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Review

Environmental epigenetics and phytoestrogen/phytochemical exposures

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ABSTRACT

One of the most important environmental factors to promote epigenetic alterations in an individual is nutrition and exposure to plant compounds. Phytoestrogens and other phytochemicals have dramatic effects on cellular signaling events, so have the capacity to dramatically alter developmental and physiological events. Epigenetics provides one of the more critical molecular mechanisms for environmental factors such as phytoestrogens/phytochemicals to influence biology. In the event these epigenetic mechanisms become heritable through epigenetic transgenerational mechanisms the impacts on the health of future generations and areas such as evolutionary biology need to be considered. The current review focuses on available information on the environmental epigenetics of phytoestrogen/phytochemical exposures, with impacts on health, disease and evolutionary biology considered.

This article is part of a Special Issue entitled 'Phytoestrogens'.

Contents

1. Introduction

Endocrine disruptors are present in the environment from both synthetic and natural origins and have been shown to influence the physiology and development of organisms. These compounds interfere with the actions of endogenous hormones at several physiological levels [1]. Although progressive accumulation of synthetic endocrine disruptors in the environment has altered the ecological balances in natural populations and affected human health [2], nutritionally derived natural compounds provide a much more historical and quantitative exposure. Synthetic endocrine disrupting compounds are present in cosmetics, food containers, packaging materials, toys, agrochemicals and in nearly all manufactured products for humans [2–4]. However, alterations in nutritional habits and food composition provide one of the most common exposures for endocrine disrupting chemicals [2]. For example, the recent nutritional change in the incorporation of soy-derived products into human diets has dramatically increased the consumption of plant derived chemicals [5].

Plant produced compounds (secondary metabolites) with estrogenic actions in animals are known as phytoestrogens [6,7]. Phytoestrogens are readily available in the environment in food items consumed by animals [7,8]. These compounds are polyphenolic structures similar to the estradiol molecule and have the ability to trigger estrogenic activity through estrogen receptor signaling pathways [9]. Phytoestrogens have been shown to produce physiological and developmental effects in animals [10]. Phytoestrogens are classified as flavonoids, cumestans, lignans and stilbens, with flavonoids (or isoflavones) being the most prevalent in dietary sources [5,9,11] (Table 1). However, plant derived chemicals (phytochemicals) that do not contain estrogenic activity are not phytoestrogens and should be termed phytochemicals. The problem with categorizing classes of compounds as phytoestrogens is that many do not contain estrogenic activity and should be classified as phytochemicals [12]. Therefore, the nomenclature in the field is currently problematic and needs to specifically assess estrogenic or endocrine disruptor activity of individual compound prior

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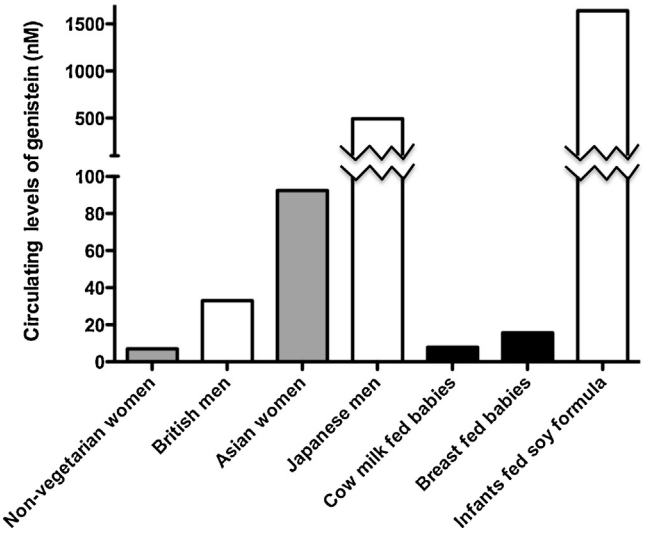

Fig. 1. Cross-studies comparison of circulating levels of genistein among different human groups. Gray bars indicate genistein serum concentrations in nM. White bars indicate genistein plasma concentrations in nM. Black bars indicate values extrapolated to nM concentrations of genistein from relations of isoflavone plasma concentrations in ug/L between differentially fed infants. Values were obtained from reviews in the literature [5,24].

to classification as phytoestrogens. The current review attempts to use the term phytoestrogen and phytochemicals appropriately.

The identification of phytoestrogens as having estrogenic or reproductive effects in animals dates back to observations from farmers in New Zealand regarding ewes becoming infertile after eating clover [13,14]. The same effect was further reported in cattle [15]. The fertility of captive cheetahs has also been shown to be affected by dietary consumption of soy [16]. Since then, reproductive effects of exposure to flavonoids have been reported in laboratory animals ranging from disruption of estrous cycle, sexual behavior, testis function, ovarian function and female reproductive tract function to early developmental effects [17]. In particular, dietary exposure of flavonoids have been shown by several studies to produce significant reproductive effects in rodents [18–26]. Interestingly, dietary intake of phytoestrogens by laboratory animals has also been shown to be high, with studies showing estrogenic effects derived from the consumption of some commercial mouse diets [27–30].

A number of epidemiological and laboratory studies have been performed with phytochemicals in the past 40 years due to their potential to affect human health through nutrition [31]. One of the main concerns is that soy products have become an important component of food products in adult and infant human diets in recent years [32]. Variable amounts of isoflavones are consumed by human populations in different regions of the world [24,33]. For example, isoflavone consumption in Asian countries (25–100 mg/day) is much higher than in western countries, such as the UK, with daily consumption below 1 mg [34]. Consequently, plasma levels of the phytoestrogens vary among western and eastern countries. For example, plasma levels of the phytoestrogens genistein and daidzein are more than 10-fold higher in Japanese men than in British men [35,36], Fig. 1. Serum levels can reach concentrations of isoflavones after a soy rich meal with estrogenic activity well above the levels of endogenously circulating hormones [37]. In regards to the potency, physiologically relevant concentrations of some phytoestrogens such as genistein, daidzein or cumestrol are able to stimulate the transcriptional activity of both estrogens receptors (in a cell based transcription assay) to the same or greater levels as synthetic compound such as diethylstilbestrol (DES), bisphenol A (BPA), dichlorodiphenyltrichloroethane (DDT), methoxychlor, or tamoxifen [38]. The modes of action of phytoestrogens include several other pathways in addition to binding to estrogen receptors. These are rapid cellular responses (AMP-activated protein kinase, mitogen-activated protein kinase and phosphoinositide 3-kinase pathways), antioxidant action, tyrosine kinase inhibition, peroxisome proliferator-activated receptor gamma (PPAR) mediated action [5] and binding to the non-classical estrogen receptor GPR30 or the aryl hydrocarbon receptor [17]. In addition, the role of phytoestrogens as selective estrogen receptor modulators (SERMs) such as tamoxifen should not be dismissed, given the ability of phytoestrogens to bind to the ER and produce tissue-specific actions that depends on the presence of cofactors that helps modulate the interaction [39]. For example, nude mice with a low-dose genistein exposure can negate the effect of tamoxifen of reducing MCF-7 breast tumor cells growth [40]. An important aspect of exposure to phytochemicals is potential combination effects with other hormonally active compounds [41,42].

2. Physiological impacts

Human studies show that isoflavone consumption has a variety of physiological effects. Intake of isoflavones has been suggested to alter sex hormone concentrations in adults [43,44] and children [45]. For example, soy isoflavone consumption by premenopausal women is associated with increased circulating luteinizing hormone (LH) and follicle stimulating hormone (FSH), and increased menstrual cycle length [46]. In postmenopausal women, changes in sex hormone-binding globulin levels have been observed [47]. A recent study found an association of high content of isoflavones in the blood with precocious puberty in Korean girls [48]. Other studies in women correlate consumption of phytoestrogens with increased sexual arousal [49], increased risk for uterine fibroids [50], and abnormal uterine bleeding [51]. Recently, a panel of experts has reviewed the literature on the use of soy in infant formulas due to the concern raised by several studies regarding adverse effects later in life [32]. In men, one study suggests that increased hypospadias could be related to a high developmental exposure to phytochemicals/phytoestrogens from a vegetarian maternal diet during gestation [52]. High intake of dietary isoflavones has been correlated with low sperm numbers in men from subfertile couples [53]. In addition to reproductive effects, consumption of flavonoids is thought to have a protective effect against cancer in specific organs [54], including breast cancer in humans [55]. However, recent studies suggest that this protective effect of flavonoids against cancer would only occur if the exposure is during childhood/adolescence [56,57].

One of the main concerns about high phytoestrogen/phytochemical diet consumption in humans is the effects on early developmental stages, such as the effects on infants consuming soy-based formulas. The effects of high consumption of isoflavones by pregnant mothers in uterus, placenta or breast milk are also a concern in terms of their influences on the developing embryo. Circulating plasma concentrations of isoflavones is considerably high in infants consuming soy-formula, being 50–100 times higher than levels in pregnant women, 10–50 times higher than in Asian women, 100–700 times higher than in non-vegetarian US women [5,24] (Fig. 1). The equivalent estrogenic activity in these infants is 13,000–22,000 higher than normal endogenous estrogen levels [5]. Maternal exposures are also crucial during embryogenesis, when the fetal microenvironment is susceptible to maternal influences due to dietary compounds [58] or hormonal changes [59]. One important maternal exposure route is through the placenta. It has been shown that genistein aglycone can cross the placental barrier and reach the fetal brain in rats [60,61]. Effects in the early embryo are also mediated by physiological