Original Research Paper

Volume-9 | Issue-1 | January-2019 | PRINT ISSN - 2249-555X

Chemistry

THE DESIGNER ESTROGENS IN THE TREATMENT OF BREAST AND UTERINE CANCERS

Jaya Pandey Department of Chemistry, Amity School of Applied Sciences, Amity University, UP, Lucknow-226016, India,

D K Awasthi* Department of Chemistry,J.N.(PG) College, Lucknow *Corresponding Author

KEYWORDS

Designer estrogens is the term currently being used to describe the actions of a medication that acts as an estrogen on one tissue and an anti-estrogen on others. These are also called Selective Estrogen Receptor Modulators.). An engineered drug that possesses some, but not all, of the actions of estrogen. For example, raloxifene (brand name: Evista) is classified as a designer estrogen because, like estrogen, it prevents bone loss and lowers serum cholesterol; however, it does not stimulate the endometrial lining of the uterus. The role of estrogen is documented in the prevention of heart disease, the preservation of cognition and even the prevention of colon cancer The ideal designer estrogen medication would switch of or off the effects of estrogen at different sites in the woman's body.

Selective Estrogen-Receptor Modulator (SERM) can truly be called as a "designer estrogen" because it possesses some, but not all, of the actions of estrogen. They provide both estrogen agonist and antagonist properties, depending on the target tissue. For example, raloxifeneprevents bone loss (like estrogen) and lowers serum cholesterol; (like estrogen) but (unlike estrogen) does not stimulate the endometrial lining of the uterus. Principally,they *maximize the beneficial effects of estrogen on bone and minimize its deleterious effects on the breast and endometrium*

Estrogen and synthetic versions can enhance the repair of blood vessels after injury or improve metabolism in the liver and adipose tissue, but they can also cause breast or uterine cancer, because they stimulate cell proliferation in these reproductive tissues. Madak-Erdogan *et al.* designed estrogen-like molecules that had reduced receptor affinity and that did not enhance ductal mammary gland branching (a sign of mammary gland growth) or increase uterine weight in ovariectomized mice. These estrogens provided vascular and metabolic benefits and thus could be further developed as postmenopausal hormone replacement therapies.

There is great medical need for estrogens with favorable pharmacological profiles that support desirable activities for menopausal women, such as metabolic and vascular protection, but that lack stimulatory activities on the breast and uterus. We report the development of structurally novel estrogens that preferentially activate a subset of estrogen receptor (ER) signaling pathways and result in favorable target tissue–selective activity. Through a process of structural alteration of estrogenic ligands that was designed to preserve their essential chemical and physical features but greatly reduced their binding affinity for ERs, we obtained “pathway preferential estrogens” (PaPEs), which interacted with ERs to activate the extranuclear-initiated signaling pathway preferentially over the nuclear-initiated pathway. PaPEs elicited a pattern of gene regulation and cellular and biological processes that did not stimulate reproductive and mammary tissues or breast cancer cells. However, in ovariectomized mice, PaPEs triggered beneficial responses both in metabolic tissues (adipose tissue and liver) that reduced body weight gain and fat accumulation and in the vasculature that accelerated repair of endothelial damage. This process of designed ligand structure alteration represents a novel approach to develop ligands that shift the balance in ER-mediated extranuclear and nuclear pathways to obtain tissue-selective, non-nuclear PaPEs, which may be beneficial for postmenopausal hormone replacement. The approach may also have broad applicability for other members of the nuclear hormone receptor superfamily.

Role of Estrogens

Researchers are on the verge of learning much more about the role estrogen plays -- not just in a woman's reproductive system, but in heartheart disease, Alzheimer's disease, depression, osteoporosis, disease, Alzheimer's disease, depression, osteoporosis, and autoimmune disorders.

Brain

Studies of cognition have also implicated a positive influence of estrogen. Several studies have indicated that estrogen has a positive effect on memory and cognition. In epidemiological studies, estrogen delayed the onset of Alzheimer disease,and in small clinical trials, women with Alzheimer disease who are treated with estrogen show improvement in cognitive functioning.

Effects in deficiency/ Menopause

Absence of estrogen action occurs at other target sites such as bone, heart, and brain.

Estrogen deficiency in the postmenopausal woman results in numerous symptomatic and asymptomatic manifestations, including vasomotor symptoms including hot flushes leading to disturb sleep patterns fatigue, depression, insomnia, and irritability,

Bone

osteoporosis, leading to severe disability with pulmonary, gastrointestinal, or bladder symptoms and loss of independence due to compression fractures of the spine and hip fractures, heart disease, bladder and vaginal symptoms, and

Heart

Cardiovascular diseases: The cardioprotective effect of estrogen is due to additional properties such as regulation of vasoconstriction, improvements in hepatic cholesterol metabolism, and production of nitrous oxide.

	Breast	Uterine lining	Bone	Raises HDL
Estrogen	Stimulates breast tissues	Increases uterine lining	Increase bone mass	Increase HDL Decreases LDL
Tamoxifen	Blocks effects of estrogen on breast tissues	Increases uterine lining	Increase bone mass	Decrease LDL
Raloxifene (Evista)	Blocks effects of estrogen on breast tissues	No effect on uterine lining	Increase s bone mass	Decrease LDL
Phytoestrogens	Blocks effects of estrogen on breast tissues	Uncertain	Increase s bone mass	Uncertain

Estrogen replacement therapy is associated with amelioration of these problems can be done by SERMs and Phytoestrogens.

SERMs: Target Tissues

Phytoestrogens are widely used in the United States, but little information is available regarding their potential long-term effects

Benefits	Standard dose Hormone replacement. Premarin	Evista (Raloxifene)
Cardiovascular	35-50% in Cardiac Disease* 15% LDL (lousy cholesterol) 5-15% HDL (healthy cholesterol)	Cardiovascular disease not studied. LDL
Osteoporosis	Proven Fractures Vertebral fractures: 50%-80% Hip, wrist and other fractures :25% 5%-8% BMD spine/hip	Fracture risk benefit unknown. 2% BMD (spine/hip)
Menopausal Symptoms	hot flashes, night sweats, vaginal drying and painful intercourse, mood swings and skin wrinkles&tone	No effect (may increase hot flashes)
Alzheimer's Disease	Studies indicate positive affects on memory	Not studied
Risks		
Breast Cancer	In some studies with 8-10 yrs of standard dose estrogen , relative risk of 1.25	No increase risk in studies up to 3 yrs.
Breast Tenderness	Rare, usually limited to first few months of therapy	None
Vaginal Bleeding	Cyclic regime declining menses Daily regime beyond 9-10 months of therapy there should be no bleeding	No menses

Phytoestrogen: The natural estrogen

Phytoestrogens have long had a role in the treatment of various disorders.

A plant phytoestrogen is supposed to enhance contraception. Studies have suggested a protective role for phytoestrogens against several types of cancer, including breast,uterine, and prostate.

Many phytoestrogens with mixed estrogen agonist and antagonist properties have been identified. Isoflavonoids are a class of flavonoids derived from soybean-based foods. Two dietary isoflavonoids, genistein and daidzein, have estrogen like activity

A wide variety of commonly consumed foods contain appreciable amounts of different phytoestrogens. Phytoestrogens consist of at least 20 compounds from 300 plants and are found in such common foods as parsley, garlic, soybeans, wheat, rice, dates, pomegranates, cherries, and coffee. In general, they are weaker than natural estrogens health benefits of phytoestrogens in relation to cardiovascular diseases, cancer, osteoporosis and menopausal symptoms.

Herbs have traditionally been used for treating various health problems, and many herbs contain estrogen receptor-binding properties; the most common are soy,licorice, red clover, thyme, turmeric, hops, and verbena. Other herbs that may contain progesterone-binding properties include oregano, verbena, turmeric, thyme, red clover and damiana.

Estrogen receptor-binding herbal extracts tend to behave as estrogen agonists, similar to estradiol,whereas progesterone-binding extracts could be neutral or act as estrogen antagonists.

Overall, assessing an appropriate formulation and dosage of phytoestrogens is difficult, and long-term effects on other target tissues (uterus, heart, brain) remain unknown. Little is known about the actions of phytoestrogens on the uterus, heart, brain, and bone. Although these compounds have recently gained widespread use, optimal dose and potential adverse effects remain unknown. Definitive long-term studies in a controlled clinical setting are necessary to assess efficacy vs risk for the phytoestrogens

Conclusion

"Designer" estrogen replacement, tailored to individual needs. New estrogens will be designed to act only on specific parts of the body. "We may want estrogen for maintaining bone health, but don't want the estrogen effect on the uterus. The study is also looking at just how much a diet low in fat and high in fruits, vegetables and grains reduces the risk of breast cancer, colorectal cancer, and heart disease.

"As we better understand the molecular and genetic bases of disease, we will be able to design drugs specifically to correct the defects,"

REFERENCES

1. Z., Erdogan, John A. Katzenellenbogen *et al* "Design of pathway preferential estrogens that provide beneficial metabolic and vascular effects without stimulating reproductive tissues" *Sci. Signal.* 24 May 2016: Vol. 9, Issue 429, pp. ra53
2. October 07, 2011 | Hysterectomy, Sexual Health By Judith A. Norris, RNP
3. Tham OM, Gardner CD, Haskell WL. Clinical review 97: potential health benefits of dietary phytoestrogens; a review of the clinical, epidemiological, and mechanistic evidence. *J Clin Endocrinol Metab. 1998;83:2223-2235.*
4. Murkies AL, Wilcox G, Davis SR. Clinical review 92: phytoestrogens. *J Clin Endocrinol Metab. 1998;83:297-303.*
5. Hodgson JM, Puddey IB, Beilin LJ, Mori TA, Croft KD. Supplementation with isoflavonoid phytoestrogens does not alter serum lipid concentrations: a randomized controlled trial in humans. *J Nutr.1998;128:728-732.*
6. Maskarinec G, Singh S, Meng L, Franke AA. Dietary soy intake and urinary isoflavone excretion among women from a multiethnic population. *Cancer Epidemiol Biomarkers Prevo 1998;7:613*619.
7. Shoff SM, Newcomb PA, Mares-Perlman JA, et a1. Usual consumption of plant foods containing phytoestrogens and sex hormone levels in postmenopausal women in Wisconsin. *Nutr Cancer.* 1998;30:207-212.
8. Lees CJ, Ginn TA. Soy protein isolate diet does not prevent increased cortical bone turnover in ovariectomized macaques. *Calclf Tissue Int. 1998;62:557-558.*
9. Gennari C, Agnusdei 0, Crepaldi G, et a1. Effect of ipriflavone-a synthetic derivative of natural isoflavones--on bone mass loss in the early years after menopause. *Menopause.* Spring 1998;5:9-15.