10.4172/2167-7662.1000e120

Editorial Open Access

New Insights into Estrogen Signaling

Peizhong Mao[1, 2*]

[1]*Department of Physiology & Pharmacology, Oregon Health and Science University, Portland, OR, USA*

[2]*Division of Neuroscience, Oregon National Primate Research Center, Oregon Health and Science University, Beaverton, OR, USA*

[*]**Corresponding author**: Peizhong Mao, Ph.D, Research Assistant Professor, Department of Physiology & Pharmacology, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098, USA; E-mail: maop@ohsu.edu

Rec date: May 27, 2014, **Acc date:** May 29, 2014, **Pub date:** May 31, 2014

Editorial

Many important molecules have a dual role in the human body. As a key representative, 17β-estradiol (E2), a fundamental steroid hormone, has diverse physiological functions in different parts of the body, while its cellular proliferation or mitogen role is somehow implicated in the induction and promotion of cancinogenesis. E2 actions in the reproductive system are via the classic mechanism, which is a nuclear receptors-involved genomic-associated pathway, to affect the expression of target genes. Recent years, the fact that estrogens function in other systems such as brain, especially via non-genomic pathways, has drawn attention.

Recently, a French population-based prospective study including more than 5,000 postmenopausal women aged 65 years or older investigated the association of endogenous estrogen (total- and bioavailable-E2) with the 4-year incidence of all-cause dementia [1]. They found that high E2 level is an independent predictor of incident dementia, particularly in postmenopausal women with diabetes; total and bioavailable-E2 showed similar results but not testosterone. Interestingly values of E2 in the lower quartile were also associated with dementia and Alzheimer's disease (AD), indicating there is a significant role for estrogen at both physiological and pathological levels in the brain and dementia development.

This investigation is consistent with the recent reports that postmenopausal women treated with a lower dose of E2 showed improvement in learning and memory functions [2,3]. E2 is made in adipose, brain and other tissues in the postmenopausal women via aromatase [1,4,5]. It has been shown that blockage of estrogen syntheses impairs cognitive function in breast cancer patients that have been treated with an aromatase inhibitor [6]. In addition, increasing data from experimental animals have demonstrated that estrogen has a neuroprotective role in the brain [7]; estrogen also modulates neuronal synaptic plasticity via multiple mechanisms, such as facilitating long-term potentiation (LTP) and increasing spine numbers in hippocampus [8-10].

Classic steroid signaling is the widely accepted mechanism by which estrogens exert their biological effects via binding and activating nuclear estrogen receptor alpha (ERα) and beta (ERβ), which result in alterations in gene transcription and protein synthesis [11,12]. Disruption of the ERα (esr1) in humans is not lethal but confers a profoundly estrogen-resistant state [13,14]. A young woman with a homozygous esr1 missense mutation in a highly conserved Gln residue within the ligand-binding domain of ERα showed abnormalities mainly in the reproductive system, such as persistently elevated serum estrogen levels, mildly elevated gonadotropin levels, and intermittent pelvic pain caused by hemorrhagic ovarian multicysts, as well as no breast development [14]. This case report indicates that ERα acts primarily in the reproductive system in women, and that ERβ is not a substitute on ERα, even though ERβ is expressed in breast and other tissues, in many cases there is an opposite role or yin-yang relationship between these two receptors [15-17].

Notably the multiple ovarian cysts and elevated serum testosterone suggest that the woman is a polycystic ovary syndrome (PCOS) patient, the cause and mechanism of the disease is currently unknown. In addition to the mildly elevated levels of gonadotropins, probably the dramatically high levels (10 times) of estrogens and other ER or receptor-like partners cannot be excluded, since ERβ and newly identified 3rd estrogen receptor, the membrane G protein coupled receptor (GPR30) are expressed in the ovaries [18-20]. This consideration is an agreement of the animal study that demonstrated both elevated LH and ERβ are required for the formation of ovarian cysts [21]. Furthermore, it is not sure the bilateral painful hemorrhagic ovarian cyst is a potential vascular/circulatory problem in this patient, as high levels estrogen may affect bleeding/coagulation, and other ers1 mutations have shown dysfunctional epithelium and early cardiovascular disease [5]. Similarly, hemorrhagic cysts have been seen in the ovary of ERα knockout mice [21,22], which suggest that esr1 is a causative gene for PCOS, and provide a useful animal model for human polycystic ovary syndrome.

In both cases, esr1 mutations result in low bone mass (man and woman) [13,14], which indicates an important role for estrogen signaling in bone maturation and metabolism. Differentially from women, men with esr1 mutation also showed impaired glucose tolerance, and hyperinsulinemia, as well as increased body weight (body mass index >30), suggesting abnormal glucose metabolism, and estrogen's effect on energy homeostasis may be sex different [13,14,23].

It is interesting to note that a typical patient is as a good textbook, in which we can learn something, the exquisite hormone feedback mechanism has been shown clearly in these ers1 mutant patients [13,14]. The increased serum gonadotropins (FSH and LH) exist in both cases of man and woman, indicating that the estrogen positive feedback on the hypothalamus and pituitary for gonadotropin production is dominant in such patients with esr1 function-loss mutations. The precise mechanisms are unclear but probably ERβ and/or other interaction partners underlie this estrogen function. On the other hand, the negative feedback of the estrogen may be mainly ERα-mediated. Interestingly this analysis or concept is supported by recent animal studies, in which increased estrogen induced an ERβ-dependent GnRH secretion (positive feedback), while ERα is essential for negative feedback and ERβ only had a modulatory role for the negative feedback [24,25].

As new techniques and methods are developed and applied in the biomedical field, more functions or pathways of estrogen and its

receptors may be explored. Some functions may be separated from its classic partner, i.e. small molecule estrogen can pass most cellular membranes including the mitochondria by passive diffusion, and have actions without its classic receptors in some cases. Also, ERs may have a function that is independent of binding its ligand, E2. Very surprisingly, optogenetic manipulation has shown that $Esr1^+$ neurons in the murine ventromedial hypothalamus are sufficient to initiate attack behavior in male mice [26]. Furthermore, weaker optogenetic activation of these neurons promoted mounting behavior, rather than attack behavior, towards both males and females, as well as sniffing and close investigation [26]. The anatomical, physiological, pathological circuits and significance of this new esr1 action are worthy further investigation. It is more likely connected to some pathological conditions rather than physiological levels since the manipulation may cause much more genes expression than Esr1 and c-Fos. Regardless it indicates that estrogen/estrogen receptor is strongly involved in behavioral and societal regulation.

Esr1 mutations in young people are rare, however the genomic instability is commonly seen in patients with cancer and some other diseases. It has been shown that mitochondrial dysfunction leads to nuclear genome instability by inhibiting the production of iron-sulfur cluster-containing proteins [27]. Estrogen and E2-assiciated receptors/proteins/peptides can be found in mitochondria, the powerhouse of the most cells, and they have broad effects on the organelles, such as biogenesis or mitochondrial protective role [28-30]. Interestingly esr1 mutations were recently found in patients with metastatic ER-positive breast cancer [31,32]. Importantly, some mutant receptors drive ER-dependent transcription and proliferation in the absence of hormone and reduce the efficacy of ER antagonists [31], indicating a new mechanism for clinical resistance to hormonal therapy, and it suggests that more potent ER antagonists are needed for such group of cancer patients.

The Esr2 mutations with a strong reproductive phenotype have not been reported. However, Esr2 mutations or polymorphisms may be associated with cardiovascular diseases and metabolism disorders, such as dyslipidemia [33,34]. It has been suggested that homozygotic mutation of the Esr2 gene is an independent risk marker for premature coronary artery disease [33].

The developmental and physiological roles, as well as the pathological effects of estrogen are mediated by estrogen receptors as mentioned early. Traditionally, regulation of expression of various cellular genes is the most important component of estrogen and ER action through the estrogen response element (ERE), this genomic pathway of estrogen action usually takes several minutes to hours to days. Recent years, the rapid actions of estrogen have become to a hot theme to pursue [35-37]. It normally occurs in the cells in a very short time, such as milliseconds to minutes. In contrast to the classical signaling of estrogen, it is called non-genomic mechanism; in fact it also induces genomic changes in some cases, further indicating the broad role of the hormone in the mammalian and human body.

This rapid action of E2, can be mediated by its known receptors ERα, ERβ and GPR30 [10,35,36,38,39]. Although these receptors can be found in the plasma membrane, their expression is predominantly in the cytoplasm, nuclear or endoplasmic reticulum, respectively [36,40]. Their involvement for the E2 fast action is controversial as a major route, and thought to be the less economical pathway.

Accumulated evidence has indicated that a new G protein coupled membrane receptor exists in the brain and other tissues/cells, and it can be mimicked by STX, but not other three ER agonists [37,41-44]. The identifying of this new membrane receptor or receptor-like protein(s) will provide new insights for estrogen signaling, especially in regards to the recently recognized rapid actions of estrogen.

References

1. Carcaillon L, Brailly-Tabard S, Ancelin ML, Rouaud O, Dartigues JF, et al. (2014) High plasma estradiol interacts with diabetes on risk of dementia in older postmenopausal women. Neurology 82: 504-511.
2. Valen-Sendstad A, Engedal K, Stray-Pedersen B, Strobel C, Barnett L, et al. (2010) Effects of hormone therapy on depressive symptoms and cognitive functions in women with Alzheimer disease: a 12 month randomized, doubleblind, placebo-controlled study of low-dose estradiol and norethisterone. Am J Geriatr Psychiatry 18: 11–20.
3. Wroolie TE, Kenna HA, Williams KE, Powers BN, Holcomb M, et al. (2011) Differences in verbal memory performance in postmenopausal women receiving hormone therapy: 17ß-estradiol versus conjugated equine estrogens. Am J Geriatr Psychiatry 19: 792–802.
4. Roselli CE, Liu M, Hurn PD (2009) Brain aromatization: classic roles and new perspectives. Semin Reprod Med 27: 207-217.
5. Puzianowska-Kuźnicka M (2012) ESR1 in myocardial infarction. Clin Chim Acta 413: 81-87.
6. Tralongo P, Di Mari A, Ferrau F (2005) Cognitive impairment, aromatase inhibitors, and age. J Clin Oncol 23: 4243.
7. Liu M, Kelley MH, Herson PS, Hurn PD (2010) Neuroprotection of sex steroids. Minerva Endocrinol 35: 127-143.
8. Babayan AH, Kramár EA (2013) Rapid effects of oestrogen on synaptic plasticity: interactions with actin and its signalling proteins. J Neuroendocrinol 25: 1163-1172.
9. Briz V, Baudry M (2014) Estrogen Regulates Protein Synthesis and Actin Polymerization in Hippocampal Neurons through Different Molecular Mechanisms. Front Endocrinol (Lausanne) 5: 22.
10. Huang GZ, Woolley CS (2012) Estradiol acutely suppresses inhibition in the hippocampus through a sex-specific endocannabinoid and mGluR-dependent mechanism. Neuron 74: 801-808.
11. Hewitt SC, Korach KS (2002) Estrogen receptors: structure, mechanisms and function. Rev Endocr Metab Disord 3: 193-200.
12. Kumar R, McEwan IJ (2012) Allosteric modulators of steroid hormone receptors: structural dynamics and gene regulation. Endocr Rev 33: 271-299.
13. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, et al. (1994) Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 331: 1056-1061.
14. Quaynor SD, Stradtman EW Jr, Kim HG, Shen Y, Chorich LP, et al. (2013) Delayed puberty and estrogen resistance in a woman with estrogen receptor α variant. N Engl J Med 369: 164-171.
15. Platet N, Cathiard AM, Gleizes M, Garcia M (2004) Estrogens and their receptors in breast cancer progression: a dual role in cancer proliferation and invasion. Crit Rev Oncol Hematol 51: 55-67.
16. Sugiyama N, Barros RP, Warner M, Gustafsson JA (2010) ERbeta: recent understanding of estrogen signaling. Trends Endocrinol Metab 21: 545-552.
17. Leygue E, Murphy LC (2013) A bi-faceted role of estrogen receptor β in breast cancer. Endocr Relat Cancer 20: R127-139.
18. Jayes FL, Burns KA, Rodriguez KF, Kissling GE, Korach KS (2014) The naturally occurring luteinizing hormone surge is diminished in mice lacking estrogen receptor Beta in the ovary. Biol Reprod 90: 24.
19. Pang Y, Thomas P (2010) Role of G protein-coupled estrogen receptor 1, GPER, in inhibition of oocyte maturation by endogenous estrogens in zebrafish. Dev Biol 342: 194-206.
20. Mendez C, Morales-Vasquez F, Perez-Montiel D, Gomora MJ, Espinola-Zetina C, et al. (2013) Estrogen and androgen receptor expression in surface epithelium and inclusion cyst in the ovary of premenopausal and postmenopausal women. J Ovarian Res 6: 85.

21. Couse JF, Yates MM, Sanford R, Nyska A, Nilson JH, et al. (2004) Formation of cystic ovarian follicles associated with elevated luteinizing hormone requires estrogen receptor-beta. Endocrinology 145: 4693-4702.
22. Antonson P, Omoto Y, Humire P, Gustafsson JA (2012) Generation of ERα-floxed and knockout mice using the Cre/LoxP system. Biochem Biophys Res Commun 424: 710-716.
23. Barros RP, Gustafsson JA (2011) Estrogen receptors and the metabolic network. Cell Metab 14: 289-299.
24. Hu L, Gustofson RL, Feng H, Leung PK, Mores N, et al. (2008) Converse regulatory functions of estrogen receptor-alpha and -beta subtypes expressed in hypothalamic gonadotropin-releasing hormone neurons. Mol Endocrinol 22: 2250-2259.
25. Cheong RY, Porteous R, Chambon P, Abrahám I, Herbison AE (2014) Effects of neuron-specific estrogen receptor (ER) α and ERβ deletion on the acute estrogen negative feedback mechanism in adult female mice. Endocrinology 155: 1418-1427.
26. Lee H, Kim DW, Remedios R3, Anthony TE3, Chang A3, et al. (2014) Scalable control of mounting and attack by Esr1+ neurons in the ventromedial hypothalamus. Nature 509: 627-632.
27. Veatch JR, McMurray MA, Nelson ZW, Gottschling DE (2009) Mitochondrial dysfunction leads to nuclear genome instability via an iron-sulfur cluster defect. Cell 137: 1247-1258.
28. Chen JQ, Cammarata PR, Baines CP, Yager JD (2009) Regulation of mitochondrial respiratory chain biogenesis by estrogens/estrogen receptors and physiological, pathological and pharmacological implications. Biochim Biophys Acta 1793: 1540-1570.
29. Mao P, Ardeshiri A, Jacks R, Yang S, Hurn PD, et al. (2007) Mitochondrial mechanism of neuroprotection by CART. Eur J Neurosci 26: 624-632.
30. Mao P, Meshul CK, Thuillier P, Goldberg NR, Reddy PH (2012) CART peptide is a potential endogenous antioxidant and preferentially localized in mitochondria. PLoS One 7: e29343.
31. Toy W, Shen Y, Won H, Green B, Sakr RA, et al. (2013) ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet 45: 1439-1445.
32. Robinson DR, Wu YM, Vats P, Su F, Lonigro RJ, et al. (2013) Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 45: 1446-1451.
33. Mansur Ade P, Nogueira CC, Strunz CM, Aldrighi JM, Ramires JA (2005) Genetic polymorphisms of estrogen receptors in patients with premature coronary artery disease. Arch Med Res 36: 511-517.
34. Smiderle L, Mattevi VS, Giovenardi M, Wender MC, Hutz MH, et al. (2012) Are polymorphisms in oestrogen receptors genes associated with lipid levels in response to hormone therapy? Gynecol Endocrinol 28: 644-648.
35. Russell KS, Haynes MP, Sinha D, Clerisme E, Bender JR (2000) Human vascular endothelial cells contain membrane binding sites for estradiol, which mediate rapid intracellular signaling. Proc Natl Acad Sci U S A 97: 5930-5935.
36. Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER (2005) A transmembrane intracellular estrogen receptor mediates rapid cell signaling. Science 307: 1625-1630.
37. Kelly MJ, Rønnekleiv OK (2012) Membrane-initiated actions of estradiol that regulate reproduction, energy balance and body temperature. Front Neuroendocrinol 33: 376-387.
38. Stefano GB, Cadet P, Breton C, Goumon Y, Prevot V, et al. (2000) Estradiol-stimulated nitric oxide release in human granulocytes is dependent on intracellular calcium transients: evidence of a cell surface estrogen receptor. Blood 95: 3951-3958.
39. Thomas P, Pang Y, Filardo EJ, Dong J (2005) Identity of an estrogen membrane receptor coupled to a G protein in human breast cancer cells. Endocrinology 146: 624-632.
40. Wang A, Ji L, Shang W, Li M, Chen L, et al. (2011) Expression of GPR30, ERα and ERβ in endometrium during window of implantation in patients with polycystic ovary syndrome: a pilot study. Gynecol Endocrinol 27: 251-255.
41. Qiu J, Bosch MA, Tobias SC, Krust A, Graham SM, et al. (2006) A G-protein-coupled estrogen receptor is involved in hypothalamic control of energy homeostasis. J Neurosci 26: 5649-5655.
42. Sylvia VL, Boyan BD, Dean DD, Schwartz Z (2000) The membrane effects of 17beta-estradiol on chondrocyte phenotypic expression are mediated by activation of protein kinase C through phospholipase C and G-proteins. J Steroid Biochem Mol Biol 73: 211-224.
43. Benten WP1, Stephan C, Lieberherr M, Wunderlich F (2001) Estradiol signaling via sequestrable surface receptors. Endocrinology 142: 1669-1677.
44. Guo Z1, Krucken J, Benten WP, Wunderlich F (2002) Estradiol-induced nongenomic calcium signaling regulates genotropic signaling in macrophages. J Biol Chem 277: 7044-7050.