The Role of Flavonoids in Preventing Neuroinflammation and Cognitive Decline

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Significant advances in medical science during the last century have resulted in a gradual, but highly significant, increase in human life span. On the surface this is a great achievement, but as people age, their cognitive function is threatened by the normal aging process, as well as increasing risk for dementia. The precise cause of the neuronal degeneration underlying these disorders, and indeed normal brain aging, remains elusive, although it is thought that several cellular and molecular events are involved, including increases in oxidative stress, impaired mitochondria function, activation of neuronal apoptosis, the deposition of aggregated proteins, and neuroinflammation.

In most cases, neuroinflammation constitutes a beneficial process that ceases once the threat is eliminated and homeostasis is restored. However, sustained neuroinflammatory processes may contribute to the cascade of events culminating in the progressive neuronal damage observed in many neurodegenerative disorders. For many years, a great deal of ongoing research has shown declines in both motor and cognitive functions, even in absence of neurodegenerative disease, in both animals and humans.

Alterations in cognition appear to occur primarily in secondary memory systems that reflect the storage of newly acquired information. For example, aging is associated with a decline in memory performance (eg, delayed recall of a story presented once), processing, working memory, and executive function. Furthermore, the use of nonsteroidal anti-inflammatory drugs, such as ibuprofen, is thought to delay or even prevent the onset of such neurodegenerative disorders, and epidemiologic studies have indicated that the risk for developing Alzheimer’s disease (AD) was reduced in regular anti-inflammatory drug users. However, thus far, the majority of existing drug treatments for neurodegenerative disorders are unable to prevent the underlying degeneration of neurons, consequently creating a desire to develop alternative strategies capable of preventing the progressive loss of specific neuronal populations.
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During the last decade, vast and growing research literature has focused on the potential of dietary flavonoids for aiding preservation of cognitive function during aging, while reducing risk for AD and other dementing disorders.\textsuperscript{10,11} Flavonoids comprise the most common group of polyphenolic compounds in the human diet and are found ubiquitously in plants. They consist of two aromatic carbon rings (A and B) that are bound together by three carbon atoms that form an oxygenated heterocycle (ring C) (Fig 1), and may be divided into six subgroups based on the degree of the oxidation of the C-ring, the hydroxylation pattern of the ring structure, and the substitution of the 3-position.

The main dietary groups of flavonoids are 1) flavonols (eg, kaempferol, quercetin), which are found in onions, leeks, and broccoli; 2) flavones (eg, apigenin, luteolin), which are found in parsley and celery; 3) isoflavones (eg, daidzein, genistein), which are mainly found in soy and soy products; 4) flavanones (eg, hesperetin, naringenin), which are mainly found in citrus fruit and tomatoes; 5) flavanols (eg, catechin, epicatechin, epigallocatechin, epigallocatechin gallate), which are abundant in green tea, red wine, and chocolate; and 6) anthocyanidins (eg, pelargonidin, cyanidin, malvidin), which are found in red wine and berry fruits.

Among berries, blueberries are particularly rich in flavonoids, with anthocyanidins (delphinidin, cyanidin, petunidin, peonidin, and malvidin), flavanols (monomers: catechin and epicatechin; oligomers: procyanidins B type), and flavonols (quercetin and myricetin) being the most represented.\textsuperscript{12}

In general, it was assumed that the health benefits of flavonoids were linked to their capacity to directly scavenge free radicals and other nitrogen species in vitro.\textsuperscript{13} However, it is not likely that the concentrations at which they exert such antioxidant activity are easily achieved in vivo, because many flavonoids have very limited bioavailability and are extensively metabolized, therefore reducing their antioxidant potential.\textsuperscript{14}
During the last years, a new realization of how nutritional antioxidants may function has surfaced, and recent findings have suggested that in lower amounts, typical of those attained in the diet, flavonoids may exert pharmacological activity within the cells. Although the precise site of their interaction with signaling pathways is unclear, evidence indicates that they are capable of acting in a number of ways, including 1) the modulation of intracellular signaling cascades that control neuronal survival, death, and differentiation, 2) changes in gene expression, and 3) interactions with mitochondria.\textsuperscript{15,16}

For example, flavonoids and their in vivo metabolites are shown to modulate signaling through tyrosine kinase, phosphoinositide 3-kinase, protein kinase C, and mitogen-activated protein kinase pathways.\textsuperscript{17} 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.\textsuperscript{18,19} By affecting such pathways, flavonoids are not only suggested as novel dietary strategies for the reduction of the deleterious effects of neuroinflammation in the brain, but also as having a direct influence on memory acquisition, consolidation, and storage through the induction of new protein synthesis in neurons (Fig 2).

**Fig 2. Schematic representation of the possible effects of aging on cognitive performances and known effects of flavonoids in improving the cognitive decrements.**

\text{A\beta}=\text{amyloid beta, APOE-\epsilon4}=\text{apolipoprotein E4, CRP}=\text{C-reactive protein, CysDA}=\text{cysteinyldopamine, DHBT-1}=\text{dihydrobenzothiazine-1, IL1/6}=\text{interleukin 1 and 6, IL-1\beta}=\text{interleukin-1 beta, JNK}=\text{c-Jun N-terminal kinase, LTP}=\text{long-term potentiation, MAPK}=\text{mitogen-activated protein kinase, NF-\kappaB}=\text{nuclear factor kappa B, NO}=\text{nitric oxide, PI3K}=\text{phosphoinositide 3-kinase, TNF-\alpha}=\text{tumor necrosis factor alpha}
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Alternatively, the well-established effects of flavonoids on the vascular system also may induce increases in cerebral blood flow capable of having an impact on acute cognitive performance, or may lead to an increase in hippocampal vascularization capable of inducing new neuronal growth.

References


