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Effects of perinatal daidzein exposure on subsequent behavior and central estrogen receptor α expression in the adult male mouse

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ABSTRACT

Daidzein is one of the most important isoflavones present in soy and it is unique as it can be further metabolized to equol, a compound with greater estrogenic activity than other isoflavones. The potential role of daidzein in the prevention of some chronic diseases has drawn public attention and increased its consumption in human, including in pregnant women and adolescent. It is unclear whether perinatal exposure to daidzein through maternal diets affects subsequent behavior and central estrogen receptor α (ERα) expression in male adults. Following developmental exposure to daidzein through maternal diets during perinatal period, subsequent anxiety-like behavior, social behavior, spatial learning and memory of male mice at adulthood were assessed using a series of tests. The levels of central ER α expression were also examined using immunocytochemistry. Compared with the controls, adult male mice exposed to daidzein during the perinatal period showed significantly less exploration, higher levels of anxiety and aggression. They also displayed more social investigation for females and a tendency to improve spatial learning and memory. The mice with this early daidzein treatment demonstrated significantly higher levels of ERα expression in several brain regions such as the bed nucleus of the stria terminalis, medial preoptic, arcuate hypothalamic nucleus and central amygdaloid mucleus, but decreased it in the lateral septum. Our results indicated that perinatal exposure to daidzein enhanced masculinization on male behaviors which is assocciated with alterations in ERα expression levels led by perinatal daidzein exposure.

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1. Introduction

Phytoestrogens are abundant in fruit, vegetables, legumes, whole grains and especially flaxseed, clover and soy products. They have many of the physicochemical and physiological properties of estrogens (Lephart et al., 2002), and may influence the brain and behavioral development through similar mechanisms as estrogen during perinatal development. Phytoestrogens can be divided into three classes: isoflavones, lignans and coumestans (Branca and Lorenzetti, 2005). Of all phytoestrogens, soy-derived isoflavones are the most abundant in rodent and human diets and the most studied in both animal and clinical research.

The primary isoflavones in soy are genistein and daidzein (Messina, 2000). Although many studies have reported the effects of soy isoflavone or genistein on behaviors (Hartley et al., 2003; Lund and Lephart, 2001; Moore et al., 2004; Patisaul et al., 2005; Simon et al., 2004; Wisniewski et al., 2005), because of various constituents in isoflavones, the mechanism underlying effects of isoflavones on behavior is not well understood. For example, few studies focus on daidzein's effects on behaviors such as exploration, anxiety, aggression, sociality, spatial learning and memory (Zeng et al., 2010). This may be due to the report that daidzein has lower affinities in cell culture assays than genistein and other phytoestrogens for both estrogen receptor alpha (ERα) and beta (ERβ) (Kuiper et al., 1998; Patisaula and Polstonb, 2008; Takemura et al., 2007). However, daidzein can be further metabolized to equol, a potent and abundant molecule in both rodents and humans (Fonseca and Ward, 2004; Muthyala et al., 2004; Setchell et al., 2002). Equol is an estrogenic compound alleged to have greater estrogenic activity than its precursor daidzein (Fonseca and Ward, 2004; Setchell et al., 2002), and binds with greater affinity to the ER than other isoflavones (Latonnelle et al., 2002; Muthyala et al., 2004; Setchell et al., 2005). The direct estrogenic effects of daidzein may not be greater than that of other isoflavones, but its metabolite, equol, may have impacts comparable to that of other isoflavones. Given that daidzein's potential role in the prevention of chronic diseases has increased consumption in humans (Lephart et al.,

Abbreviations: AH, anterior hypothalamus; Arc, arcuate hypothalamic nucleus; BST, bed nucleus of the stria terminalis; CeA, central amygdaloid nucleus; EPM, Elevated plus-maze; ER, estrogen receptor; ERα, estrogen receptor α; ERβ, estrogen receptor β; ERα-IR, ERα-immunoreactive; KO, knockout; LS, lateral septum; MeA, medial amygdala; MPO, medial preoptic; PPT, propylpyrazoletriol; WT, wild type.

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2002), it is very important to reevaluate the effects of daidzein on behavior and its underlying mechanism.

The prenatal and early postnatal period is a very critical phase in which estrogen sculpts the size of brain nuclei in a sex- and region-dependent manner. Estrogen mimics phytoestrogen may also have organization effects, inducing subsequent long-lasting effects at adulthood. A study of seven Japanese women and their newborns revealed that isoflavones transfer from mothers to their fetuses (Adlercreutz et al., 1999). Since equol is a metabolite of daidzein, it reaches its circulating concentration peak several hours after daidzein peaks (Watanabe et al., 1998). If the mother is exposed to high levels of daidzein and produces high levels of equol, it is possible that her fetus will consequently be exposed to high concentrations of equol (Todaka et al., 2005). Daidzein exposure through maternal diet during gestational and postnatal periods may affect fetuses and alter behaviors such as exploration, anxiety, aggression, sociality, spatial learning and memory which are closely associated with estrogen system.

Previous studies have found that gene expression of the two nuclear ERs, ERα and ERβ, is influenced by phytoestrogen exposure during the perinatal period (Patisaul et al., 2007; Ren et al., 2001). These two receptors differ in expression pattern and ligand specificity (Kuiper et al., 1996; Shughrue et al., 1997) and function. Studies using the ER knockout (ERKO) method and treatment with the ER agonist indicate that both ERα and ERβ are involved in anxiety, social interaction and reproductive behavior (Lund et al., 2005; Rocha et al., 2005). Previous findings also show that maternal exposure to daidzein masculinizes female memory and social behavior, reducing ERα in female bed nucleus of the stria terminalis (BST) and medial amygdala (MeA) (Yu et al., 2010). It is predicted that perinatal exposure to daidzein may first alter ER expression in adult males, from which their adult behaviors are then altered.

In addition to the extensive medical use of daidzein, soy is a major source of daidzein and plays an important part in the food culture of Asian countries. There has also been a sharp increase in soy consumption in the West (Messina and Messina, 1991; North et al., 2000; Price and Fenwick, 1985). Given fetal sensitivity, the effect of daidzein exposure on males through maternal diet requires further study. The purpose of our study was to examine the effects of perinatal daidzein exposure on exploration, anxiety, aggression, sociality, spatial learning and memory in males. We also examined male ER expression in the brain to analyze the mechanisms via which daidzein affects these behaviors. The current study could provide some important insights on the effects of daidzein on male behavior and brain while we used it on other medical purposes.

2. Methods

2.1. Animals and standard housing conditions

Adult male and female Balb/cJ mice (Xian Jiaotong University Laboratory Animal Center, Shaanxi, China) at 7–8 weeks of age were housed in groups of four in standard transparent Makrolon cages (Beijing Biological Science and Technology Limited Company, Beijing, China) (42 cm × 26 cm × 20 cm). Mice were maintained under a reversed light:dark 12:12 cycle (lights on at 22:00 h) at 21 ± 2 °C; food and water were continually available. The Animal Care and Use Committee of Shaanxi Normal University approved all protocols.

2.2. Procedure

After habituation of 1 week, one male and two female mice were randomly assigned to each cage. Gestation day 1 was determined by the presence of a vaginal plug. Cages containing pregnant mice were randomly assigned to either the daidzein-free diet group (control, 6 cages) or the daidzein diet group (6 cages, 200 mg daidzein/kg diet; 99% daidzein obtained from Shaanxi Huike Botanical Development Corporation, Shaanxi, China). Food (Xian Jiaotong University Laboratory Animal Center) was crushed, added and mixed with daidzein, and conglutinated to produce daidzein diet of the same appearance and hardness with the daidzein free diet. Specified diets were supplied to mothers during gestation and lactation until weaning of offspring. After birth of the pups, they were culled to six pups including three female and three males.

Mice were weaned on postnatal day 21 and only 24 males offspring of 24 female mice were chosen for our experiments (for daidzein-free diet group: n = 12; daidzein diet group: n = 12). They were housed in same-sex group in each cage. The experiments were performed until the animals reached adulthood (60–70 days); each male underwent every behavioral test in a sequence designed that the least stressful test was performed first. The intervals between different types of behavioral tests were three days. All behavioral tests were conducted between 14:00–18:00 h. After the behavioral testing components of our study, the control and treatment group mice were deeply anesthetized for immunocytochemistry analysis.

2.3. Behavioral tests

Observers were blind to both the rearing condition and daidzein treatment of the mice in all experiments. In every behavioral test, the apparatus was cleaned with 70% ethanol between each animal.

2.3.1. Elevated plus maze test

The elevated plus maze apparatus was made of gray glacial polyvinyl chloride and consisted of two open arms and two closed arms with walls 20 cm high (arms were 30 cm × 7 cm) elevated 1 m from the floor. Each mouse was placed in the center of the maze facing an open arm, and was allowed to explore for 5 min. Total distance traveled, number of crossings between closed and opened arms, and time spent in both open and closed arms were recorded using a digital video camera and Videomot2 (TSE Systems, Bad Homburg, Germany).

2.3.2. Novel cage test

Mice were individually introduced into a clean cage identical to their home cage containing clean sawdust. They were observed for 5 min under a light intensity of approximately 200 lx. Behaviors including climbing (walking on the edges of the walls of the arena), immobility (sitting or lying immobile), rearing (standing on hind legs), wall rearing (standing on hind legs with forepaws leaning against a wall), self-grooming (shaking, scratching, wiping or licking body parts (fur, ears, nose, and tail)), investigating (exploring floor, cage walls or air trough olfactory activity), digging (moving substrate forward with front paws and nose, or backwards with hind paws) and locomotion (locomotive behavior with normal body posture) (Marques et al., 2007) were recorded using Observe 11.0 (Noldus, Wageningen, Netherlands).

2.3.3. Male–male resident–intruder test

Mice were retained in the novel cage following the experiment for one night to allow for habituation. A male stimulus mouse of the similar background was then placed on the other side of the cage. Behaviors of the resident male were recorded using a 50 cm video camera (NV-GS15; Panasonic, Osaka, Japan) located near the cage. Duration and frequency of the following behaviors were recorded for 5 min using Observe 11.0 (Noldus): biting, boxing, immobility, following, wall rearing, self-grooming, digging, sniffing the stimulus mouse (head, body or anogenital region) and locomotion. Light intensity at the arena floor was 200 lx.

2.3.4. Male–female resident–intruder test

A female stimulus mouse of the same age and in anoestrum was placed in a cage with the resident male. The stage of the cycle was determined by examining the cell type composition of vaginal smears (Bronson et al., 1975). A NV-GS15 video camera (Panasonic) positioned

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