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Review

The role of polyphenols in the modulation of sirtuins and other pathways involved in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is characterised by extracellular amyloid deposits, neurofibrillary tangles, synaptic loss, inflammation and extensive oxidative stress. Polyphenols, which include resveratrol, epigallocatechin gallate and curcumin, have gained considerable interest for their ability to reduce these hallmarks of disease and their potential to slow down cognitive decline. Although their antioxidant and free radical scavenging properties are well established, more recently polyphenols have been shown to produce other important effects including anti-amyloidogenic activity, cell signalling modulation, effects on telomere length and modulation of the sirtuin proteins. Brain accessible polyphenols with multiple effects on pathways involved in neurodegeneration and ageing may therefore prove efficacious in the treatment of age-related diseases such as AD, although the evidence for this so far is limited. This review aims to explore the known effects of polyphenols from various natural and synthetic sources on brain ageing and neurodegeneration, and to examine their multiple mechanisms of action, with an emphasis on the role that the sirtuin pathway may play and the implications this may have for the treatment of AD.

Contents

1. Introduction

The accumulation of oxidative damage from free radical production during normal oxidative metabolism increases with age and is thought to be linked to age-related diseases (Harman, 1956). Oxidative stress results when pro-oxidant and anti-oxidant activities in the body are not occurring at a balanced rate, leading to the production of excess reactive oxygen species, such as peroxides and free radicals (Barnham et al., 2004). The generation of free radicals is catalysed by redox-active metals such as copper and iron (Smith et al., 1997a). For example, hydrogen peroxide in the presence of copper or iron produces hydroxyl radicals *via* the Fenton reaction (Buettner and Jurkiewicz, 1996). Brain tissue is vulnerable

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to oxidative damage due to its high oxygen consumption, relatively low antioxidant levels, high content of redox-active metals (copper and iron), and limited regenerative capacity, and thus free radicals have been hypothesised to play an important role in the brain ageing process (Honda et al., 2004; Reiter, 1995; Romano et al., 2010; Smith et al., 1996).

Ageing is also the main risk factor in the development of Alzheimer's disease (AD), with the vast majority of cases developing after the age of sixty-five. Thus, oxidative damage is also thought to be an important factor in the pathogenesis of this disease and indeed seems to be one of the earliest events (Jomova et al., 2010; Nunomura et al., 2001; Smith et al., 1996). Markers of free-radical damage such as increased protein and DNA oxidation, enhanced lipid peroxidation, advanced glycation end products, carbonyls, dityrosine, malondialdehyde, and peroxynitrite damage have all been reported to occur in AD (Aksenov et al., 2001; Greilberger et al., 2008; Hensley et al., 1998; Lovell and Markesbery, 2007; Montine et al., 2002; Munch et al., 1997; Sasaki et al., 1998; Smith et al., 1997b). Furthermore, decreased levels of plasma antioxidants have been seen in AD patients (Kim et al., 2006).

A hallmark of AD is the presence in the brain of extracellular amyloid plaques, mainly containing aggregated amyloid β (Aβ) peptides. These Aβ plaques are another source of oxidative stress in AD as they sequester divalent metals such as copper and iron, which have the potential to catalyse free radical formation (Atwood et al., 2003). Copper and iron in abnormally high concentrations and markers representing oxidative stress have been found in amyloid plaques, and are elevated in the neocortex of the AD brain (Jomova et al., 2010; Lovell et al., 1998; Maynard et al., 2005; Roberts et al., 2012; Smith et al., 2000). Iron has been shown to facilitate the aggregation and deposition of Aβ and also induce aggregation of the major constituent of neurofibrillary tangles, hyperphosphorylated tau (Mantyh et al., 1993; Yamamoto et al., 2002). Amyloid plaques are sites of chronic inflammation in the AD brain, and this represents another source of oxidative stress due to the release of superoxide and nitric oxide (Butterfield, 2002; Reynolds et al., 2007; Wang et al., 2004).

Polyphenols may hold potential therapeutic benefits in age-related disorders due to their potent free-radical scavenging and antioxidant effects (Salah et al., 1995). Polyphenols are secondary plant metabolites that are involved in plant defence against pathogens and ultraviolet damage (Manach et al., 2004). They are found in many fruits, herbs and vegetables and thus serve as important dietary micronutrients. Chemically, polyphenols include a wide variety of biomolecules which contain several hydroxyl groups on one or more aromatic rings. They can be divided into various groups according to chemical structure – including flavonoids, stilbenes and lignans (D'Archivio et al., 2007; Tsao, 2010). Natural phenolics are compounds which contain hydroxyl groups on only a single aromatic ring and therefore are smaller in size than polyphenols. They include phenolic acids and phenolic alcohols (see Table 1 for further details).

Recently, the potential role of polyphenols in ageing and neurodegeneration has widened with discoveries that they can modulate various important pathways in the pathogenesis of AD by reducing amyloid aggregation and inflammation and modulating a class of proteins called sirtuins which are involved in longevity and cell survival. This review aims to highlight some of these new effects of polyphenols with a focus on how polyphenols may influence amyloid aggregation and the sirtuin family of proteins.

2. Modulation of oxidative stress by polyphenols

Polyphenol are well known as antioxidants and direct scavengers of free radicals (Lodovici et al., 2001; Robak and Gryglewski, 1988; Salah et al., 1995). In addition, polyphenols can act as metal chelators (Brown et al., 1998; Hider et al., 2001; Moridani et al., 2003), which adds to the antioxidant effects of these compounds through inhibition of transition metal-catalysed free radical formation (Jomova et al., 2010). Chelation of transition metals such as Fe^{2+} can directly reduce the rate of the Fenton reaction thus preventing oxidation caused by highly reactive hydroxyl radicals (Cheng and Breen, 2000; Lopes et al., 1999). Epigallocatechin gallate (EGCG), a green tea polyphenol, for examples has also been shown to be a potent chelator of transition metals such as copper and iron (Mandel et al., 2008a), and inhibits over 90% of iron-mediated DNA damage caused by Fe^{2+} and H_2O_2 (Mandel et al., 2011). It has also been found that polyphenols are involved in the regeneration of essential vitamins (Mandel et al., 2008c; Pedrielli and Skibsted, 2002). Polyphenols can induce antioxidant enzymes such as gluthathione peroxidase, catalase, superoxide dismutase, as well as hydrogen peroxide and superoxide anions, and inhibit the expression of enzymes such as xanthine oxidase, which is involved in the generation of free radicals (Alvarez-Suarez et al., 2011; Frei and Higdon, 2003; Lee et al., 2006; Luceri et al., 2002; Luczaj et al., 2004; Mandel et al., 2008b, 2011; Moskaug et al., 2005; Sanbongi et al., 1997). These multiple antioxidant effects prevent oxidative damage to important cellular components and have lead to investigation of polyphenols as therapeutic agents for the treatment of AD, to combat the increase in oxidative stress seen in this disease.

3. Effects of polyphenols on amyloid and tau aggregation

The Aβ deposited in AD is derived from the larger amyloid precursor protein (APP). Surface APP can be endocytosed, and then undergo various forms of processing, one of which results in the formation of Aβ peptides (Selkoe, 1998). These peptides have ability to aggregate and generate the amyloid that is found in the AD brain. The toxic potential of the Aβ peptide depends on its conformational state and peptide length, with Aβ (1–42) being more toxic than Aβ (1–40) and Aβ(1–42) oligomers are thought to be the most toxic form (Walsh and Selkoe, 2007). Metal ions such as copper, iron and zinc also influence the aggregation state of Aβ peptides (Mantyh et al., 1993).

Several studies have suggested that polyphenols may have anti-amyloidogenic effects. A number of polyphenols including tannic acid, quercetin, kaempferol, curcumin, catechin and epicatechin were shown to dose-dependently inhibit the formation of Aβ fibrils as well as their elongation (Ono et al., 2003, 2004). In addition, polyphenols can bind directly to Aβ or mature aggregates and impair their stability, as all the compounds tested destabilised preformed Aβ fibrils (Ono et al., 2003). EGCG significantly inhibits Aβ aggregation and has the ability to remodel large Aβ fibrils into smaller aggregates which displayed no toxic effects (Bieschke et al., 2010) (see Fig. 1). Fish oil has been shown to have a synergistic effect in combination with EGCG with co-treatment leading to a reduction in Aβ plaque formation and levels of Aβ(1–40) and Aβ(1–42) in AD transgenic Tg2576 mice (Giunta et al., 2010).

Tannic acid was shown to reduce Aβ deposits as well as Aβ species including oligomers in the transgenic AD mouse brain (Mori et al., 2012; Ono et al., 2003). Tannic acid decreased cleavage of the β-carboxyl-terminal APP fragment, lowered APP-β production, and attenuated neuroinflammation (Mori et al., 2012). It is thought to work by inhibiting amyloidogenic APP metabolism as a result of reducing β-site APP cleaving enzyme 1 expression and lowering β-secretase activity (Mori et al., 2012). EGCG was also shown to down-regulate APP levels and cerebral amyloidosis in Alzheimer transgenic mice (Rezai-Zadeh et al., 2005).

Curcumin, found in the spice turmeric, has been shown to prevent brain lipid peroxidation in rats and increase gluthathione

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