BRAIN RESEARCH 1593 (2014) 76–82

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Central inflammatory response to experimental stroke is inhibited by a neuroprotective dose of dietary soy

Maryam Shambayati[1], *Maharshi Patel*[1], *Yulin Ma*[2], *Rebecca L. Cunningham*, *Derek A. Schreihofer*[*]

Department of Pharmacology and Neuroscience and Institute for Aging and Alzheimer's Disease Research, University of North Texas Health Science Center at Fort Worth, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107, United States

ARTICLE INFO

Article history:
Accepted 17 September 2014
Available online 28 September 2014

Keywords:
Isoflavone
Stroke
Inflammation
Cytokine
Neuroprotection
Cerebral ischemia

ABSTRACT

Dietary soy and soy isoflavones are neuroprotective in experimental cerebral ischemia. Because the isoflavones in soy that are responsible for this neuroprotective effect act as phytoestrogens, we hypothesized that they would mimic the beneficial effects of estrogens on the innate inflammatory response to cerebral ischemia. Ovariectomized Sprague-Dawley rats were fed a soy free diet or a diet containing high dietary levels of soy for 5 weeks, after which they were subjected to transient middle cerebral artery occlusion (tMCAO) for 90 min. Dietary soy was associated with a reduced inflammatory response in the cerebral cortex during the acute innate period 4 and 24 h after tMCAO, including significant (>2-fold) reductions in interleukins 1 beta, 2, and 13, and the chemokine CXCL1. However, there was no effect of soy on tumor necrosis factor-alpha or interferon-gamma. Dietary soy was also associated with a 40 percent reduction in the nuclear translocation of p65 nuclear factor kappa B despite an increase in the expression of p65 RELA mRNA. In support of an early effect on the innate immune response to stroke, soy-fed rats had 44 percent fewer activated microglia in the infarct core than soy free rats. Interestingly, despite increased expression following injury, the steady state mRNA levels of inflammatory factors were not altered in soy-fed rats even though inflammatory proteins were. These data suggest that dietary soy isoflavones, like estrogens, inhibit of the innate immune response to injury. However, post-transcriptional mechanisms may play an important role in the mechanism of this action. Coupled with previously published data, these results support an early and rapid effect of dietary soy on the evolution of brain injury following stroke.

© 2014 Elsevier B.V. All rights reserved.

[*]Corresponding author.
E-mail address: Derek.Schreihofer@UNTHSC.edu (D.A. Schreihofer).
[1]These authors contributed equally to this work.
[2]Present address: Department of Urology, The Second Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong 515041, China.

http://dx.doi.org/10.1016/j.brainres.2014.09.042
0006-8993/© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Dietary soy and soy isoflavones are neuroprotective in experimental cerebral ischemia. Both ovariectomized female and male rats on a high soy diet show a significant reduction in infarct size, neurological deficit, and cerebral apoptosis following transient or permanent middle cerebral artery occlusion (Schreihofer et al., 2005; Burguete et al., 2006; Lovekamp-Swan et al., 2007a; Castello-Ruiz et al., 2011). The addition of the soy isoflavones genistein or equol to the diet has similar protective effects in both sexes (Ma et al., 2010; Castello-Ruiz et al., 2011; Qian et al., 2012). Because soy isoflavones have properties of phytoestrogens and can bind and activate estrogen receptors, these protective effects are likely to include those implicated in estrogen-dependent neuroprotection. Like estrogens (Dubal et al., 1999; Alkayed et al., 2001; Won et al., 2006), dietary soy isoflavones enhance the expression of antiapoptotic members and inhibit pro-apoptotic members of the Bcl-2 family of proteins (Bu and Lephart, 2005; Lovekamp-Swan et al., 2007a). Similarly, both estrogens (Razmara et al., 2008; Zhang et al., 2009) and soy isoflavones (Ma et al., 2010, 2013; Qian et al., 2012) reduce oxidative stress in response to cerebral ischemia. Estrogen-induced protection of the blood–brain-barrier after cerebral ischemia (O'Donnell et al., 2006) is also observed in soy-fed animals (Ma et al., 2013). Thus, many of the beneficial effects of chronic estrogen exposure in the brain are mimicked by dietary soy isoflavones.

In addition to oxidative stress, edema, and apoptotic pathways, cerebral ischemia is associated with increased levels of inflammation in both the periphery and the brain (Denes et al., 2010). As with other steroids, estrogen is anti-inflammatory in the brain (Vegeto et al., 2008), and this activity is evident in cerebral ischemia. For example, acute estradiol treatment inhibits cortical interleukin 1-beta (IL-1β) expression in male rats two hours after reperfusion from transient middle cerebral artery occlusion (Chiappetta et al., 2007). Similarly, acute estrogen treatment reduces nuclear factor-kappa B (NFκB) and inducible nitric oxide synthase (iNOS/NOS2) expression after experimental stroke (Wen et al., 2004). In male rats, acute estrogen treatment inhibits microglial activation, interleukin 6 (IL6), and CCL2 and CCL5 chemokine expression in the ischemic cortex (Dang et al., 2011). In addition to these acute anti-inflammatory effects of estrogen in stroke, chronic physiological estrogen treatment inhibits ischemia induced increases in IL6 and tumor necrosis factor-alpha (TNFα) and prevents the down-regulation of vascular endothelial growth factor (VEGF) in female mice (Suzuki et al., 2007).

Although soy isoflavones have anti-inflammatory effects in the peripheral cardiovascular system, much of the support for an anti-inflammatory role comes from in vitro studies (Rimbach et al., 2008), and a generalized anti-inflammatory role in humans remains controversial (Beavers et al., 2009). However, studies of cultured human brain microendothelial cells reveal that the isoflavone genistein can inhibit cytokine-induced proinflammatory responses including TNFα and IL1-β (Lee and Lee, 2008). Similarly, genistein inhibits TNFα, IL1-β, cyclooxegenase-2 (COX-2) and iNOS in cultured astrocytes exposed to beta amyloid (Valles et al., 2010). These data suggest that soy isoflavones may be anti-inflammatory in the brain. In the present study, we hypothesized that the central inflammatory response to cerebral ischemia would be reduced in animals eating a high soy diet.

2. Results

Measurements of inflammation-related protein levels in the ischemic cortex of soy-free and soy-fed rats were compared to sham stroked rats using MesoScale Discovery (MSD) MultiArray technology. IL1-β and TNFα increased in the ischemic hemisphere after stroke (Fig. 1), and dietary soy significantly reduced IL1-β 24 h after reperfusion (Fig. 1). In contrast, interferon-gamma (IFN-γ) fell 4 h after transient middle cerebral artery occlusion (tMCAO) and returned to basal levels, with no differences between treatment groups (Fig. 1). The cytokine CXCL1, which acts as a chemokine to recruit leukocytes, increased dramatically after tMCAO, and soy diet significantly blunted this response (Fig. 1). A significant interaction between time and diet was observed with interleukin 2 (IL2), with a significant decrease 4 h after stroke (Fig. 1). However, it is worth noting that IL2 was below the limit of detection in all soy-fed rats 4 h after tMCAO (Fig. 1). Dietary soy also suppressed interleukin 13 (IL13) levels 4 and 24 h after stroke (Fig. 1). No significant differences in IL6 levels were observed (data not shown), and interleukin 4, 5, and 10 levels were below detection in most samples (not shown).

Because NFκB is a primary transcriptional driver of the intracellular inflammatory response we examined nuclear localization of NFκB protein 24 h after ischemia. Immunoblotting revealed a significant ($P<0.05$) increase in nuclear NFκB in the cortex of soy-free rats from 2.4±0.6 to 6.5±1.4 relative units

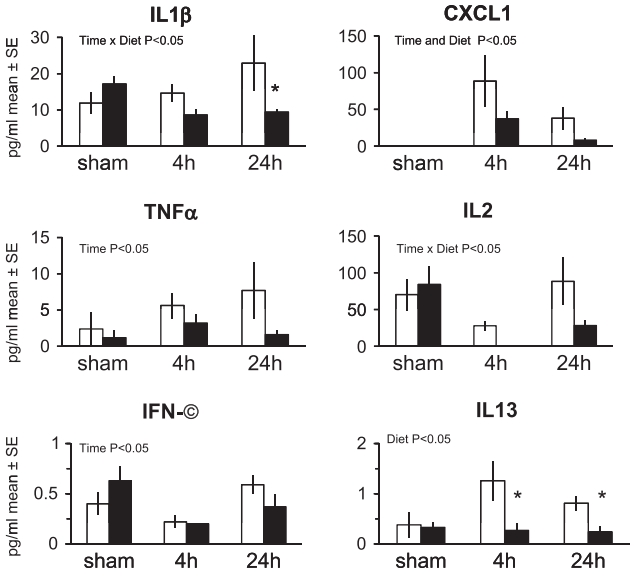

Fig. 1 – Effect of dietary soy on stroke-induced changes in IL1β, TNFα, IFNγ, CxCL1, IL2, and IL13 protein levels in the cerebral cortex 4 and 24 h after tMCAO in soy-free (open bars) and soy-fed (filled bars) rats ($n=4$–6). Data represent mean±SE of protein lysate levels in pg/ml. Data was analyzed by 2-way ANOVA with diet and time as factors. Significant overall effect is noted on each graph. Significant group differences at specific time points was determined with Bonferroni *post hoc* tests (*$P<0.05$).

Download English Version:

https://daneshyari.com/en/article/4323949

Download Persian Version:

https://daneshyari.com/article/4323949

Daneshyari.com