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Review

Neuroinflammation: Modulation by flavonoids and mechanisms of action

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ABSTRACT

Neuroinflammatory processes are known to contribute to the cascade of events culminating in the neuronal damage that underpins neurodegenerative disorders such as Parkinson's and Alzheimer's disease. Recently, there has been much interest in the potential neuroprotective effects of flavonoids, a group of plant secondary metabolites known to have diverse biological activity *in vivo*. With respect to the brain, flavonoids, such as those found in cocoa, tea, berries and citrus, have been shown to be highly effective in preventing age-related cognitive decline and neurodegeneration in both animals and humans. Evidence suggests that flavonoids may express such ability through a multitude of physiological functions, including an ability to modulate the brains immune system. This review will highlight the evidence for their potential to inhibit neuroinflammation through an attenuation of microglial activation and associated cytokine release, iNOS expression, nitric oxide production and NADPH oxidase activity. We will also detail the current evidence indicting that their regulation of these immune events appear to be mediated by their actions on intracellular signaling pathways, including the nuclear factor-κB (NF-κB) cascade and mitogen-activated protein kinase (MAPK) pathway. As such, flavonoids represent important precursor molecules in the quest to develop of a new generation of drugs capable of counteracting neuroinflammation and neurodegenerative disease.

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1. Introduction

Neuroinflammation is a defense mechanism aimed at protecting the central nervous system (CNS) against infectious insults and injury. In most cases, it constitutes a beneficial process that ceases once the threat has been eliminated and homeostasis has been restored (Glass et al., 2010). However, sustained neuroinflammatory processes may contribute to the cascade of events culminating in the progressive neuronal damage observed in many neurodegenerative disorders, most notably Parkinson's disease (PD) and Alzheimer's disease (AD) (Hirsch et al., 2005; McGeer and McGeer, 2003), and also with neuronal injury associated with stroke (Zheng et al., 2003). As such, the use of non-steroidal anti-inflammatory drugs, such as ibuprofen, has been proposed to delay or even prevent the onset of such neurodegenerative disorders (Casper et al., 2000; Chen et al., 2003) and epidemiologic studies have indicated that the risk for developing AD was reduced in regular users of anti-inflammatory drugs (Vlad et al., 2008). However, to date, the majority of drug treatments treat the symptoms of these neurodegenerative disorders rather that preventing the underlying degeneration of neurons. Consequently there is a desire to develop novel therapies capable of preventing the progressive loss of specific neuronal populations that underlie pathology in these diseases (Legos et al., 2002; Narayan et al., 2002).

Recently, there has been much interest in the neuroprotective effects of flavonoids (Fig. 1), which have been shown to be effective in protecting against both age-related cognitive and motor decline *in vivo* (Joseph et al., 1999; Vauzour et al., 2008; Williams et al., 2008). This potential may reside in a number of physiological functions, including their antioxidant properties (Bastianetto et al., 2000), their interactions with intracellular signaling pathways, the regulation of cell survival/apoptotic genes and mitochondrial function (Spencer, 2009b; Spencer et al., 2009; Williams et al., 2004). For example, flavonoids and their *in vivo* metabolites have been shown to modulate signaling through tyrosine kinase, phosphoinositide 3-kinase (PI3 kinase), protein kinase C (PKC) and mitogen activated protein kinase (MAP kinase) pathways (Spencer, 2009a). These signaling cascades are also critical for the control of inflammatory processes in the brain, including the activation of microglia in response to cytokines and the induction of iNOS and nitric oxide production (Bhat et al., 1998; Kaminska et al., 2009; Wen et al., 2011). As a consequence, flavonoids have been suggested as novel therapeutic agents for the reduction of the deleterious effects of neuroinflammation in the brain and thus also as potential preventive drugs for neurodegenerative disease development.

The aim of this review is to highlight the potential of dietary flavonoids to exert neuroprotection through their ability to modulate neuroinflammation in the central nervous system. We provide an outline of the role glial cells play in neuroinflammation and describe the involvement of inflammatory mediators, produced by glia, in the cascade of events leading to neuronal degeneration. Then we highlight the current evidence that indicates flavonoids may modulate neuroinflammation via their potential to modulate signaling pathways controlling the activation of glial cells and those determining neuronal apoptosis.

2. Components of the neuroinflammatory cascade

In the mid-nineteenth century, the German pathologist Rudolf Virchow described for the first time a connective tissue in brain and spinal cord, known as *Nervenkitt* (nerve glue) (Somjen, 1988). These were later termed neuroglia cells and were attributed as having merely a passive, supportive function in the nervous system. However, over the past decade there function has undergone re-evaluation, with a greater focus on their function in both healthy and diseased brains. Microglial cells are the primary immune cells in the CNS and have similar actions to that of peripheral macrophages (Kreutzberg, 1996). Being immune cells, their primary functions are to promote host defense by destroying invading pathogens, removing deleterious debris, promoting tissue repair and facilitating tissue homeostasis, partly through their influence on surrounding astrocytes and neurons (Glass et al., 2010). However, sustained, uncontrolled activation of microglia can lead to an excess production of various factors that contribute to neuronal injury, most notably, nitric oxide, pro-inflammatory cytokines (IL-1β, TNF-α) (Gibbons and Dragunow, 2006), reactive oxygen species (ROS) (Wang et al., 2006) and glutamate (Takeuchi et al., 2006).

On activation, microglia may produce excessive levels of nitric oxide via the increased expression of inducible nitric oxide synthase (iNOS) (Brown, 2007) and these events can lead to a disruption of neuronal mitochondrial electron transport chain function (Stewart and Heales, 2003). In particular, nitric oxide selectively inhibits mitochondrial respiration at cytochrome *C* oxidase (complex IV), resulting in a disruption of neuronal ATP synthesis and an increased generation of ROS (Moncada and Bolanos, 2006). Furthermore, excessive nitric oxide production may also be detrimental as it is capable of inducing protein modifications, in particular S-nitrosylation and nitration (Zhang et al., 2006). Therefore, an uncontrolled activation of iNOS in glial cells constitutes a critical event in inflammatory-mediated neurodegeneration. In addition to iNOS, the activation of NADPH oxidase (Mander and Brown, 2005), which mediates both superoxide anion radical production and the release of