Effects of phytoestrogens on the central nervous system (CNS)

Introduction

1. Estrogen receptors have been identified in a number of brain regions indicating a role for estrogens in brain development &/or function. Few studies have examined the biochemical or the functional effects (adverse or beneficial) that occur as a result of this exposure.

Transfer of isoflavones to the CNS

2. The few studies that have looked at CNS transfer of isoflavones suggest that transfer to the CNS is limited. Levels of 2/5 & 0.3/0.3ng/mL of free & conjugated daidzein & genistein were found following oral and ip administration to rats. In contrast 2/282, 1/45 & 4/144ng/mL of free & conjugated daidzein, genistein & equol were found in plasma (Gamache et al.).

3. Sprague-Dawley rats were continuously exposed to isoflavones in utero & during lactation from mothers fed genistein (5, 100 and 500µg/g of feed). Exposed offspring were fed the supplemented feed to day 140. Levels of genistein in the brain were 0.3 & 0.7pmol/mg in males fed 100 & 500µg/g of diet and 0.1, 1.7 & 7.3pmol/mg in 5, 100 & 500µg/g of diet in females. In contrast, serum levels of genistein were 0.06, 0.59 & 6µmol/L in males and 0.1, 0.94 & 17.9µmol/L in females fed 5, 100 & 500µg/g of diet. Measurements in the brain were only made at day 140 (Chang et al., 2000).

Biochemical changes

4. Ovariectomised rats were fed isoflavones at a level equivalent to humans consuming 150mg isoflavones/d for 8 weeks. Levels of brain derived neurotrophic factor (BDNF) (Pan et al 1999a) & nerve growth factor (NGF) (Pan et al 1999b) mRNA were increased in the frontal cortex. Similar effects were observed when rats were fed a diet supplemented with estradiol. BDNF and NGF have been suggested to protect against injury & age-related degeneration of cholinergic neurons.
5. Adult Sprague-Dawley rats were fed a isoflavone-free diet & a diet containing 600µg isoflavones/g for 35 days. Levels of calbindin & calrethin, calcium binding proteins and 5αreductase & aromatase, androgen metabolising enzymes, were measured in the male brain at day 105. Levels of genistein and daidzein were measured in plasma & the medial basal hypothalamic & preoptic (MBH-POA) area of the brain (Lephart et al., 2000).

6. Plasma levels of genistein, daidzein & equol were 422, 1000 & 1031ng/mL, respectively (78x higher than controls) (n=18). Brain levels of daidzein & genistein were 69.1 and 8.8ng/g, respectively in the MBH-POA (8x higher than controls) (n=6).

7. Aromatase or 5αreductase activities were not significantly altered in the MBH-POA or amygdala of the treated group compared to controls (n=20). Levels of calbindin were reduced in the MBH-POA (approx 40%) & amygdala (approx 50%) in treated animals. Levels of calrectin did not significantly change in MBH-POA but decreased in the amygdala (approx 30%).

8. The authors suggest that plasma levels achieved in this study (2465ng isoflavones/mL) are equivalent to levels in adult humans ingesting 20-40g/d of soy. They propose that this data suggests that consumption of isoflavones from soy diet for short periods can elevate systemic & brain isoflavone levels, decreasing brain calcium binding protein levels without altering aromatase & 5αreductase activities.

**Functional effects**

9. Rats were subcutaneously administered genistein (1, 10, 100, 200, 400 & 1000µg/d) on days 1-10 and were ovariectomised at day 21. Pituitary responsiveness to GnRH & effects on the sexually dimorphic nucleus of the preoptic area (SDN-POA) were measured (Faber et al., 1993). GnRH-induced LH secretion increased with 10µg of genistein but decreased at >10µg of genistein. SDN-POA volume increased on exposure to 500 & 1000µg of genistein.

10. Pregnant Sprague-Dawley rats were fed genistein (0, 2, 20 or 100mg/kg/d) from day 7 of gestation. The offspring were also fed on this diet until day 77. Males & females were assessed for levels of sexually dimorphic behaviors such as open field activity, play behavior, running wheel activity and consumption of saccharine & salt solutions. Genistein treatment affected play behavior but this was not significantly different from controls. No differences were observed in running wheel activity or consumption of saccharine. Maternal body weight & food intake as well as birth weight & body weights at day 42-77 of offspring were significantly decreased on treatment of genistein (100mg/kg/d). Increased consumption of salt solution was observed with this treatment. The authors concluded that levels that decrease maternal & offspring body weights cause subtle changes in sexually dimorphic behavior (Flynn et al., 2000).
Human studies

10. A prospective study of Japanese-American men residing in Hawaii examined associations of mid-life tofu consumption & brain function & structure later in life (Annex 1). Tofu consumption was assessed from interviews conducted in 1965-67 and again in 1971-74. Tests of cognitive function (n=3734) & brain atrophy (n=574) as well as autopsy (n=290) data were used. The authors suggest that poor cognitive performance & lower brain weights were significantly & independently associated with higher mid-life tofu consumption. The odds ratios for these endpoints when comparisons were made between low level & high level consumers were in the range of 1.6-2.0 (White et al., 2000).

References


