MINIREVIEW

Neuroprotective Mechanisms of Natural Polyphenolic Compounds

Maria Kovacsova, Andrej Barta, Jana Parohova, Stanislava Vrankova, Olga Pechanova

Institute of Normal and Pathological Physiology and Centre of Excellence for Cardiovascular Research, Slovak Academy of Sciences, Bratislava, Slovak Republic

Correspondence to: Olga Pechanova, PhD, DSc., Institute of Normal and Pathological Physiology, Slovak Academy of Sciences, Sienkiewiczova 1, 813 71 Bratislava, Slovak Republic. PHONE:+421-2-52926271, FAX: +421-2-52968516, E-MAIL: olga.pechanova@savba.sk

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Abstract

Natural polyphenols have been reported to exert beneficial effects in preventing cardiovascular diseases but their neuroprotective mechanisms were studied much less. The review is focused on biochemical pathways and molecular neuroprotective mechanisms of natural polyphenols in the brain particularly; of course in close relation to neurophysiological and pathophysiological consequences. This review provides the evidence that antioxidant activity, mainly inhibition of the NADPH oxidase and subsequent reactive oxygen species generation; a balance in NO production from different NO synthase isoforms; reduction of neuroinflammation via attenuation of the release of cytokines and downregulation of the pro-inflammatory transcription factors; and the potential to modulate signalling pathways such as mitogen-activated protein kinase cascade and cAMP response element-binding protein are responsible for the neuroprotective actions of different natural polyphenols. These beneficial effects are mainly in demand in prevention of brain damage including ischemic stroke and neurodegenerative diseases, in the reduction of neuronal death, in memory improvement, as also for learning and general cognitive ability.

Introduction

Many epidemiological studies have shown that regular flavonoid intake is associated with reduced risk of cardiovascular diseases (Middleton *et al* 2000). In the coronary heart disease, the protective effects of flavonoids include mainly antithrombotic, antiischemic, antioxidant, and vasorelaxant activities (Pechanova *et al* 2006; Galleano *et al* 2010; Zenebe *et al* 2003; Karvaj *et al* 2007). Besides cardiovascular system, the protective effect of natural polyphenols, and red wine polyphenolic compounds particularly, was described in the respiratory and immune system (Franova *et al* 2010; Aquilano *et al* 2008) kidney (Buffoli *et al* 2005) and in the brain (Aquilano *et al* 2008; Karvaj *et al* 2007).

Brain especially suffers from the long-term impact of the increased production of reactive oxygen species (ROS) (Schaffer *et al* 2006). Because of low activity of antioxidant defense system, brain is susceptible to oxidative stress more than other organs. Brain has low catalase activity and only moderate levels of the antioxidant enzymes like superoxide dismutase and glutathione peroxidase. The high levels of iron and ascorbate in this organ participate significantly on the catalysis of lipid peroxidation. Moreover, many neurotransmitters are autoxidized to generate ROS (for review see Lau *et al* 2005). In agreement with these observations, there is evidence that increased oxida-

tive stress plays an important role in the pathogenesis of neurodegenerative diseases such as Alzheimer and Parkinson diseases (Esposito *et al* 2002). It has also been shown that modulation of nitric oxide (NO) availability is an important determinant of ischemic stroke risk (McCarty 2000). Thus optimal NO/ROS balance in the brain seems to be a crucial parameter in the prevention of brain damage including ischemic stroke and neurodegenerative diseases as well.

The neuroprotective effects of many polyphenols rely on their ability to permeate brain barrier and here directly scavenge pathological concentration of reactive oxygen and nitrogen species and chelate transition metal ions (Aquilano *et al* 2008). Different polyphenolic compounds were shown to have scavenging activity and the ability to activate key antioxidant enzymes in the brain and thus breaking the vicious cycle of oxidative stress and tissue damage (Lau *et al* 2005; Esposito *et al* 2002). Moreover, red wine polyphenolic compounds have been documented to increase endothelial NO synthase (eNOS), while downregulate inducible NO synthase (iNOS) activity in different structures (Pechanova *et al* 2004; Ritz *et al* 2008). Corder *et al* (2001) documented that red wines strongly inhibit the synthesis of endothelin-1, wellknown vasoactive peptide, that is crucial in the development of coronary atherosclerosis. Previosly, the pathophysiological role of endothelin in the brain was documented as well (Piechota *et al* 2010). Attenuation of the release of cytokines, such as interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha) was also ascriptius to different polyphenols (Vafeiadou *et al* 2007). Thus, natural polyphenolic compounds may protect and/or improve physiological brain functions by different mechanisms that include mainly antioxidant activity, eNOS/iNOS balance, inhibition of endothelin production and attenuation of cytokine release.

Antioxidant activity

Red wine polyphenolic compounds are wellknown by their ability to scanveng free radicals (Pechanova *et al* 2006) and also to preserve the production of natural free radical scavengers during ischemic conditions (Ritz *et al* 2008). Recently, the inhibitory effect of polyphenolic compounds on ROS producing systems was described also in the brain (Figure 1).

NADPH oxidase–dependent production of superoxide radical (O_2^-) has been identified as one of the major contributor to oxidative injury in the brain (Bokoch & Knaus 2003; Burckhardt *et al* 2008). Red wine polyphenols were shown to inhibit the activation of NADPH oxidase and subsequent reactive oxygen species generation in different brain regions (Jendekova *et al* 2006). Recent studies have shown that resveratrol, a nonflavonoid polyphenol, naturally found in red wine and grapes, provided neuroprotective effects against ischemia, seizure, and neurodegenerative disorders. Zhang *et al* (2010) clearly demonstrated that resveratrol protected progressive loss of dopamine neurons against lipopolysaccharide (LPS)-induced neurotoxicity in concentration- and time-dependent manners through the inhibition of microglial activation and the subsequent reduction of proinflammatory factor release. Mechanistically, resveratrol-mediated neuroprotection was attributed to the inhibition of NADPH oxidase. This conclusion was supported by the facts that resveratrol reduced NADPH oxidase-mediated generation of reactive oxygen species; LPS-induced translocation of NADPH oxidase cytosolic subunit p47 to the cell membrane was significantly attenuated by resveratrol; and most importantly resveratrol failed to exhibit neuroprotection in cultures from NADPH oxidase-deficient mice. Furthermore, this neuroprotection was also related to an attenuation of the mitogen-activated protein kinases and nuclear factor-kappaB (NF-κB) signaling pathways in microglia (Zhang *et al* 2010). Burckhard *et al* (2008) provided further support for the hypothesis that intermittent hypoxia increases NADPH oxidase subunit protein expression in hypoxia sensitive brain regions involved in learning and memory and that catechin polyphenols administration was able to attenuate the increase in NADPH oxidase gene expression under intermittent hypoxia conditions. These findings are consistent with reports that high doses of epigallocatechin were able to lessen neuronal NADPH expression in rats exposed to acute hypoxia (Wei *et al* 2004). Simonyi *et al* (2010) noticed to the fact, that polyphenolic compounds may protect against oxidative damage associated also with Alzheimer's and other neurodegenerative diseases by decreasing NADPH oxidase activity.

NO production

In addition to the antioxidant properties, the beneficial mechanisms of red wine polyphenolic compounds involve mainly the activation of endothelial NO release through an increase in calcium level and activation of the phosphoinositide-3 kinase/Akt pathway by a redox-sensitive pathway in endothelial cells (Ritz *et al* 2008). Red wine polyphenolic compounds may also regulate NO activity at the level of eNOS protein expression in endothelial cells (Wallerath *et al* 2003), and blood vessels (Pechanova *et al* 2004). Chronic upregulation of eNOS by red wine polyphenolic compounds might constitute a preventive approach to reduce tissue injury associated with a risk of cerebral ischemia. Resveratrol protects spinal cord from ischemia-reperfusion injury via decreased oxidative stress and increased NO release. Resveratrol-induced neuroprotection is thus mediated by both antioxidant and NO promoting properties (Kiziltepe *et al* 2004).

Moreover, previously we have shown that Provinols™ (red wine polyphenolic powder) increased NO synthase activity after 4 weeks of treatment in the cerebral cortex, cerebellum and brainstem (Jendekova *et al* 2006). Simi-

larly, Provinols™ increased NO synthase activity in the heart and aorta of N^G-nitro-L-arginine methyl ester (L-NAME)-treated rats (Pechanova *et al* 2004). These data strongly suggest that Provinols™ is a potent activator of NO synthase activity in both the cardiovascular and nervous systems. Interestingly, prolonged Provinols™ treatment for 7 weeks had no effect on NO synthase activity decreased by L-NAME treatment (Jendekova *et al* 2006; Pechanova *et al* 2009). Recently, Han *et al* (2006) suggested that the neuroprotective action of various polyphenols and resveratrol analogues could be mediated by the activation of common "receptor" binding sites particularly present at the level of the cellular plasma membrane in the rat brain. It is hypothesized that binding polyphenols to this receptor may be associated with increased NO synthase activity in the brain. Prolonged action of polyphenols on its receptor could, however, lead to decreased receptor sensitivity and/or increased tolerance. Similarly, low and high doses red wine polyphenolic compounds have respectively pro- and anti-angiogenic properties on postischemic neovascularization in vivo (Baron-Menguy *et al* 2007). This unique dual effect of red wine polyphenolic compounds offers important perspectives for the treatment and prevention of different diseases.

According to the recent studies (for review see Parohova *et al* 2009) NO produced by eNOS is responsible for rather beneficial effects of this factor. On the hand, NO produced by neuronal nitric oxide synthase (nNOS) and even iNOS represent the negative sites of this molecule in the brain (***Figure 1***). Interestingly, red wine polyphenolic compounds inhibit the expression of the inducible form of NO synthase (iNOS), which is induced after ischemia and other pathophysiological precesses and contributes to the late-phase tissue damage (Ritz *et al* 2008; Pechanova *et al* 2004).

The results of Wei *et al* (2004) showed a significant increase in the expression of NADPH-d/nNOS reactivity in neurons of the nodose ganglion at various time intervals following hypoxia. However, the hypoxia-induced increase in NADPH-d/nNOS expression was significantly depressed only in the hypoxic rats treated with high dosages of epigallocatechin gallate (25 or 50 mg/kg). These data suggest that epigallocatechin gallate may attenuate the oxidative stress and nNOS activity following acute hypoxia (Wei *et al* 2004). Both epigallocatechin gallate and curcumin were able to attenuate quinolinic acid-induced Ca(2+) influx and nNOS activity in human neurons. Although Ca(2+) influx was not attenuated by catechin hydrate, nNOS activity was reduced, probably through direct inhibition of the enzyme (Braidy *et al* 2010). In addition to the well-known antioxidant properties of these natural phytochemicals, the inhibitory effect of some of these compounds on specific excitotoxic processes, such as Ca(2+) influx, provides additional evidence for the beneficial health effects of polyphenols in excitable tissue, particularly within the central nervous system.

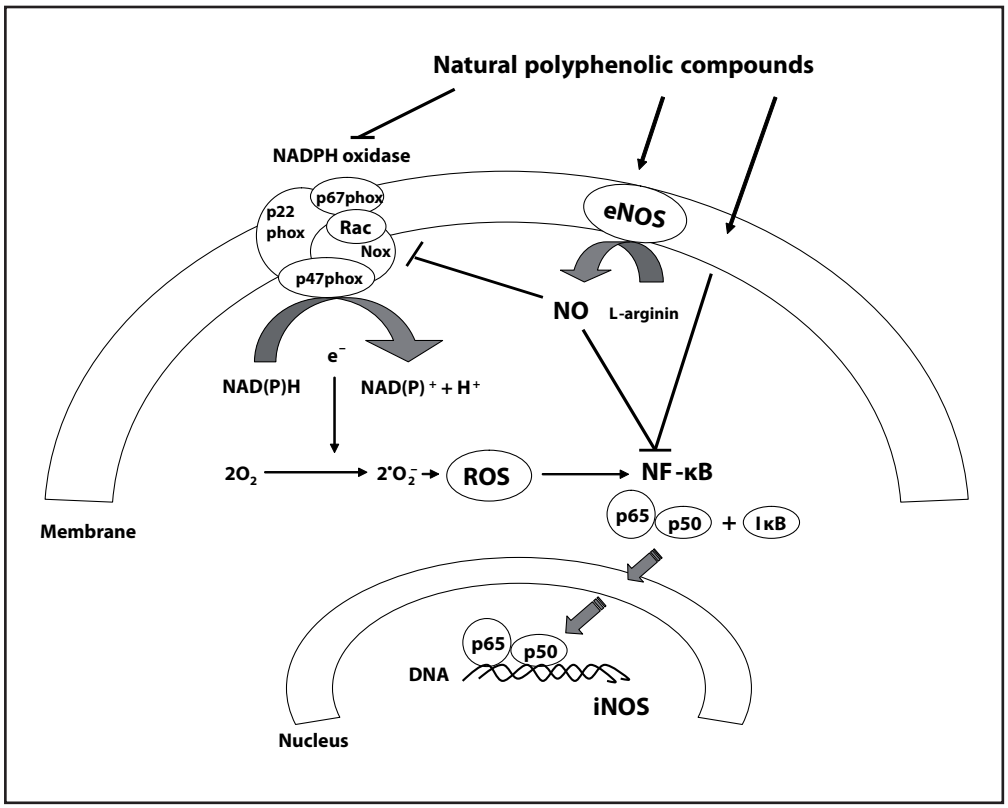

Fig. 1. In the brain, natural polyphenolic compounds inhibit both NADPH oxidase and nuclear factor-kappaB (NF-κB) activities and activate endothelial nitric oxide synthase (eNOS). Produced NO further inhibits NADPH oxidase and NF-κB activities. On the other hand, reactive oxygen species (ROS) activate NF-κB leading to dissociation of NF-κB subunits (p50 and p65) from its inhibitor IκB. The subunits transfer to the nucleus and activate number of genes including inducible nitric oxide synthase (iNOS).

Reduction of neuroinflammation

Neuroinflammatory processes in the brain are believed to play a crucial role in the development of neurodegenerative diseases as well as in neuronal injury associated with stroke (Zheng *et al* 2003). Activation of microglia and astrocytes leads to the production of cytokines and other inflammatory mediators which may contribute to the apoptotic cell death of neurons observed in many neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Treatments with blueberry polyphenolic extract have been shown to inhibit production of the inflammatory mediators like cytokines, interleukin-1beta and tumor necrosis factor-alpha, in cell conditioned media from LPS-activated microglia. Also, mRNA and protein levels of iNOS and cyclooxygenase-2 in LPS-activated cells were significantly reduced by this treatment (Lau *et al* 2007). Quercetin was demonstrated to attenuate microglia mediated neuroinflammation via mechanisms that include downregulation of iNOS gene transcription by inhibition of pro-inflammatory factor NF-κB (Chen *et al* 2005). Similarly our study provided the evidence about reduction of iNOS expression in the blood vessels from rats cotreated with Provinols™ plus L-NAME (Pechanova *et al* 2004). Furthermore, we documented that iNOS downregulation was accompanied by inhibition of NF-κB activity (Parohova *et al* 2009; Pechanova *et al* 2009). Moreover, Campos-Esparza *et al* (2009) observed that natural polyphenols inhibit glutamate-induced activation of calpains, normalize the levels of phosphorylated Akt kinase and cytosolic Bax, and regulate the nuclear translocation of NF-κB. Each of these effects contributes to the substantial reduction of apoptotic neuronal death induced by glutamate. Thus it seems that polyphenolic compounds may inhibit NF-κB activity leading to downregulation of iNOS gene transcription. These mechanisms together with NADPH oxidase inhibition finally result in significant reduction of neuronal death.

Memory and cognitions

There is a growing interest in the potential of natural polyphenols to improve memory, learning and general cognitive ability. Recent evidence has indicated that flavonoids may exert especially powerful actions on mammalian cognition and may reverse age-related declines in memory and learning. In particular, evidence suggests that foods rich in three specific flavonoid sub-groups, the flavanols, anthocyanins and/or flavanones, possess the greatest potential to act on the cognitive processes. Isoflavone supplementation has been observed to have a favorable effect on cognitive function mainly in post menopausal women (for review see Pilsakova *et al* 2010). Also red wine polyfenols interference with oestrogen signaling was suggested in rat hippocampus (Monteiro *et al* 2008).

Although the precise mechanisms by which these polyphenols act within the brain remain unresolved, the present studies are focused on their ability to protect vulnerable neurons and enhance the function of existing neuronal structures. From the molecular point of view, selective interactions of different polyphenols with protein kinase and lipid kinase signaling cascades (i.e. phosphoinositide-3 kinase/Akt and mitogen-activated protein kinase pathways), which regulate transcription factors and gene expression, may have a significant impact on both synaptic plasticity and cerebrovascular blood flow. Their abilities to activate the extracellular signal-regulated kinase (ERK1/2) and the protein kinase B/Akt signalling pathways, leading to the activation of the cAMP response element-binding protein (CREB), a transcription factor responsible for increasing the expression of a number of neurotrophins important in defining memory, represent the key pathways leading to the improvement of memory and cognitive performance in different experimental models as well as in humans (Spencer, 2010).

For example, the flavanol epicatechin, especially in combination with exercise, has been observed to enhance the retention of rat spatial memory by a mechanism involving increased angiogenesis and neuronal spine density in the dentate gyrus of the hippocampus, and an up-regulation of genes associated with learning in the hippocampus (van Praag *et al* 2007). Results for the Morris water maze showed that the blackberry-fed rats had significantly greater working, or short-term memory performance than the control rats. These data support the previous investigations in which same authors have seen improved motor and cognitive performance in aged rats after supplementation with other berry fruits (Shukitt-Hale *et al* 2009). Moreover, previously we have documented that red wine polyphenols positively affect the performance of healthy volunteers in the visual space memory task (Jagla *et al* 2009).

Conclusion

This minireview tries to summarize the most important neuroprotective actions of natural polyphenolic compounds in the brain predominantly. We accentuate the evidence suggesting their mechanism of action involves: 1) antioxidant activity, mainly inhibition of the NADPH oxidase and subsequent reactive oxygen species generation; 2) an activatory effect on endothelial and inhibitory action on both neuronal and inducible nitric oxide synthase activity and subsequent NO production; 3) reduction of neuroinflammation via attenuation of the release of cytokines, such as interleukin-1beta and tumor necrosis factor-alpha and downregulation of the pro-inflammatory transcription factors such as NF-κB; and 4) the potential to modulate signalling pathways such as mitogen-activated protein kinase cascade and cAMP response element-binding protein leading to the improvement of memory and cognitive performance.

All these neuroprotective effect of natural polyphenolic compounds may be important in the prevention of brain damage including ischemic stroke and neurodegenerative diseases, in significant reduction of neuronal death, in memory improvement, learning and general cognitive ability.

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