

Membrane Steroid Receptor-Mediated Action of Soy Isoflavones: Tip of the Iceberg

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Abstract Soy isoflavone's (genistein and daidzein in particular) biological significance has been thoroughly studied for decades, so we started from the premise that refreshed investigation approach in this field should consider identification of their new molecular targets. In addition to recently described epigenetic aspects of polyphenole action, the cell membrane constituents-mediated effects of soy isoflavones are worthy of special attention. Accordingly, the expanding concept of membrane steroid receptors and rapid signaling from the cell surface may include the prominent role of these steroid-like compounds. It was observed that daidzein strongly interacts with membrane estrogen receptors in adrenal medullary cells. At low doses, daidzein was found to stimulate catecholamine synthesis through extracellular signal-regulated kinase 1/2 or protein kinase A pathways, but at high doses, it inhibited catecholamine synthesis and secretion induced by acetylcholine. Keeping in mind that catecholamine excess can contribute to the cardiovascular pathologies and that catecholamine lack may lead to depression, daidzein application promises to have a wide range of therapeutic effects. On the other hand, it was shown in vitro that genistein inhibits LNCaP prostate cancer cells invasiveness by decreasing the membrane fluidity along with immobilization of the androgen receptor containing membrane lipid

rafts, with down regulation of the androgen receptors and Akt signaling. These data are promising in development of the molecular pharmacotherapy pertinent to balanced soy isoflavone treatment of cardiovascular, psychiatric, and steroid-related malignant diseases.

Keywords Cell membrane · Membrane steroid receptor · Soy isoflavones

Introduction

After decades of working in the field of biological significance of soy isoflavones, it can be easily thought that all the opened issues are elaborated in detailed manner or even completely encircled, and the “golden era” of research seems to be irretrievably gone as well as the critical mass of data accumulated, so the definitive conclusions appear to be achievable. However, what does actually exist represents a complex mosaic of various authors' projections and conclusions, indistinct in some segments, and certainly incomplete. In addition to the steps toward clarifying the current uncertainties, we believe that the investigation approach in this field should be refreshed, some up to date objectives in terms of identification of new targets of soy isoflavone action established, while the methodological breakthrough also needs to be done. In this regard, the recent works of Milenkovic et al. (2012), (2013) may be inspiring. Namely, the authors marked microRNAs (miRNAs) as molecular targets of natural sourced polyphenols, underlying their biological effects (Milenkovic et al. 2013). miRNAs represent noncoding, single-stranded RNAs of 22 nucleotides, annotated to control the post-transcriptional regulation of 30 % of mammalian genes (Bartel 2004; Esquela-Kercher and Slack 2006). Various cellular

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processes, such as division, differentiation, growth, and apoptosis are performed by means of the miRNAs regulation (Miska 2005). Over 100 miRNAs were identified to have modulated expression by polyphenols (Milenkovic et al. 2013). So, in addition to the classic, well-known routes of gene expression regulation, it emerges one entirely new form of the indirect influence of natural originated compounds on the regulation of gene expression, underlying the physiological and pathological processes, with the participation of miRNAs. Pertinent to this, in a series of our previous works (Ajdžanović et al. 2010, 2011, 2012, 2013, 2014), we have described the membrane biophysics-related effects of soy isoflavones, with an emphasis on different cells function and various systemic implications after their application. Besides anchorage to the extracellular matrix/neighborhood cells, cytoskeleton organization and vesicle trafficking, membrane tension/fluidity represents the crucial definer of the cell mechanical status (Asnacios and Hamant 2012; Ajdžanović et al. 2014), and may be increased, unaltered, or decreased after soy isoflavone intercalation (Ajdžanović et al. 2014). The character of membrane tension/fluidity changes depends on polarity and a number and arrangement of applied isoflavone functional groups (Ajdžanović et al. 2014), and diversely fashions cell rheological properties (dynamics/deformation behavior) and function (Zicha et al. 1999). The accumulation of data in previous decades, concerning the concept of membrane steroid receptors and the steroid hormones membrane-initiated, rapid actions (Watson and Gametchu 1999; Falkenstein et al. 2000; Norman et al. 2004) define an additional, potentially very interesting, vector of soy isoflavone ‘molecular’ action (Ajdžanović et al. 2014), considering the well-known fact that their similarity with 17- β -estradiol (Setchell 1998) results in the binding to classical estrogen α and β , but also to androgen and progesterone receptors (Kuiper et al. 1997; Beck et al. 2005; Kalaiselvan et al. 2010). It should be emphasized that membrane-localized pools of steroid receptors include classical as well as putative (some new protein candidates) steroid receptors, which mediate steroid/steroid-like ligand actions, originating as signaling from the cell surface (Levin 2011). Interestingly, miRNAs functions may also be affected by the activation of these signaling cascades (Levin 2011). The role of membrane steroid receptors in various physiological (neuronal excitability, neurotransmitter release, vasodilation, insulin production and secretion, renal tubular absorption, and osteoblasts differentiation) and pathological (cardiomyocyte survival in ischemia, breast and prostate cancer cells proliferation, migration, and invasion) events has increasingly been demonstrated (Hammes and Levin 2011; Roepke et al. 2011; Xie et al. 2011). Our objective herein is to highlight the membrane steroid receptor-mediated action of soy

isoflavones, with an attempt to evaluate biomedical significance of the phenomenon and propose the perspectives and outcomes in this research segment development.

Membrane Steroid Receptors

The cellular effects of estrogens are predominantly initiated via activation of classical estrogen receptors α and β , localized in the nucleus or cytoplasm of the target cells, which belong to the nuclear steroid receptor superfamily members and act as transcription factors (Kumar et al. 2011). Coupled with the ligands—estrogens or estrogen-like compounds, they bind to the estrogen-responsive elements within specific genes and may alter their rate of transcription (Jacob et al. 2006). As previously mentioned, some recent studies focused on membrane-initiated, rapid actions of steroid hormones have given the invaluable insight into their non-classical mechanisms of action (Levin 2011; Marino et al. 2012; Adlanmerini et al. 2014). Namely, these “non-genomic effects” could be mediated by extranuclear estrogen receptors (non-classical membrane bound receptors) such as G protein-coupled estrogen receptor, also named GPR30/GPER, which has been identified as a novel estrogen receptor (Filardo et al. 2007; Madeo and Maggiolini 2010). It was observed that estradiol through GPER rapidly activates different signaling pathways, including the stimulation of adenylyl cyclase, mobilization of intracellular calcium (Ca^{2+}) stores, and activation of mitogen-activated protein kinase (MAPK) as well as phosphoinositide 3-kinase (PI-3K) pathways (Soltysik and Czekaj 2013). Because estrogen receptors do not have the intrinsic kinase activity, these molecular interactions are critical to direct estrogen-stimulated rapid action and may occur in a cell type-dependent fashion (Watson et al. 2007). Interestingly, membrane estrogen receptors have been shown to interact with the caveolar structural protein caveolin-1, so this molecular interaction is essential for the estrogen receptor plasma membrane localization (Sud et al. 2010). De facto, membrane estrogen receptor represents the central component of a multimolecular “signalsome,” which orchestration results in the rapid signaling cascades (Moriarty et al. 2006; Soltysik and Czekaj 2013).

Testosterone and dihydrotestosterone generally exert their effects through binding and activation of the intracellular androgen receptors, which results in the receptor dimerization and nuclear translocation, followed by expression of the androgen-specific target genes (Heinlein and Chang 2004). Similar to estrogens, besides the long-term genomic outcome of androgen effects (Liao et al. 2013), a numerous studies have shown the rapid effects of androgens, occurring within minutes in various cell types

(Benten et al. 1999; Kampa et al. 2002, 2006; Kallergi et al. 2007; Yu et al. 2012). These rapid androgen effects consider activation of the membrane androgen receptors and triggering some non-genomic signals (Rahman and Christian 2007; Foradori et al. 2008). Although the molecular identity of membrane androgen receptors remains still largely unknown, it is assumed that these receptors may include the pool of intracellular androgen receptors targeted to the cell membrane and associated with the membrane structures (such as lipid rafts or caveolae), or represent some undetermined G protein-coupled receptors (GPCRs), triggering a variety of signaling cascades (Papadopoulou et al. 2008). Increasing body of evidence indicates that membrane androgen receptor coupling with ligands leads to the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) (Peterziel et al. 1999), PI-3K/Akt (Papakonstanti et al. 2003; Papadopoulou et al. 2008), Protein kinase C (Peterziel et al. 1999; Lu et al. 2001), and MAPK (Heinlein and Chang 2002) signaling pathways. Occasionally, the rapid action realized through membrane androgen receptors cannot be blocked by anti-androgens (Kampa et al. 2002; Papakonstanti et al. 2003), but remains sensitive to *pertussis* toxin inhibition, indicating the concrete receptors most likely GPCR nature (Kampa et al. 2005; Sun et al. 2006).

Finally, it should be mentioned that membrane steroid receptor actions frequently collaborate with nuclear steroid receptor initiated pathways, establishing the complex transcriptional interactions, critical to overall biological functions of steroids (Levin 2011).

The Action of Soy Isoflavones Realized Through Membrane Steroid Receptors

The concept of long-term genomic action of estrogens, mediated by their binding to nuclear estrogen receptors, was earlier well established (Greene et al. 1986; Giguère et al. 1988), while the outcoming, *inter alia* neuroregulatory function is especially well elaborated in the area of hypothalamus and other brain regions related to reproduction (McEwen 2002). However, evidence has grown that estrogens exert non-genomic, rapid action via activation of membrane estrogen receptors (Falkenstein et al. 2000; Norman et al. 2004), and even soy isoflavone daidzein was shown to strongly inhibit the specific binding of [³H]17 β -estradiol to bovine adrenal medullary cell (a model of catecholaminergic brain neurons) membranes, suggesting its' interaction with the membrane estrogen receptors (Yanagihara et al. 2006) (Fig. 1). Incubation of these cells with daidzein (20 min) was shown to increase the catecholamine synthesis in a concentration-dependent manner (10–1,000 nM) (Liu et al. 2007). Furthermore, the

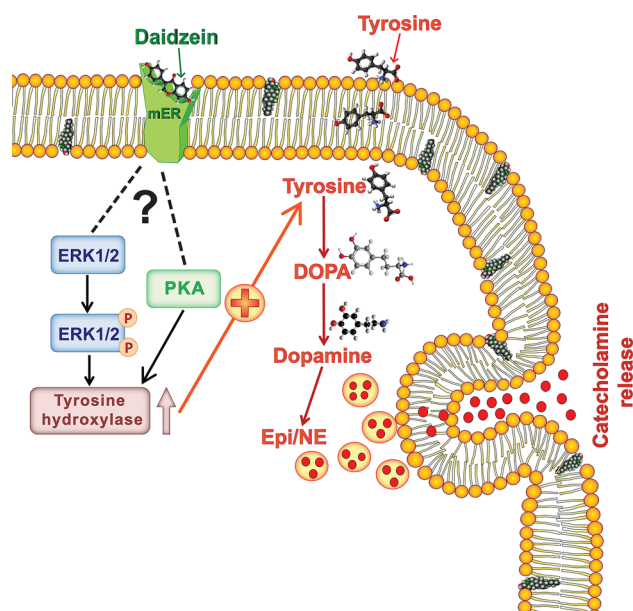


Fig. 1 The cascade of events after low-dose daidzein binding to membrane estrogen receptors (mER) in adrenal medullary cells. ERK1/2 extracellular signal-regulated kinase 1/2, PKA Protein kinase A, DOPA L-3,4-dihydroxyphenylalanine, Epi/NE Epinephrine/Norepinephrine

observed stimulatory effect was not inhibited by ICI182,780, a classical estrogen receptor inhibitor, but abolished by U0126, an inhibitor of ERK1/2 (Liu et al. 2007; Yanagihara et al. 2008). H-89, an inhibitor of protein kinase A (PKA), also eliminated the stimulatory effect of daidzein in adrenomedullary cells (Liu et al. 2007; Yanagihara et al. 2008). Interestingly, a physiological, acetylcholine-stimulated synthesis of catecholamine, in the same model, was suppressed by daidzein at 1 μ M (Liu et al. 2007). The authors suggest that daidzein may exert the action of dual nature in adrenal medullary cells: to stimulate catecholamine synthesis (probably at the tyrosine hydroxylase step) through membrane estrogen receptors/-ERK1/2 or -PKA pathways (Fig. 1), at low concentrations; but at high concentrations to inhibit catecholamine synthesis and secretion induced by acetylcholine (Liu et al. 2007). Considering that catecholamine excess can mediate the heart failure, atherosclerosis, coronary heart disease, and hypertension (Westfall and Westfall 2005), the latter finding may additionally support our previous thesis of adequately dosed daidzein as the remedy of good choice in cardioprotection (Ajdžanović et al. 2012). Furthermore, the catecholamine lack in certain neuropsychological disorders such as major depression and some potential benefit of low doses of soy isoflavones should not be disregarded (Yanagihara et al. 2008), especially having in mind the observed antidepressant potential of daidzein metabolite—equol (5 mg/kg b.w./day) in female rat behavior models (Blake

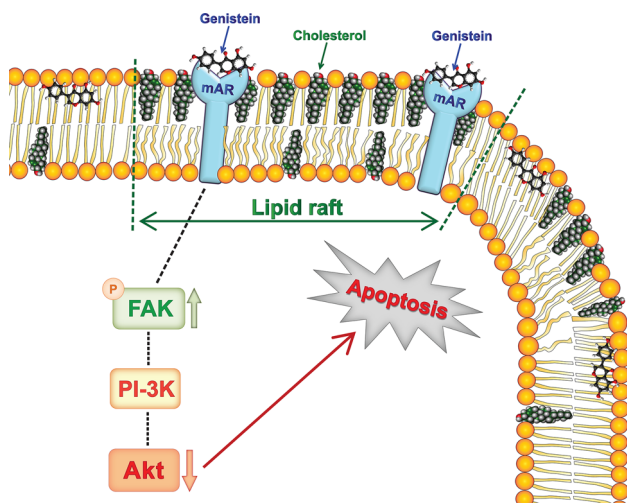


Fig. 2 Genistein binding to membrane androgen receptors (mAR) in LNCaP cells and the following apoptosis induction. The cascade of molecular events implies focal adhesion kinase (FAK), phosphoinositide 3-kinase (PI-3K), and Akt signaling participation. Membrane lipid rafts mobility, and their androgen receptors assembling could be reduced due to genistein-caused membrane fluidity decrease (Ajdžanović et al. 2013; Tarahovsky et al. 2014)

et al. 2011). Considering the wider frame of membrane estrogen receptors distribution, comprising endothelial nitric oxide generating cells, pancreatic islets, or breast cancer (Nadal et al. 1998; Liu et al. 2009; Hammes and Levin 2011), some other therapeutic strategies of soy isoflavone application may also be possible.

Similar to estrogens, androgens may bind to androgen receptors at or in close proximity to the cell membrane, and affect ERK, Akt, or NF- κ B signaling, as well as increase free intracellular calcium (Lyng et al. 2000; Gatson et al. 2006; Papadopoulou et al. 2008; Hammes and Levin 2011). Membrane androgen receptors could be identified not only in T-lymphocytes, monocytes, and osteoblasts, but also in certain prostate cancer cell line (Kampa et al. 2002). Micro-localization of some of the receptors, which appear to be soy isoflavone sensitive, is intriguing (Cinar et al. 2007; Oh et al. 2010). Namely, the fraction of androgen receptors was found to localize to the lipid rafts, a cholesterol-rich membrane microdomains, in LNCaP metastatic prostate cancer cells (Cinar et al. 2007) (Fig. 2). Lipid rafts represent the specific milieu where the accumulation and assembling of the signal transduction machinery occurs and various stimulatory or inhibitory inputs, essential for the cell function and fate, generate (Pralle et al. 2000; Oh et al. 2010). Combination of the androgen receptors containing lipid rafts dispersion with soy isoflavone genistein (2.5–10 μ M) treatment led to a decrease of LNCaP cell viability through the induction of apoptosis (Oh et al. 2010). Genistein alone attenuated the

Akt signaling pathway, important in cell survival, via up regulation of the phosphatase and down regulated lipid rafts (as well the entire) androgen receptors in the prostate cancer cells (El Touny and Banerjee 2007; Oh et al. 2010; Mahmoud et al. 2014). To note, Akt signaling and androgen receptors in lipid rafts represent the entities earlier shown to be tightly connected (Cinar et al. 2007) (Fig. 2). These data imply the membrane androgen receptor-associated, signaling processes interfering role of soy isoflavones, responsible for their significant anticancer activity. In support of this observation, application of genistein (IC₅₀ concentration—46 μ M) reduced in vitro invasiveness of survived metastatic LNCaP cells, which was strongly linked with the cells decreased superficial membrane fluidity (Ajdžanović et al. 2013). It is reasonable to believe that membrane-related suppression of metastatic properties of LNCaP cells, induced by genistein, links membrane fluidity decrease and the following immobilization of androgen receptor containing lipid rafts, with down regulation of the androgen receptors and subsequent signaling pathways silencing (Oh et al. 2010; Ajdžanović et al. 2013; Tarahovsky et al. 2014).

Conclusion

Based on the above elaborated membrane steroid receptor action of soy isoflavones and the potential biomedical implications, the impression is that this research segment would necessarily have to be expanded. Some new, soy isoflavone sensitive candidates' characterization and identification of various downstream signaling pathways represent crucial steps in this regard. Keeping in mind that membrane steroid receptor-mediated events frequently collaborate with nuclear steroid receptor-regulated gene expression (Levin 2011), the mode of this complex interactions (including polyphenol-targeted miRNAs involvement (Milenkovic et al. 2012, 2013) should be of particular interest. Also, the influence of membrane fluidity changes observed upon flavonoid positioning in the membrane bilayer, especially the compounds tendency to accumulate in lipid rafts, and the pronounced lipophilicity following their complexation with transient metal cations (Ajdžanović et al. 2014; Tarahovsky et al. 2014) are worthy of attention from the perspective of membrane steroid receptors availability, assembling, and linkage to the signal transduction machinery.

Sublimation of these issues may be extrapolated to some practical solutions in molecular pharmacotherapy, concerning the balanced soy isoflavone-based treatment of widespread cardiovascular, psychiatric, metabolic, and steroid-related malignant diseases.

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Conflict of interest Vladimir Ajdžanović, Ivana Medigović, Jasmina Živanović, Marija Mojić and Verica Milošević declare that they have no conflict of interest.

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