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Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease

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Abstract

Recent studies have implicated resveratrol and pterostilbene, a resveratrol derivative, in the protection against age-related diseases including Alzheimer's disease (AD). However, the mechanism for the favorable effects of resveratrol in the brain remains unclear and information about direct cross-comparisons between these analogs is rare. As such, the purpose of this study was to compare the effectiveness of diet-achievable supplementation of resveratrol to that of pterostilbene at improving functional deficits and AD pathology in the SAMP8 mouse, a model of accelerated aging that is increasingly being validated as a model of sporadic and age-related AD. Furthermore we sought to determine the mechanism of action responsible for functional improvements observed by studying cellular stress, inflammation, and pathology markers known to be altered in AD. Two months of pterostilbene diet but not resveratrol significantly improved radial arm water maze function in SAMP8 compared with control-fed animals. Neither resveratrol nor pterostilbene increased sirtuin 1 (SIRT1) expression or downstream markers of sirtuin 1 activation. Importantly, markers of cellular stress, inflammation, and AD pathology were positively modulated by pterostilbene but not resveratrol and were associated with upregulation of peroxisome proliferator-activated receptor (PPAR) alpha expression. Taken together our findings indicate that at equivalent and diet-achievable doses pterostilbene is a more potent modulator of cognition and cellular stress than resveratrol, likely driven by increased peroxisome proliferator-activated receptor alpha expression and increased lipophilicity due to substitution of hydroxy with methoxy group in pterostilbene.

Keywords: Pterostilbene; Resveratrol; SAMP8; Alzheimer's disease; Cognition; Aging; Cell signaling; mnSOD; NKF beta; Tau; PPAR alpha

1. Introduction

Aging poses the greatest risk factor in the development of Alzheimer's disease (AD). With an ever-increasing population, AD incidence in the United States will jump from 4 million individuals currently affected with the disease to 14 million by 2050 (Larson et al., 1992). Of concern, despite valiant effort by the scientific field to understand the molecular underpinnings of this insidious disease, little progress has been made with regard to mechanisms, diagnostic tests, or treatments.

Research to identify mechanisms associated with AD and new therapies is currently being carried out in rodent models of AD. However, despite that 95% of AD cases are age-related, a mouse model of late-onset and/or age-related AD does not exist. Instead, current studies are carried out in mouse models which overexpress AD-related pathology

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(amyloid-beta plaques and tau hyperphosphorylation inclusions [tangles]) associated with specific mutations present in early-onset AD (< 5% of total AD cases; Pallas et al., 2008a; Teruel, 2004). On the other hand, the SAMP8 model has many of the histopathological and behavioral indicators of AD (increased levels of oxidative stress [OS], hyperphosphorylation of tau, cognitive decline, amyloid-beta levels; Castillo et al., 2009; Pallas et al., 2008a). Importantly, this mouse is a model of accelerated aging, therefore it provides an excellent model to study the chronology of neurodegenerative changes associated with AD development and therapeutic opportunities from an aging perspective.

Over the years polyphenols, endogenously produced by plants as protection against predation, have been a source of interest due to their many beneficial effects on health and disease (Casadesus et al., 2004; Joseph et al., 2005). These biochemicals have shown numerous protective properties including antibiotic, anti-inflammatory, antioxidant, and anticarcinogenic amongst others, both in vivo and in vitro (Joseph et al., 2008; Rimando and Suh, 2008). One popular polyphenol is resveratrol, which is found in grapes and red wine has shown to have neuroprotective and cognitive enhancing properties (Bhavnani, 2003; Valenzano et al., 2006; Wang et al., 2006) and to induce apoptosis in cancer cells (Rimando and Suh, 2008), however only at high doses. In vitro, resveratrol is a potent activator of sirtuin 1 (SIRT1) (Borra et al., 2005; Howitz et al., 2003), thought to provide protection through downstream pathways including forkhead box (FOXO) proteins and manganese superoxide dismutase (MnSOD) modulation (Brookins Danz et al., 2009). In this context, increasing SIRT1 has been found to protect cells against amyloid-beta-induced reactive oxygen species (ROS) production and DNA damage, thereby reducing apoptotic death (Della-Morte et al., 2009; Kim et al., 2007). In vitro effects of resveratrol, through SIRT1 activation (Yeung et al., 2004), also include inhibition of proinflammatory nuclear factor-kappa B (NFκB) transcription (Holmes-McNary and Baldwin, 2000; Jang et al., 1997; Manna et al., 2000). Moreover, it has been demonstrated that AD neurons are rescued by the activation of SIRT1, through the administration of resveratrol (Camins et al., 2010; Della-Morte et al., 2009; Sun et al., 2010).

Pterostilbene is a phenolic compound chemically similar to resveratrol. Initially isolated from sandalwood, it is also found in fruits including grapes and blueberries, known for their beneficial effects on cognition and neuronal function during aging (Casadesus et al., 2004). Pterostilbene is a potent antioxidant and anti-inflammatory agent shown to have beneficial effects in the aging brain (Joseph et al., 2008; Remsberg et al., 2008; Rimando et al., 2002). Interestingly, in vitro, it has higher potency at inducing apoptosis in cancer cells than resveratrol (Mikstacka et al., 2007; Tolomeo et al., 2005), and shows powerful agonistic properties on the peroxisome proliferator-activated receptor (PPAR) alpha receptor (Rimando et al., 2005), a receptor complex that is intimately associated with fatty acid metabolism, inflammation, and oxidative stress regulation (Pyper et al., 2010).

To date, little is known about the biochemical and molecular mechanisms associated with pterostilbene's effects on neuronal function and cognitive function and whether this compound has protective effects in age-related pathological events. Given that the effects of resveratrol on neuronal function and SIRT1 activation have often been observed only when administered at high doses, the goal of this study was to (1) determine and evaluate the effectiveness of resveratrol at diet-achievable dose on cognition and neuronal function in a model of pathological aging and/or early AD while directly comparing it to pterostilbene; and (2) determine the mechanisms associated with the observed changes in both supplementation groups.

2. Methods

2.1. Animals and diet preparation

Five-month-old male and female SAMP8 were fed with either resveratrol or pterostilbene at an identical dose (120 mg/kg of diet) for 8 weeks or control diet, 120 mg/kg of diet equated to the content of resveratrol of in 2 glasses of wine. Animals were kept on a 12-hour light and 12-hour dark cycle with free access to food and water. Pterostilbene dose was kept identical to that of resveratrol to determine potency differences. In addition, an age-matched control SAMR1 group was included to be able to determine the magnitude of improvement produced by our experimental diets. Resveratrol (ChemPacific Corporation, Baltimore, MD, USA) and pterostilbene (synthesized according to Joseph et al., 2008), both nuclear magnetic resonance pure, were incorporated, separately, into Irradiated ProLab IsoPro RMH 3000 (TestDiet, Richmond, IN, USA). Compound incorporation was carried out by Harlan Teklad (Madison, WI, USA) at low drying temperature to prevent any degradation of the compounds. Body weight and diet consumption were tracked twice across the study to ensure that there were no diet intake related differences (i.e., diet taste preference).

2.2. Radial arm water maze

The radial arm water maze is a spatial learning and memory task that involves the use of distal visual cues to locate a hidden platform in 1 of 6 arms. Behavioral testing was carried out during the light cycle. Briefly, the test was carried out within a pool (120 cm diameter) with 6 swim arms; water temperature was kept constant at 24 °C for the duration of the testing sessions. One constant goal arm with a platform was used for the duration of the training and was randomized across animals to avoid spatial preference confounds. Animals were introduced into the water maze from different arms at every trial. On Day 1, 12 trials occurred (1-minute periods), alternating between a visible and hidden goal platform, with the exception of the last 3 trials where