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REVIEW ARTICLE

MEMBRANE LIPID-ESTROGEN INTERACTION AND MANAGEMENT OF MEDICAL DISORDERS: BIOPHYSICAL MEDICINE

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ABSTRACT

Estradiol-17beta (E2) is an important gonadosteroid present in large concentration in women and in low levels in men, but it is important for both women and men in various reproductive and non-reproductive functions. Information in the present article is provided about the estrogen-membrane interaction and biophysical mechanisms of drug interaction. Role of membrane lipid- estrogen interaction in various diseases and drug interaction has been described for: health and environmental issues, cytotoxicity, human cell damage by 17 α-ethinylestradiol (EE2) on fluid lipid monolayers, cerebral aneurysms, estrogen signaling and a variety of other aspects. The therapeutic role of the interactions of estrogenic drugs with membrane lipids have been emphasized for: anticancer therapy, breast cancer and hormone dependent tumors, E2-HDL (estradiol-high density lipoprotein)-targeted drug therapies, genistein for treatment of cancer, chlorpromazine and anticancer activity of tamoxifen, membrane disruptions and alpha-tocopherol. Hopefully the future studies would provide further information for physiological, physicochemical and pharmaceutical aspects for better management of diseases and advancement of membrane interaction related studies. The future studies in biophysical medicine may bring a revolution for management of membrane interaction associated diseases and interpretation of the processes at biophysical level.

KEY WORDS: Drug interaction; Estrogen; Lipid; Membrane; Membrane lipid-estrogen.

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INTRODUCTION

Estradiol-17beta or E2 is an important gonadosteroid present in large concentration in women and in low concentrations in men, but it is important for both women and men in various reproductive and non-reproductive processes/ functions. Its functions are carried out via its receptors (estrogen receptors: ERs) that are present inside the cells as ERα and ERβ and in membranes as membrane estrogen-receptors (mERs). Estrogen is involved in a variety of functions including the regulation of menstrual cycle/ other reproductive functions, antithrombotic risks, cardiovascular risk development, intracellular signaling, remodeling of synaptic plasticity, dendritic spine formation, learning and memory, and specifically the neurotransmission, neurodevelopment and cognitive processes.[1-3] Variations of estrogen concentrations in men and women associate with emotional dysregulation, schizophrenia, autism spectrum condition (ASC) and clinical depression especially in women, bipolar disorder (BPD), increased vulnerability to depression, attention deficit hyperactivity disorder (ADHD), cognitive and mood changes before, during and after the menopause, anxiety disorders, substance use disorder (SUD), autoimmune diseases, metabolic disorders e.g., muscle damage and antioxidant activity, degenerative diseases etc.[3-7]

A variety of physiological and pathological conditions along with therapeutic approaches are summarized in Table-1 & Table-2 for: E2-membrane interactions;[8-11] E2-membrane interactions in various diseases;[12-14] and therapeutic aspects.[15-17] Human aromatase (P450 19A1) has been revealed to catalyze three sequential oxygenations of 19carbon-steroids to estrogens and it gets expressed much in different body tissues, and that can be identified on the basis of varying composition of cholesterol.[18] Since the formation of cell-specific microparticles is the characteristic marker, estrogen controls the antithrombotic risk characteristics in

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vascular endothelium/ blood element interaction with vascular surface. The total numbers of microparticles positive for tissue factor and phosphatidylserine were also greater in low-estrogen non-diabetic and non-hypertensive women group.[1]

Bacillus stearothermophilus that is a thermophilic eubacterium-a best bacterial membrane model for the identification of physical properties of membranes and membrane associated cytotoxic influences of 4-hydroxytamoxifen, provides significant information about the interaction between this lipophilic drug and bacterial membrane[19] Interaction of synthetic estrogen with membranes and localization has been studied for understanding the mode of action of the drug and adverse effects while using it as a therapy for prostate cancer and metastatic carcinoma.[10] It was investigated that extracellular classical mitogen-activated protein kinase-1/ kinase 2 and sphingosine kinase (SphK) get interaction with an estrogen receptor (ER)-dependent way to affect the breast cancer cell growth and their migration.[20] Interaction of peptide ERα17p with breast cancer cell membranes related to its folding into β sheet was investigated as the mechanism of action.[21] Tamoxifen (TAM) that is considered estrogen antagonist and as a best choice and first line therapy in the list of anticancer drugs for breast cancer interacts with respiratory components and causes the effects after interacting with membrane.[22] The present review article provides information in general about the interaction of estrogen/ estrogenic products or drugs with the lipid part of various types of membranes, and in special about the role of estrogen-membrane lipid interaction for various drugs and diseases. Hopefully the future studies would provide further information for physiological/ pathophysiological, physicochemical and pharmaceutical aspects employing biophysical medicine for better management of diseases and advancement of membrane interaction related studies.

LIPID MEMBRANE-ESTROGEN INTERACTION

There are a number of studies conducted to understand the influence of the interaction of estrogens/ estrogenic drugs with membranes[8-11,19,23-28] shown in Table-1. Drug-membrane interaction study revealed lipophilic estradiol (ES)- acyl chains of lipid membrane interaction.[29] It is known that diethylstilbestrol (DES) is employed for the treatment of metastatic carcinomas/ and prostate cancer. The interaction of DES and membrane reveals the localization near the first carbons of fatty acyl chains, mode of action and side effects.[10] Highly sensitive estrogen detecting biosensor was developed that is a new advancement in understanding the biophysical

Table 1: Lipid membrane-estrogen interaction and medical disorders

Interaction Type	Techniques	Conditions/ Diseases	References
E2-membrane interaction	^{1}H MAS, NMR), ^{2}H NMR, ssNMR	The upper membrane area mainly contains estradiol, and as it has two hydroxyl ions on each side, it rotates with high dynamic property	(Scheidt et al., 2010)[25]
E2- DES	DSC, SAXD, WAXD, ^{31}P-NMR spectroscopy, ^{1}H-NOESY-MAS-NMR, MDS	interaction of DES and membrane reveals the localization near the first carbons of fatty acyl chains, mode of action and side effects	(Ausili et al., 2021)[10]
Estrogen-ER binding in Au modified s-BLM	Development of nanostructure EB; CV; IS	The developed biosensor has ability for finding with required sensitivity the type of estrogens, and estrogen-estrogen receptor binding in Au modified s-BLM for in various conditions	(Xia et al., 2010)[26]
Bioflavonoids (genistein and daidzein)- DOPC and DPhPC	XS, volume, measurements, MDS	Bioflavinoids (genistein and daidzein) insert into the hydrocarbon region near to lipid carbonyls, reduce the thickness of the bilayer and help softening the bilayers.	(Raghunathan et al., 2012)[28]
Lipid membrane interaction with SERM	Label-free technique of SHG	The SERM activity in various conditions in vivo is investigated for the absorption of tamoxifen and metabolite products with the membrane	(Stokes and Conboy, 2014)[8]
TAM-bacterial biomembrane	Biophysical techniques for drug-membrane interaction	TAM-associated toxicity occurs by TAM-biomembrane interaction	(Luxo et al., 2001)[22]
Genistein-liposome and glioma cells	DLS, DSC, FTIR spectroscopy. NMR, UV-vis spectroscopy	Genistein hydroxyl group & lipid hydrogen bonds show potential involvement in DMPC phosphate and restriction of choline motion	(de Azambuja Borges et al., 2019)9

E2:Estradiol 17-β; ER:Estrogen receptor; ^{1}H MAS:^{1}H Magic-angle spinning; NMR:Nuclear magnetic resonance; ssNMR:Solid-state NMR; DES:Diethylstilbestrol; DSC:Differential scanning calorimetry; EB:Electrochemical biosensor; CV:Cyclic voltammetry; IS:Impedance spectroscopy; SAXD:Small-angle X-ray diffraction; WAXD:Wide-angle X-ray diffraction; ^{1}H-NOESY-MAS-NMR:^{1}H -Nuclear Overhauser Effect Spectroscopy-magic angle scanning-NMR; MDS:Molecular dynamics simulation; Au:Aurum or gold; s-BLM:Supported bilayer lipid membrane; DOPC:Dioleoylphosphatidylcholine; PC:Phosphatidylcholine; DPhPC:Diphytanoyl phosphatidyl choline; XS:X-ray scattering; SHG:Second harmonic generation ;SERM:Selective estrogen receptor modulators; TAM:Tamoxifen; DLS:Dynamic light scattering; FTIR:Fourier transform infrared; UV-vis:Utraviolet-visible; DMPC:dimyristoylphosphatidylcholine

mechanisms of diseased processes.[26] It was found that the membrane bilayer having intercalation with prenylated chalcones & flavanones in relation to molecular shape and lipophilicity cause decrease in the melting temperature.[30]

In DOPC bilayer with cholesterol, genistein as well as daidzein shows overall less pronounced effect overall on the water permeability for transbilayer.[11] Genistein increases permeability for water, and reduces the phase transition temperature and enthalpy of transition.[11] At increasing concentration, it causes packing disorder in DOPC membrane. This investigation at membrane level may explain the cellular processes for physiological and pathophysiological mechanisms. Thickness and the softening of the bilayers have a prominent role in normal and diseased processes. It was investigated that interaction of genistein-lipid membranes and daidzein-lipid membranes show insertion of these bioflavonoids into the area of the bilayer nearby lipid carbonyls, and lead to decreased bilayer thicknesses and softening of bilayers.[28]

While studying the administration of free genistein to the central nervous system (CNS), physico-chemical properties of liposome-containing genistein, and in vitro action against DPPH and glioma cells were determined. Genistein hydroxyl group and lipid hydrogen bonds show potential involvement in dimiristoylphosphatidylcholine phosphate and restriction of choline motion.[9] Genistein intercalates mainly with headgroup lipid region are and with some part of polar-apolar interfacial area, while a little intercalation into hydrophobic core.[27]

Tamoxifen serves as a lipophilic anticancer drug while interacting with bacterial membranes and provides a molecular mechanism of the membrane-drug interaction.[19] The membrane adsorption with tamoxifen and its related metabolites provides information about a number of aspects including membrane partitioning, lipid phase, cholesterol contents and packing density that provide understanding in vivo activity of selective estrogen receptor modulators (SERM).[8] Disruption and hole formation transiently along with decreased phase transition temperature (Tm) in view of membrane-tamoxifen interaction was obtained showing tamoxifen-induced carboxy-

Table-2: Biophysical mechanisms of estrogenic drug-membrane interaction and biophysical medicine

Estrogenic Drugs-Membrane Interaction	Techniques	Conditions/ Diseases	References
BPA-membrane	BAM, model biomembranes, XRD under the grazing incidence, Langmuir membranes; setup for measuring the surface potentials	Bisphenol causes changes in membrane structure and fluidity properties of membranes. It produces environmental problems/ public health risks	(Broniatowski et al., 2016)[12]
EE2-monolayers	Langmuir films, SUVs, GUVs, surface pressure-mean molecular area (π-A), isotherms measurements	Strong effects of EE2 on fluid monolayer membranes demonstrates a potential characteristic for identifying human cell damage	(Ruiz et al., 2021)[14]
2-ME-lipid membrane	PDT with 2-ME in breast adenocarcinoma and ovarian carcinoma, immunocytochemistry, western blott; immunofluorescence by confocal microscopy	Serves as an efficient therapy for cancer for producing oxidative modification using the mechanism of causing oxidative stress in the malignant cells	(Saczko et al., 2015)[16]
Pyrene involvement via the lipid-lipid/ protein-lipid RBC membrane layers	CE/ microviscosity measurement	The RBC membrane layers (pyrene involvement via the lipid-lipid/ protein-lipid) with little steroid hormone requirements in breast cancer patients and raised microviscosity might be additional factors for identifying tumor of hormone dependent type.	(Tsyrlina et al., 2014)[38]
E2/ E2 oleate - membranes/HDLs orientation	NMR, MDS, and analytic theory	E2/ E2 oleate - membranes/HDLs orientation provides new E2 interacted HDL- therapeutic approaches	(Vogel et al., 2014)[15]
Genistein-DPPC interaction	FTIR spectroscopy, 1H NMR and EPR; fluorescence / electron microscopy	The interaction of genistein-membrane expresses cellular changes via membrane changes. The genistein may serve pharmacologically as a therapy for cancer and various other disorders	(Pawlikowska-Pawlega et al., 2012)[37]

BPA:Bisphenol A; BAM:Brewster angle microscope; XRD:X-ray diffraction; EE2:17 α-ethinylestradiol; SUVs:Small unilamellar vesicles; GUVs:Giant unilamellar vesicles; ME:Methoxyestradiol; PDT:Photodynamic therapy; RBC:Red blood cell: CE:Coefficient of eximerization; NMR:Nuclear magnetic resonance; MDS:Molecular dynamics simulation; DPPC:Dipalmitoylphosphatidylcholine; FTIR:Fourier transform infrared; EPR:Electron paramagnetic resonance

fluorescein (CF) release.[31] Toxic effects (on growth of bacteria- B. stearothermophilus and respiratory activity) of Tamoxifen-membrane interaction have been observed.[22]

The Ca (2+) or Mg (2+) are involved in membrane perturbations and ordering instead of disordering of lipid membrane in TAM-induced growth impairment activity.[32] It was studied that intracellular changes that may produce normal and abnormal activities correlate with the biophysical status and organization of membrane under the influence of interaction between lipid membrane and genistein.[33]

BIOPHYSICAL MECHANISMS OF DRUG INTERACTIONS AND BIOPHYSICAL MANAGEMENT OF MEDICAL DISORDERS

Table-2 provides information about the biophysical mechanisms of disease and drug interaction. Role of membrane lipid- estrogen interaction in various diseased processes/ diseases and drug interaction described are: health and environmental issues, cytotoxicity, human cell damage by 17 α-ethinylestradiol (EE2) on fluid lipid monolayers, therapeutic role of estrogen-membrane interaction, and cerebral aneurysms and estrogen signaling.[12-14,34,35]

Therapeutic role of estrogen-membrane interaction was uncovered by calculating free energy estrogen while interacting and crossing lipid bilayer[34] While studying HCVECs (human cerebral vascular endothelial cells), dose responsive property of 17β-estradiol and GPER1 (G-protein-coupled receptor 1) interaction was revealed in the formation of cerebral aneurysm using HCVECs in women during menopause and post-menopause[35] The therapeutic role of the interactions of estrogenic drugs with membrane lipids has been emphasized for: anticancer therapy breast cancer and hormone dependent tumors, E2-HDL-targeted drug therapies, genistein for treatment of cancer, chlorpromazine and anticancer activity of tamoxifen, membrane disruptions and alpha-tocopherol (alpha-T).[15-17,36-38]

The interaction of membrane with 2-methoxyestradiol (2-Me) serves as an efficient therapy for cancer for producing oxidative modification using the mechanism of causing oxidative stress in the malignant cells[16] Increased microviscosity could be an important additional key factor to identify hormone dependent tumors,[38] as the RBC membrane layers (pyrene involvement via the lipid-lipid/ protein-lipid) with little steroid hormone requirements in breast cancer patients and raised microviscosity might be additional factors for identifying tumor of hormone dependent type. It was noted that the interactions of lipid-E2 determines the molecular localization and E2/ E2 oleate - membranes/HDLs orientation provides new E2 interacted HDL- therapeutic approaches. [15] Genistein that presents altered membrane properties in a Genistein-membrane (DPPC liposomes) interaction model is considered as a promising pharmacological treatment of cancer and other related disorders.[37]

Interaction of chlorpromazine with lipid bilayer had enhanced permeability that indicates that it is a potential and significant chemical that increases the toxic level of tamoxifen via the mediation of estrogen receptor-mechanism.[36] Tamoxifen (TAM) associated membrane disruption can be controlled by low concentrations of alpha-tocopherol (alpha-T) that shows that TAM activity of disrupting the membrane is not an oxidative damage, and actually these membrane disruptions might indicate the anticancer activity.[17]

CONCLUSIONS

The present review article provides information in general about the interaction of estrogen/ estrogenic products or drugs with the lipid part of various types of membranes, and in special about the role of estrogen-membrane lipid interaction in various drugs and diseases. Hopefully the future studies would provide further information for physiological, pathophysiological, physicochemical and pharmaceutical aspects for better management of diseases and advancement of membrane interaction related studies-biophysical medicine. The future studies may bring a revolution in the management of membrane interaction associated diseases and interpretation of medical/ biomedical processes at the level of biophysical medicine.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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