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Does phytoestrogen supplementation affect cognition differentially in males and females?

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Abstract

Phytoestrogens are plant-derived compounds found mainly in soy with known estrogenic properties and a potential for benefits to human health. Increased intake in phytoestrogens stemmed from the search for safe alternatives to hormone replacement therapies. Based on epidemiologic evidence comparing Western and Asian population and clinical studies, phytoestrogens show promise to improve health and brain function. This review will focus on the effects of phytoestrogens on cognition by examining clinical and animals studies, with special attention placed on (1) a window of therapeutic opportunity which may explains the discrepancy amongst studies, and (2) whether a sex/gender difference exists in response to phytoestrogen intake and what the possible underlying mechanisms may be.

1. Introduction

Plant-derived, non-steroidal compounds with estrogen-like actions (phytoestrogens) are found in soy and a variety of other food products (e.g., legumes, fruits, flaxseed, clover). While numerous phytoestrogens of various classes have been identified, the isoflavones genistein and daidzein are the most widely studied based on their abundance in soy products, their potency as estrogen agonists at tissue specific targets (e.g., Thigpen et al. 2004; Zhao and Brinton 2005), and their ability to enhance transcriptional activity mediated by estrogen receptors (ER) ER α and ER β (Kuiper et al. 1998; Kostelac et al. 2003; Zhao et al. 2009).

Soy has been consumed as a staple food by Asian populations for a considerable period of time, whereas phytoestrogen intake via soy or other foods among Western populations has traditionally remained relatively low. However, based on the variety of health benefits now associated with phytoestrogens, intake of phytoestrogen-containing foods and soy-based supplements has grown several fold in Western countries within the last decade (Nurmi et al. 2002; Kurzer 2003; Vergne et al. 2008). In the United States, the sales in soy food has quadrupled in 15 years (NAMS 2011), with now one third of Americans consuming soy-based products monthly. In particular, soy foods and supplements have been viewed as alternatives to estrogen therapy as they are believed to provide the benefits of such therapy without the risks of uterine and breast cancer (Vincent and Fitzpatrick 2000; Glazier and Bowman 2001).

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Phytoestrogens appear to have additional actions that may contribute to lowering of cancer risk, including the ability to inhibit tyrosine kinase (Akiyama et al. 1987), to act as antioxidants (Mitchell et al. 1998; Tikkanen et al. 1998), to lower cholesterol (Anthony et al. 1998), and to inhibit cell proliferation and DNA synthesis (Pan et al. 2001). Indeed, animal, clinical, or epidemiological studies suggest phytoestrogens have beneficial effects in the prevention of hormone-dependent cancers (e.g., breast, endometrial, and prostate cancers), cardiovascular disease, osteoporosis, and in the relief of the symptoms of menopause (reviewed by Lephart et al. 2002; Kurzer 2003; NAMS 2011).

Based on the apparent health benefits, as well as the suggested outcomes based on epidemiologic comparison of Western and Asian populations, increasing phytoestrogen intake may well improve overall health, longevity and cognitive capacity. Due to their promising potential as hormone therapies, most research of genistein, daidzein and soy supplements has focused on women, in particular middle-aged women. The evidence indicates that the effects of phytoestrogens may be dependent upon a window of opportunity for treatment, and may affect males differentially than females due to the tyrosine kinase activity and diminished presence of ER-mediated protective mechanisms with a potentially deleterious outcome of the supplements. The purpose of this review is to discuss (1) whether there is evidence of a window of opportunity for beneficial effects on cognition, and (2) whether a sex/gender difference in cognitive response to phytoestrogen intake exists and what may be the underlying reasons for such discrepancies.

2. Phytoestrogens and cognition

An accumulation of evidence based on human and animal studies suggests that estrogens are positive modulators of learning and memory function (reviewed by Sherwin 2002; Sherwin 2006; Sherwin and Henry 2008), and that in females, age-associated cognitive decline is at least partially attributable to cessation of estrous cycling and declining estrogen levels (Boulware et al. 2012). Based on their ability to bind and activate estrogen receptors, intake of high soy diets or isoflavone supplements could be expected to modify cognitive processes directly and, in particular, they should improve cognition in aged females. However, it is possible that age and duration of post-menopausal hormone deprivation affect the response of the brain to phytoestrogen intake.

2.1 Human studies

Clinical outcomes may depend upon a critical window of therapeutic opportunity, which signifies that phytoestrogen or estrogen intake may be beneficial when initiated early enough but could become deleterious when started later in life. This critical period may explain the equivocality of clinical trials findings.

A study of young student volunteers suggested that intake of a high soy diet (100 mg isoflavones/d) for 2.5 months was associated with improvement in both short- and long-term memory and cognitive flexibility (File et al. 2001). The results in younger postmenopausal women indicate similar outcomes, suggesting that perhaps soy isoflavones can exert biological modification of brain function independently of age. In the Soy and Postmenopausal Health in Aging (SOPHIA) study, women aged 55-74 years who consumed a soy-isoflavone based supplement (110 mg/d) for 6 months showed better verbal memory than the placebo control group (Kritz-Silverstein et al. 2003). Similarly, in women aged 50-65, Duffy et al. (2003) found that intake of 60 mg/d for 3 months resulted in cognitive improvement in several categories related to frontal cortical functions, and this finding was confirmed in a larger, double blind, placebo-matched parallel groups study involving women aged 51-66 (File et al. 2005). Another study, involving younger postmenopausal women receiving 160 mg/d isoflavones, failed to demonstrate an improvement in cognitive

flexibility. These studies suggest that in young pre- or postmenopausal women, intake of phytoestrogens is beneficial on frontal-cortical function.

However, a well-controlled study conducted in the Netherlands involving a large sample of older postmenopausal women aged 60-75 years (Kreijkamp-Kaspers et al. 2004) did not report significant improvement following 99 mg/d of soy isoflavones for 12 months. In the SOPHIA study, it was reported that the older group of women (60-74 y.) did not show improvement in all categories tested and that the beneficial effects were diminished compared to the younger group (Kritz-Silverstein et al. 2003). A study of Chinese postmenopausal women who received 80 mg isoflavones/d for 6 months showed no effect on cognition, even when separated by age groups (Ho et al. 2007). This discrepancy might be confounded by a history of soy intake from food as part of their daily diet.

The hypothesis that intake of soy phytoestrogens could delay or attenuate age-associated cognitive decline in women has also been tested by considering cognitive performance of older women in high soy consuming populations. In studies of Japanese and Chinese women (46-56 years) enrolled in the Study of Women's Health Across the Nation (SWAN) (Huang et al. 2006) and in a study of Dutch women aged 60-75 years (Kreijkamp-Kaspers et al. 2007), no significant associations were found between dietary isoflavone intake and cognitive function. However, in a study of relatively older males aged 71-91 years, enrolled in the Honolulu-Asia Aging Study (HAAS), a high intake of soy (tofu) during midlife was found to be associated with poor cognitive test performance, ventricular enlargement and low brain weight (White et al. 2000). It is noteworthy that when the food survey data for the males in this study were used as proxy for the wife's consumption, a similar pattern of negative association was evident in females. A larger study that should provide important new information is ongoing: the Women's Isoflavone Soy Health (WISH) trial is primarily studying the effect of isoflavone intake (150 mg isoflavones/d for 2.5 years) on the progression of atherosclerosis, however longitudinal changes in cognitive function will also be determined (NCT00118846).

Overall, while the data are fragmentary, they provide a clear suggestion that both chronic and relatively short-term intake of soy phytoestrogens may significantly modify brain functions and cognition, especially in women. However, these outcomes also indicate that the effectiveness of such treatment may be diminished with increasing age after 60 years and may even be deleterious. These studies are indicative of a critical window of therapeutic opportunity, suggesting that age and/or duration of hormone deprivation adversely affect the beneficial effects of phytoestrogens.

2.2 Animal studies

Animal studies of phytoestrogen intake reported in the literature confirm the potential for either beneficial or deleterious effects on cognition, and have provided the additional suggestion that such effects are *gender-dependent* (reviewed by Lephart et al. 2002; Lee et al. 2005; Lephart et al. 2005). The rodent studies have compared cognitive functions in adult rats or mice maintained on diets that are either phytoestrogen-free or enriched in soy phytoestrogens to an extent producing plasma genistein and daidzein levels approximating that for humans consuming a traditional Asian diet. These studies have focused on behavioral tests of visually-mediated spatial memory performance, which has been linked to processes of hippocampal synaptic plasticity (Burke and Barnes 2006) and is significantly modulated by estrogens (e.g. Frick et al. 2002).

In studies of young adult female rats, phytoestrogen intake has consistently resulted in an improvement in visually-mediated spatial memory performance. Ovariectomized retired female breeders received soy phytoestrogens with three doses and had improved working

memory performance in a dose-dependent manner (Pan et al. 2000). Young ovariectomized rats also showed improvement in spatial memory task as well as increased spine density after 9 weeks on a soy rich diet (Luine et al. 2006). In intact females, lifelong exposure resulted in similar outcome by improving visual spatial memory performance of the adult rats (Lund et al. 2001; Lephart et al. 2002). Though limited, most studies of females suggest a beneficial effect of phytoestrogens on cognition, however it is noteworthy that the duration of hormone deprivation was relatively short in these studies. A recent study in non-human primates demonstrated that responsiveness of the brain to estrogen and equol (an intestinal by-product of daidzein with health benefits (Ingram et al. 1997; Setchell et al. 2002) was diminished with long hormone deprivation duration (Hamilton et al. 2011). More studies are needed to understand the mechanisms underlying this critical window of opportunity and possibly extending it.

Despite this critical therapeutic window, phytoestrogens have been mostly beneficial in studies of females, however the data on males are very limited and equivocal. On a phytoestrogen-rich diet, male rats performed worse on the visuo-spatial task than the controls (Lund et al. 2001; Lephart et al. 2002). This deleterious effect of phytoestrogens observed in males is apparently reversed following cessation of phytoestrogen intake (Lund et al. 2001). The deleterious effect on cognition in males may be specific to certain age groups or cognitive domains, as other studies have reported that phytoestrogen intake improved performance of older adult rats in a task requiring short-term memory (Lee et al. 2004).

Overall, these studies indicate a potential for beneficial effects of phytoestrogen intake on cognitive function, however more studies are needed for men/males to ascertain these effects, more specifically in older men/males.

3. Why the potential gender/sex-differences?

Genistein and daidzein are phenolic compounds and may act directly as antioxidants by donating hydrogen and electrons via the hydroxyl groups, a property they share with estrogens (Mitchell et al. 1998; Dykens et al. 2003). However, based on concentrations of these compounds in individuals consuming soy foods or supplements, it is unlikely that this property has a major influence on the overall cellular redox state. Phytoestrogens do, however, significantly increase expression and activity of the antioxidant defense enzymes catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase (Kurzer and Xu 1997; Borrás et al. 2006), which could have a marked effect on oxidative stress and accumulation of oxidative damage. These effects are similar to that produced by estrogens (Borrás et al. 2007) and are attributable to the ability of genistein or daidzein to preferentially bind ERs and up-regulate antioxidant defenses (Borrás et al. 2006; Raschke et al. 2006; Borrás et al. 2007). In females, the ability of phytoestrogens to improve cognitive performance could involve an ability to elicit reducing shifts in the cellular redox state, improve redox signaling, or to prevent accumulation of molecular oxidative damage, via an up-regulation of cellular antioxidative defenses.

While ERs are present in individuals of both sexes, recent studies have indicated that both expression and transcription of ER is relatively higher in adult female when compared with male mice (Sharma and Thakur 2006; Thakur and Sharma 2007). Moreover, the age-related decline in ER expression is reported to be relatively larger in male mice. The possibility that the level of oxidative stress differs in males and females has only recently been considered (Borrás et al. 2007), although it is well established that females show greater longevity than males in many mammalian species. Studies of mice and rats of different gender indeed suggest that oxidative stress is higher in adult males than females, when considered in terms

of the rates of mitochondrial hydrogen peroxide generation (Borras et al. 2003), DNA damage (Vina et al. 2003) or the ratio of reduced to oxidized glutathione (GSH) (Rebrin et al. 2005) in brain or peripheral tissues. The lower oxidative stress in mature females is correlated with a significantly higher expression of mitochondrial SOD, glutathione peroxidase and GSH (Borras et al. 2007) that is estrogen-dependent. Furthermore, the loss of GSH with increasing age is reported to be greater in males than in females (Wang et al. 2003), in accordance with the relatively greater decline in ER. Thus, owing to the gender difference in ER, oxidative stress, and antioxidant defense, it could be expected that the phytoestrogens genistein or daidzein could have different interactions with aging processes in males and females.

4. Conclusions

Studies of soy consumption and phytoestrogen supplements have focused mostly on post-menopausal women seeking alternatives to estrogen treatments. In post-menopausal women, there seem to be an age-dependent effect of phytoestrogen supplements. In males, the data are sparse and equivocal, and more studies are needed to determine whether the effects will be beneficial or deleterious. Furthermore, considerations need to be given to the combination of phytoestrogens being used in the studies. Recently, it was determined that giving genistein, daidzein and equol was more effective than single isoflavone or other combinations at increasing ER selectivity and enhancing neuroprotection (Zhao et al. 2009). Finally, these studies support the idea of a window of therapeutic opportunity and the need for studies to identify the mechanisms controlling this window in order to extend it.

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