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Editorial

Mechanistic Understanding of Antioxidants Impact on Cognitive Function in Geriatric Canines

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INTRODUCTION

Canine cognitive dysfunction syndrome (CDS) is a collection of symptoms, or behavioral changes, described specifically in dogs of advanced age unrelated to any other diagnosable illness. Symptoms may include an altered sleep-wake cycle, newly developed destructive behavior, inappropriate elimination, excessive vocalization, pacing or wandering, and altered social interaction with the owner.[1-4] In regards to aging, the brain is one of the most susceptible tissues in the body because of its high oxygen requirement, poor endogenous antioxidant capacity, and limited regenerative ability.[5,6] A number of pathologic changes have been identified in the aged canine brain, many of which have also been described in humans diagnosed with Alzheimer's disease (AD). As a result, the dog is often used as a high-relevant comparative animal model for studies on AD in humans.[7-9] The most commonly recognized changes in the canine brain include decreased total brain volume (or atrophy), enlargement of the lateral ventricles, choroid plexus, meningeal and vascular fibrosis, neuronal loss, decreased neuronal regenerative capacity, lipofuscin build-up, intracytoplasmic inclusion formation, and diffuse β-amyloid plaque formation–specifically in the frontal cortex and hippocampal regions.[5,7,10,11] Several studies have suggested a significant correlation between β-amyloid deposition and the severity of cognitive dysfunction in aged canines[4], similar to that which occurs in humans with Alzheimer's disease though the exact mechanisms between these changes and the development of cognitive dysfunction syndrome in canines is yet to be fully established.[5] However, it has been shown that oxidative damage to lipids and proteins due to reactive oxygen species increases in the brain with age.[12] As a result, diets fortified with antioxidants may help to prevent and/or mitigate some of these destructive changes, thus decreasing the incidence and/or severity of cognitive dysfunction syndrome.[1,4]

Free Radicals, Reactive Oxygen Species and Antioxidants

Generally speaking, any molecule that contains at least one unpaired electron in the outer shell is intensely reactive and is called a "free radical" or, if it contains oxygen, a reactive oxygen species (ROS).[13] The body spontaneously creates reactive oxygen species such as the superoxide, hydroxyl, peroxyl (RO2 •), alkoxyl (RO•), and hydroperoxyl (HO2 •) free radicals as by-products of cellular respiration. In low concentrations, ROS aid in maturing cellular structures, immune system destruction of foreign pathogens, and cellular signaling.[14-16] When excess ROS remain un-neutralized by the body's natural defenses, they can cause oxidative stress on the surrounding tissues. This is because the free radicals undergo further reactions with surrounding molecules leading to the formation of peroxides, subsequent degradation into smaller molecular units, and then formation of dimer aggregates. This then detrimentally affects the functional efficiency and the productive ability of these cells. The free radical theory of aging was developed in the mid-20th century and suggests that aging is caused by the continued detrimental effects of free radicals over an organism's lifespan as well as a decrease in the ability to recover from cellular damage caused by free radicals and other reactive oxygen species (ROS).[17]

Antioxidants are substances found in the diet that have the ability to reduce the effect of ROS and potentially delay the effects of aging associated with cognitive dysfunction. In order to combat ROS within cells, the body protects itself by using various antioxidant mechanisms. Antioxidants and their mechanisms are classified as either enzymatic (superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSHPx)) or non-enzymatic (vitamin E, vitamin C, plant polyphenols, carotenoids, and glutathione).[18,19] For the purposes of this editorial, we chose to focus primarily on the functions of the naturally occurring, non-enzy-

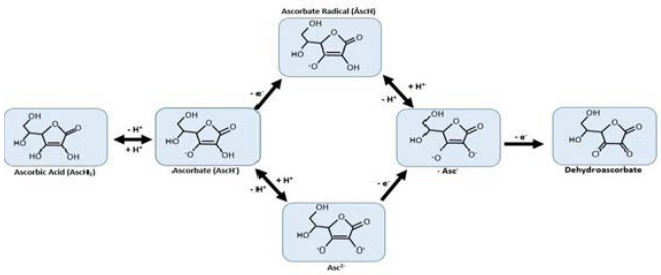
matic antioxidants, vitamin E and vitamin C, which are commonly incorporated into commercial canine diets specifically formulated to combat brain aging.[20, 21]

Vitamin E (α-tocopherol) works by impeding free radical chain reactions. It intercepts lipid peroxyl radicals (LOO•), and terminates lipid peroxidation chain reactions.[18] The resulting radical (α-tocopherol-O•) is considered stable under normal conditions, and helps prevent lipid peroxidation.

$$LOO^{\cdot} + \alpha\text{-tocopherol-OH} \rightarrow LOOH + \alpha\text{-tocopherol-O}^{\cdot}$$

Vitamin C (ascorbic acid 2) is a free radical scavenger. It generates vitamin E within cell membranes by combining with glutathione (GSH) or other compounds capable of donating reducing equivalents. Once vitamin C donates an electron to lipid radicals, the structure is converted to an ascorbate radical[18,19,22] which then prevents the lipid peroxidation chain reaction (Fig. 1).[18]

Figure 1. *Mechanism of Radical Scavaging Activity of Ascorbic Acid 2*



Antioxidants and Canine Cognitive Function

Aged dogs have been used in studies to determine the effects of antioxidant supplementation on the reduction of oxidative stress in the brain and the consequent effects on cognitive function. Several recent studies have used aged beagles to determine if a combination of behavioral enrichment and antioxidant supplementation would begin to more closely resemble cognitive function of younger beagles given the same treatment.[4,23-26] The antioxidant-rich diet contained a broad spectrum of antioxidants (vitamins E and C as well as those occurring in fruits and vegetables such as spinach, tomato, grape and carrot) as well as two mitochondrial cofactors (carnitine and lipoic acid).[25] Over a nearly three year period, the aged dogs showed significant improvement in areas such as spatial attention and oddity discrimination.[4,27] Other areas such as visual discrimination and frontal function of the brain maintained performance in antioxidant enriched diets. However, in aged dogs with untreated diets there was a significant decline.[25] Dogs subjected to both antioxidant-enriched diets as well as behavioral enrichment showed superior improvements compared to either treatment alone.[24,25] It should be noted that the young dogs with antioxidant enriched diets did not show significant difference in cognitive function from the young dog control group.[28] This finding suggests that aged dogs in particular benefit from antioxidant supplementation. Dogs progression in cognitive deficits as they age is similar to that of humans, thus making them a useful model in age-related cognitive dysfunction research. The beneficial effect of an antioxidant-rich diet on aged dogs prove a possible therapeutic approach that may be translated to humans with cognitive dysfunction, such as Alzheimer's Disease.[30]

Current Dietary Recommendations

As described above, studies have shown that a mixed diet of antioxidants is needed to reach maximum results.[29,30] Vitamin E, vitamin C, β-carotene, and trace minerals including selenium, copper, zinc, and manganese, are common antioxidant sources utilized in canine diets.[30] Additionally, antioxidants synergistically work with mitochondrial cofactors, such as alpha-lipoic acid and Acetyl-L-carnitine, to reduce the effect of ROS and oxidative stress on age-related cognitive dysfunction[4,30,31] and should be incorporated into the diet as well. Two mainstream diets enriched with antioxidants and labeled to help reduce signs of cognitive dysfunction syndrome in dogs include the Hill's Prescription Diet Canine b/d and the Purina Pro Plan Bright Mind. Both diets are enhanced with a mixture of vitamins E and C as well as carnitine and lipoic acid or selenium and vitamin A respectively.[20,21] Currently, there are no formally published daily dosage recommendations for any of the individual antioxidants in relation to canine CDS.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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