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Review

Effects of pterostilbene and resveratrol on brain and behavior

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ABSTRACT

Age is the greatest universal risk factor for neurodegenerative diseases. During aging, these conditions progress from minor loss of function to major disruptions in daily life, loss of independence and ultimately death. Because approximately 25% of the world population is expected to be older than age 65 by 2050, and no treatments exist to halt or reverse ongoing neurodegeneration, the need for effective prevention strategies is more pressing that ever before. A growing body of research supports the role of diet in healthy aging, particularly diets rich in bioactive phytochemical compounds. Recently, stilbenes such as resveratrol (3, 5, 4′-trans-trihydroxystilbene) and its analogue, pterostilbene, have gained a significant amount of attention for their potent antioxidant, anti-inflammatory, and anticarcinogenic properties. However, evidence for the beneficial effects of stilbenes on cerebral function is just beginning to emerge. In this review, we summarize the current knowledge on the role of resveratrol and pterostilbene in improving brain health during aging, with specific focus on antioxidant and anti-inflammatory signaling and behavioral outcomes.

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Among many competing theories, aging is the result of chronic, sustained inflammation and oxidative stress, leading to damage to lipids, proteins and nucleic acids, which, in the brain, cause progressive degeneration and death of neurons, leading to behavioral decline (Joseph et al., 2005; Quintanilla et al., 2012). Numerous epidemiological studies have linked diets rich in natural antioxidants and anti-inflammatory compounds from fruits, nuts, vegetables and spices to slower age-related behavioral declines and lower incidence of neurodegenerative diseases (Lau et al., 2007; Miller and Shukitt-Hale, 2012; Poulose et al., 2012). Furthermore, studies performed in our laboratory and others report improvement in cognitive and motor performance when laboratory animals were fed with diets supplemented with fruits, vegetables, or nuts (Shukitt-Hale et al., 2008; Willis et al., 2009). Early experiments revealed the antioxidant and anti-inflammatory properties of the phytochemicals found in these foods (Joseph et al., 2010); however, additional mechanisms of action have since been discovered, including synaptic plasticity, transcriptional regulation, neuronal signaling, autophagy, and receptor function (Miller and Shukitt-Hale, 2012; Poulose et al., 2014a).

In the late 1980s, French epidemiologists found that, despite high dietary cholesterol and saturated fat intake, France had a low incidence and mortality rate due to coronary heart disease, as well as certain types of cancer. These findings quickly gained popularity

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and this phenomenon was later coined the 'French paradox' (de Lorgeril et al., 2002; Renaud and de Lorgeril, 1992). In 1992, it was hypothesized that a compound found in wine, i.e., resveratrol (*trans*-3,4′,5-trihydroxystilbene; RES), may be accountable for the French paradox (Renaud and de Lorgeril, 1992). Resveratrol, a non-flavonoid polyphenol in the stilbene group, was first detected in the roots of white hellebore (*Veratrum grandiflorum*) (Tome-Carneiro et al., 2013). Today, RES has been detected in various food sources, such as grapes, berries, red wine, chocolate and peanuts (Paul et al., 2010) and remains the most well-known stilbene. Like RES, pterostilbene (trans-3,5-dimethoxy-4hydroxystilbene; PTE) is a stilbenoid, dimethylated analog of resveratrol, allowing it to have a higher bioavailability than resveratrol; it is found in grapes, blueberries and heartwood (*Pterocarpus marsupium*) (McCormack and McFadden, 2013). Over the last two decades, more than 2500 research articles have reported the health benefits of RES and other stilbenes. These beneficial health effects include life-span extension, weight loss, and protection against cardiovascular disease, neurodegenerative disease, stroke-induce brain damage, cancer, and cancer metastasis (Kasiotis et al., 2013; McCormack and McFadden, 2013). However, only more recently have the beneficial effects of stilbenes on cerebral function started to emerge. This review will summarize the current knowledge of the effects of resveratrol and pterostilbene in improving brain health during aging, with a focus on antioxidant and anti-inflammatory signaling and behavioral outcomes.

1. Structure, biosynthesis and bioavailability of resveratrol and pterostilbene

Resveratrol and PTE belong to a group of phytochemicals known as stilbenoids, which biosynthesize as part of a plant's defense mechanism in response to biotic and abiotic stress, such as infection, insect infestation, heat and ultraviolet exposure (Langcake and Pryce, 1977). All stilbenoids have two aromatic rings connected by a methylene bridge backbone, where either hydroxyl, methyl, methoxy, prenyl, or geranyl can be substituted, and sugars can be combined to form glycosides, producing a group of compounds with diverse chemical structures and properties. Stilbenes are predominantly found in the *trans*-isomer in nature due to the increase in stability; however, *cis*-isomer is sometimes detected (Borriello et al., 2010).

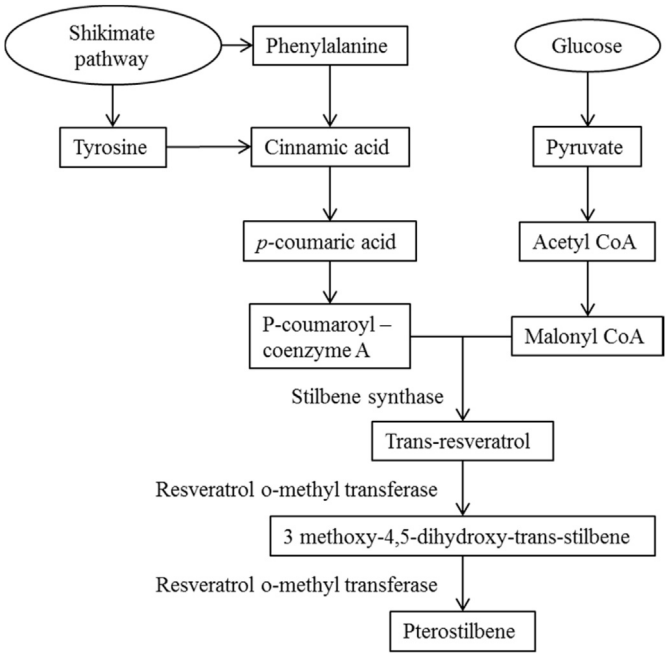

Fig. 1. General biosynthesis pathway for resveratrol and stilbenes.

In plants, stilbene biosynthesis shares similar substrates and biosynthetic pathways with flavonoids. Even though most plants produce flavonoids, only a few species of plants synthesize stilbenes. The biosynthetic pathway of stilbenes starts with phenylalanine, which undergoes multiple enzymatic reactions to produce *p*-coumaroyl-CoA. Then, in the presence of malonyl-CoA and stilbene synthase, RES is produced via aldol reaction (Fig. 1). RES is converted to produce PTE through an O-Methyltransferase-facilitated reaction. Despite their structural similarity, PTE is found to be more bioavailable (80%) than RES (20%) (Kapetanovic et al., 2011). This is, in part, due to the presence of two methoxy-groups on PTE, making it more lipophilic (Cichocki et al., 2008) and increasing oral bioavailability (Kapetanovic et al., 2011). A study by Chang and colleagues demonstrated that PTE was found at higher concentrations in the serum and brain than RES when given at the same dose to both male and female mice for 8 weeks (Chang et al., 2012).

Oral administration of RES in humans has a high absorption rate but low bioavailability due to its extensive first pass and short half-life (Cottart et al., 2010). Approximately 50–98% of absorbed RES is non-covalently bound to albumin, low density lipoprotein, and hemoglobin (Jannin et al., 2004; Lu et al., 2007). Pharmacokinetic studies in humans and animal models show that RES is rapidly metabolized by phase II enzymes in the intestine and liver to produce glucuronide and sulfate derivatives, leaving approximately 1% of the parent compound in circulation (Rotches-Ribalta et al., 2012). The major metabolites of RES detected in plasma are resveratrol-3-O-sulfate and resveratrol-3-O-glucuronice, and it has been estimated that approximately half of these metabolites are bound to plasma proteins (Burkon and Somoza, 2008). Intravenous administration of RES to rats showed that plasma RES has a half-life of 0.13 h (Marier et al., 2002) and 70–98% of RES can be recovered from urine and feces within 24 h after ingestion (Boocock et al., 2007a,b). Moreover, colon microbes have been reported to metabolize unabsorbed RES to produce dihydroresveratrol (Juan et al., 2010). The contribution of RES metabolites to resveratrol's overall health benefits has yet to be determined.

The blood–brain barrier prevents 98% of small molecules and 100% of large molecules from reaching the brain (Kanwar et al., 2012). To date, there is limited information on how RES and PTE cross the blood-brain barrier (BBB) or localize within the brain. A recent study by Ouzzine and colleagues (2014) suggests that the RES metabolites, glucuronides and sulfo-conjugates, cross the BBB via UDP-glucuronosyltransferases (UGTs). However, only a small percent of RES crossed BBB and accumulated in the brain. Vitrac and coworkers reported that when a single dose of ^{14}C-RES (50 mg/kg body weight) was given orally, only 6.1 μg of RES glucoside/g (tissue weight) was detected in the mouse brain (Vitrac et al., 2003). Few studies indicate the beneficial effect of resveratrol when administered to the rats via intraperitoneal injections (Sinha et al., 2002; Wang et al., 2002). In Mongolian gerbils, *i.p.* injections of 30 mg/kg of RES decreased neuronal death in the CA1 region of the hippocampus 4 days after ischemia, which was mediated via reduced glial cell activation (Wang et al., 2002). Similarly, in male Wistar rats, which were subjected to focal ischemia by middle cerebral artery occlusion, an *i.p.* injection of 20 mg/kg of trans-RES for 21 days prevented motor impairment (Sinha et al., 2002). It is generally assumed that PTE can also cross the BBB due to its structural similarities to and better intestinal absorption than RES (Temsamani and Merillon, 2015). Few studies offer insights into the neuroavailability and tissue distribution of PTE within the brain. Joseph and coworkers (2008) have shown that dietary