Endocrine-Mimicking Phytoestrogens:
Health Effects and Signaling

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Abstract - Phytoestrogens display estrogen-like activity because of their structural similarity to human estrogens and exhibit high affinity binding for the estrogen receptors (ERs). The prevalence of phytoestrogens in our diets and the biological effects that they may cause need to be fully examined. ER is the ancestral receptor from which all other steroid receptors have evolved. Although phytoestrogens serve specific signaling functions between the plants and insects, fungi, and bacteria, many chemical signals are often misinterpreted as estrogenic signals in non-target organisms such as vertebrates. There are no ERs in plants or in their most common partners, insects. However, *Rhizobium* soil bacteria have NodD proteins which is an intended target of phytoestrogen signaling and share genetic homology with the ER. These two evolutionarily distant receptors both recognize and respond to a shared group of chemical signals and ligands, including both agonists and antagonists. This review briefly summarizes estrogen and estrogen receptors, kinds of important phytoestrogens, their health effects as well as some of the evolutionary aspects of mechanism by which phytoestrogen mimics the endogenous ER signaling in our body.

Key words: estrogen, phytoestrogen, estrogen receptor, health effect, signaling

INTRODUCTION

Phytoestrogen are non-steroidal compounds found in a wide variety of plant foods. Phytoestrogens, plant chemicals classified as isoflavones, coumestans and lignans, display estrogen-like activity because of their structural similarity to human estrogens and exhibit high affinity binding for the estrogen receptor. The interest in phytoestrogens has recently been increased by the realization that hormone replacement therapy (HRP) for the endocrine controlled diseases in bone, cardiovascular system, cancers, central nervous system and reproductive organs is not as safe or effective as previously thought (Hays et al. 2003). The prevalence of phytoestrogens in our diets, the biological effects and mechanism by which phytoestrogen mimics the endocrine signaling in our body should be addressed.

ESTROGEN AND ESTROGEN RECEPTORS

Estrogens, largely produced in the ovaries, have many biological effects in the body beyond the reproductive system. The dominant estrogen in the body is 17β estradiol (Fig. 1). When bound to an estrogen, the estrogen receptors (ER) in the nucleus interact with the estrogen response element (ERE) which regulates transcription of estrogen responsive genes (Razandi et al. 1999; Xu et al. 2003). There are two known estrogen receptors, ERα and ERβ which are vary in tissue distributions and can
have different effects on mixed agonists and antagonists (Nilsson and Gustafsson 2002). Although any compound that induces receptor dimerization and subsequent binding to the ERE, can be considered an estrogen, antagonistic effects can occur when a compound is able to bind to ER but dimer formation either does not occur or the correct configuration to activate the ERE is not attained. Some compounds such as tamoxifen act as estrogen agonists and antagonists and are referred to as Selective Estrogen Receptor Modulators (SERMs) (Macgregor and Jordan 1998). These agonist/antagonistic effects are believed to be responsible for the differential effects of phytoestrogens compared to estradiol. Both ERα and ERβ function in normal ovarian follicles, vascular endothelia cells, myocardiad cells, smooth muscle, and breast tissue (Nilsson and Gustafsson 2002). ERα is involved in bone maturation in both males and females, however, only ERβ plays a role in bone maintenance in females (Nilsson and Gustafsson 2002). ERα is more important in maintaining follicle stimulating and luteinizing hormone concentrations in blood, and ERβ is involved in frontal lobe mediated learning and memory (Nilsson and Gustafsson 2002).

1. Isoflavonoids

The flavonoids are a large chemical class formed through the phenylpropanoid–acetate biennial pathway. Sheep grazing the red clover had multiple fertility problems including early onset of puberty, failure to get pregnant and miscarriage. The clover had high amounts of the isoflavones, formononetin and biochanin A (Rossiter and Beck 1966). Genistein and daidzein are the most studied isoflavonoids (Dixon and Ferreira 2002). Genistein (Fig. 1) has one-third the potency of estradiol in interaction with ERβ, and one thousandth of the potency of estradiol in interaction with ER (Kuiper et al. 1998) and can induce similar responses as estradiol (Wang et al. 2003). In some tissues such as mammary tissue (Murrill et al. 1996), breast tumors (Fritz et al. 1998), and prostate (Mentor–Marcel et al. 2001; Fritz et al. 2002) genistein can act as an estrogen antagonist. Genistein also shows non-genomic effects through the ER receptors in the cell membrane. However, daidzein, did not show any non-genomic effects. Some gene is upregulated by genistein and unresponsive to estradiol (Ramanathan and Gray 2003). The ability of genistein to block cell proliferation of normal mammary cells may contribute to the preventive effect of a high soy diet on risk of breast cancer. The major source of isoflavonoids in the diet is from soy-based foods. Even though genistein has relatively low potency compared to estradiol, high concentrations in plasma may be sufficient to cause a variety of physiological effects. A closely related compound to the isoflavonoids is 8–prenyl naringenin, a

![Fig. 1. Structure of 17β estradiol, genistein (isoflavonoid), coumestrol (coumestan), trans-resveratrol (stilbene), matairesinol (lignan) and 8–prenyl naringenin.](image-url)