A possible role for lutein and zeaxanthin in cognitive function in the elderly\textsuperscript{1–5}

Elizabeth J Johnson

ABSTRACT
Epidemiologic studies suggest that dietary lutein and zeaxanthin may be of benefit in maintaining cognitive health. Among the carotenoids, lutein and zeaxanthin are the only two that cross the blood-retina barrier to form macular pigment (MP) in the eye. They also preferentially accumulate in the human brain. Lutein and zeaxanthin in macula from nonhuman primates were found to be significantly correlated with their concentrations in matched brain tissue. Therefore, MP can be used as a biomarker of lutein and zeaxanthin in primate brain tissue. This is of interest given that a significant correlation was found between MP density and global cognitive function in healthy older adults. An examination of a relation between cognition and lutein and zeaxanthin concentrations in the brain tissue of decedents from a population-based study in centenarians found that zeaxanthin concentrations in brain tissue were significantly related to antemortem measures of global cognitive function, memory retention, verbal fluency, and dementia severity after adjustment for age, sex, education, hypertension, and diabetes. In univariate analyses, lutein was related to recall and verbal fluency, but the strength of the associations was attenuated with adjustment for covariates. However, lutein concentrations in the brain were significantly lower in individuals with mild cognitive impairment than in those with normal cognitive function. Last, in a 4-mo, double-blinded, placebo-controlled trial in older women that involved lutein supplementation (12 mg/d), alone or in combination with DHA (800 mg/d), verbal fluency scores improved significantly in the DHA, lutein, and combined-treatment groups. Memory scores and rate of learning improved significantly in the combined-treatment group, who also showed a trend toward more efficient learning. When all of these observations are taken into consideration, the idea that lutein and zeaxanthin can influence cognitive function in older adults warrants further study. *Am J Clin Nutr* 2012;96(suppl):1161S–5S.

INTRODUCTION
Alzheimer disease is currently the seventh leading cause of death in the United States and produces a burden of ~172 billion dollars in annual costs (1). Currently available treatments for Alzheimer disease and cognitive impairment are of limited value, with none slowing or stopping neural deterioration. Mild cognitive impairment (MCI)\textsuperscript{6} is thought to be a transitional stage between normal aging and the earliest symptoms of Alzheimer disease. Individuals with MCI have problems with memory or another essential cognitive function that are severe enough to be noticeable by others and detectable by cognitive tests but are not sufficiently severe to interfere with daily life. It has been estimated that the incidence of MCI is 19% in those aged <75 y to 29% in those aged >85 y (2). Furthermore, 13% of people aged ≥65 y are afflicted with Alzheimer disease (1). These figures are likely to increase given that the number of people aged >65 y is increasing. As with most age-related diseases, the most cost-effective way to combat age-related disease is through prevention. One possible strategy is nutrition intervention.

There is growing evidence that oxidative and inflammatory damage contribute to the pathogenesis of Alzheimer disease as well as MCI and age-related cognitive decline (3–13). The brain is especially vulnerable to free radical attacks because of its relatively low antioxidant content, high PUFA concentrations, and high metabolic activity (14). Increased lipid peroxidation and nucleic acid oxidation are found early in Alzheimer disease, and increased concentrations of inflammatory markers and proinflammatory cytokines have been found in the central nervous system of individuals with early Alzheimer disease as well as in those with MCI (3–5, 7–11). Accumulated damage to lipid membranes and DNA by free radicals may disrupt normal cell functioning and lead to neuronal death (14). If increases in sensitivity to oxidative stress and inflammation in the aging brain lead to cognitive deficits, interventions using dietary antioxidant and antiinflammatory agents may delay the extent of oxidative damage to neural tissues and may have an enormous impact on slowing cognitive and the development of neurologic diseases.

The xanthophyll carotenoids lutein and zeaxanthin function as both antioxidants and antiinflammatory agents (15–17). Intake of these dietary components may hold promise in cognitive health for the elderly. The purpose of this review is to evaluate the possible role that lutein and zeaxanthin may have in cognitive function in older adults.

\textsuperscript{1} From the Carotenoids and Health Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA.
\textsuperscript{2} Presented at the conference “New Developments in Carotenoids Research,” held in Boston, MA, March 11–12, 2011.
\textsuperscript{3} Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author and do not necessarily reflect the views of the USDA.
\textsuperscript{4} Supported by USDA grant no. 58-1950-7-707.
\textsuperscript{5} Address correspondence and requests for reprints to EJ Johnson, Carotenoids and Health Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111. E-mail: elizabeth.johnson@tufts.edu.
\textsuperscript{6} Abbreviations used: HFP, heterochromatic flicker photometry; MCI, mild cognitive impairment; MP, macular pigment.

First published online October 10, 2012; doi: 10.3945/ajcn.112.034611.
LUTEIN AND ZEAXANTHIN AS COMPONENTS OF NEURAL TISSUE

Lutein and zeaxanthin are xanthophyll carotenoids found in green leafy vegetables and brightly colored fruit. These plant pigments are distributed ubiquitously in body tissues but tend to be the dominant carotenoid in central nervous tissues. For example, lutein and zeaxanthin are the sole carotenoids in the macula of the primate retina [ie, macular pigment (MP)], where they exist in ~500-fold higher concentrations than in other body tissues (eg, serum) and are believed to be protective through their roles as blue-light filters and antioxidants (18). In these roles, lutein and zeaxanthin are believed to be protective against age-related macular degeneration (18), a leading cause of visual impairment and blindness in the United States (19).

Lutein and zeaxanthin are also among the dominant carotenoids in human brain tissue, where they account for 66–77% of total carotenoid concentration (20, 21). Cortical lutein and zeaxanthin are likely protective in nature and may also influence interneuronal communication and function via multiple mechanisms. Although the molecular basis of these neuroprotective effects of lutein and zeaxanthin remains unknown, several mechanisms have been proposed, such as decreased oxidative stress, activation of antiinflammatory pathways (22–25), and modulation of functional properties of synaptic membranes along with changes in their physicochemical and structural features (26). Lutein and zeaxanthin have also been shown to enhance gap junctional communication (27), which, in the retina, is important for light processing and may be important for the development of neural circuitry in the visual system. Lutein and zeaxanthin, as MP, have been shown to increase visual processing speed (28–30) and to reduce scotopic noise (noise associated with vision under dim light conditions).

The idea that lutein and zeaxanthin can influence cognitive function appears to be reasonable. Epidemiologic evidence from the cognitive impairment literature suggests that this might be the case.

LUTEIN AND ZEAXANTHIN CONCENTRATIONS IN DIET AND SERUM AND AGE-RELATED COGNITIVE DECLINE

Fruit and vegetable intake has been associated with cognitive function (31–33). The benefits of these fruit and vegetables are often thought to be through the antioxidant properties that foods in this class provide. The consumption of vegetables, particularly the green leafy variety that are rich sources of lutein and zeaxanthin (34), was associated with slower rates of age-related cognitive decline in 2 large cohort studies (31, 35). The work by Kang et al (35) suggested that vegetables may provide more benefit than fruit. This study in 13,388 women found that total fruit intake was not associated with cognitive function, but total vegetable intake was significantly associated with reduced cognitive decline. The strongest association was observed with greater intake of green leafy vegetables and cruciferous vegetables.

Plasma antioxidants, including lutein and zeaxanthin, are related to improved cognitive function in healthy older adult (36) and are depleted both in individuals with MCI (3, 37) and in those with Alzheimer disease (37, 38). In a cross-sectional analysis, the relation between cognitive performance and plasma carotenoids (lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene, and β-carotene) in a healthy elderly population was evaluated. Participants with the lowest cognitive functioning (25th percentile) had a higher probability of having low concentrations of plasma zeaxanthin and lycopene (first quartile) (36).

MP IS RELATED TO COGNITIVE FUNCTION IN OLDER ADULTS

MP comprises lutein and zeaxanthin embedded in neural-retinal tissue (39). MP density can be measured noninvasively by using heterochromatic flicker photometry (HFP) (40). HFP is the most widely validated MP measurement technique to date and has been validated in elderly subjects (41–44). In an evaluation of a relation between lutein and zeaxanthin status and cognitive function, 118 healthy older subjects in the Memphis, Tennessee, area (aged 76–85 y; approximately equal numbers of men and women) were assessed for serum lutein and zeaxanthin, MP density (41), and various measures of cognitive function (45). MP density was assessed by using HFP. MP density was significantly related to performance on a variety of indexes designed to assess processing speed, accuracy, and completion ability (P < 0.05). These relations remained significant after adjustment for age, sex, and ethnicity (P ≤ 0.05). Serum xanthophyll concentrations were not related to cognitive function.

MP density, unlike serum lutein and zeaxanthin concentrations, is a reflection of lutein and zeaxanthin in neural tissue. The relation between MP density and cognitive function suggests that xanthophylls embedded in neural tissue are capable of influencing cognitive function in the elderly. If this hypothesis holds, HFP could be developed as a useful clinical screening tool to assess those who would most benefit from additional intake of lutein and zeaxanthin.

MP AS A BIOMARKER OF BRAIN XANTHOPHYLL CONCENTRATIONS

Given these findings of a relation between MP density and cognitive function in the elderly, the question arises as to whether MP density can be used as a biomarker of brain xanthophyll concentrations. To test this, matched retina (4-mm sample) and brain sections from 2 groups of rhesus monkeys on a lifetime diet that was free of carotenoids, except for either lutein or zeaxanthin (46), were extracted to assess xanthophyll concentrations by using methods described by Park et al (47). Extracts were quantitated for xanthophylls by using reverse-phase HPLC methods described by our laboratory (46, 48). Lutein and zeaxanthin concentrations in the retina significantly correlated with lutein and zeaxanthin in the cerebellum. There was a trend for such a relation in the occipital cortex (P < 0.055). Zeaxanthin concentrations in the frontal cortex and pons were significantly related to zeaxanthin concentrations in the retina (49) (Table 1). Therefore, MP density can be used as a biomarker of lutein and zeaxanthin contained in primate brain tissue.

RELATION BETWEEN BRAIN CONCENTRATIONS OF LUTEIN AND ZEAXANTHIN TO PREMORTEM MEASURES OF COGNITIVE FUNCTION

The relations between MP density and cognitive function in older adults and the significant correlations between retinal lutein and zeaxanthin and brain concentrations of these carotenoids...
suggest that increased concentrations of lutein and zeaxanthin in neural tissue are related to better cognitive performance in the elderly. To better understand this, subsequent studies evaluated the relation between cognition and lutein and zeaxanthin concentrations in brain tissue of decedents aged >98 y at death for whom premortem measures of cognitive function were available. Subjects (n = 29) were from the Georgia Centenarian Study (50) and agreed to donate their brains after death. Brain tissues (cerebellum, frontal, occipital, temporal cortices) were analyzed by using standard lipid extractions and reverse-phase HPLC. Pearson correlations were performed by using SPSS software (SPSS Inc), and data were corrected for age. Cognition measures included the following: global cognition, primary degenerative dementia, delayed recall, delayed recognition, retention, intelligence quotient, and executive function.

Lutein and zeaxanthin concentrations in occipital and lutein concentrations in temporal cortices were significantly related to retention. Lutein in the temporal cortex tended to be 

TABLE 1

<table>
<thead>
<tr>
<th>Retina</th>
<th>Lutein</th>
<th>Zeaxanthin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>0.886 (0.009)</td>
<td>0.900 (0.019)</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>0.600 (NS) [4]</td>
<td>1.000 (0.019)</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>0.714 (0.055)</td>
<td>0.693 (0.052)</td>
</tr>
<tr>
<td>Pons</td>
<td>0.600 (NS) [4]</td>
<td>0.975 (0.003)</td>
</tr>
</tbody>
</table>

1 Data are from reference 49. P values are shown in parentheses; n in brackets.


dementia or executive function. These results suggest that higher concentrations of lutein and zeaxanthin in brain tissue may be important in cognitive function in the elderly.

COGNITIVE FINDINGS OF AN EXPLORATORY TRIAL OF DHA AND LUTEIN SUPPLEMENTATION IN OLDER WOMEN

In a study that evaluated a role for xanthophylls in cognitive function, the cognitive benefit of DHA and lutein in unimpaired elderly women was explored in the context of a 4-mo, double-blind intervention trial of DHA and lutein supplementation for eye health (50). Forty-nine women (aged 60–80 y) were randomly assigned to receive DHA (800 mg/d; n = 14), lutein (12 mg/d; n = 11), a combination of DHA and lutein (n = 14), or placebo (n = 10). Subjects underwent cognitive tests measuring verbal fluency, memory, and processing speed and accuracy and provided self-reports of mood at randomization and on completion of the trial (Table 2). After supplementation, verbal fluency scores improved significantly in the DHA, lutein, and combined-treatment groups (P < 0.03). Memory scores and rates of learning improved significantly in the combined-treatment group (P < 0.03), and individuals in this group also displayed a trend toward more efficient learning (P = 0.07). Measures of mental processing speed, accuracy, and mood were not affected by supplementation (Table 3). These exploratory findings suggest that DHA and lutein supplementation may work together in an additive/synergistic manner to improve cognitive functions in older adults.

TABLE 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Assessment</th>
<th>Task</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal fluency</td>
<td>Long-term memory retrieval</td>
<td>Subjects name as many items from a category as possible during a 1-min period.</td>
<td>(51)</td>
</tr>
<tr>
<td>Shopping list task</td>
<td>Short- to longer-term memory (auditory presentation)</td>
<td>Ten associated words (common food items found in a supermarket) are read to the subject in up to 5 verbally presented serial trials. Verbal recall is tested immediately after each trial and after a delay.</td>
<td>(52)</td>
</tr>
<tr>
<td>Word list memory test</td>
<td>Short- to longer-term memory (visual presentation, oral reading component)</td>
<td>Ten unassociated words are presented (at a rate of one word every 2 s on a computer monitor) in 3 serial trials. Verbal recall is tested immediately after each trial and after a delay.</td>
<td>(53)</td>
</tr>
<tr>
<td>MIR apartment test</td>
<td>Short- to longer-term memory (hands-on component)</td>
<td>Subjects place common household objects in 7 rooms of a model of an apartment. Subjects are asked to recall the names of objects and their locations after a delay.</td>
<td>(54)</td>
</tr>
</tbody>
</table>

1 Adapted from reference 54. MIR, Memory in Reality.
carotenoids may precede or be a consequence of cognitive impairment. That is, it is not known if poor cognitive performance is a risk factor for poor nutrition or whether poor nutrition results in age-related cognitive decline. The elderly may be at particular risk of poor nutrition for a variety of reasons, including economics, medication use, and decreased sense of taste and smell. Our cross-sectional and intervention studies find that increased xanthophyll medication use, and decreased sense of taste and smell. Our cross-sectional and intervention studies find that increased xanthophyll status is related to better cognitive performance in the elderly. The determination of a role for lutein and zeaxanthin in cognitive health in the elderly requires longitudinal epidemiologic studies and clinical trials of xanthophyll supplementation.

The author declared no conflicts of interest.

REFERENCES


### Table 3

Scores at baseline (0 mo) and after supplementation (4 mo) with placebo, lutein (12 mg/d), DHA (800 mg/d), or a combination of DHA and lutein in healthy women aged 60–80.

<table>
<thead>
<tr>
<th>Test</th>
<th>Placebo (n = 10)</th>
<th>DHA (n = 14)</th>
<th>Lutein (n = 11)</th>
<th>DHA and lutein (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td>Baseline</td>
<td>Final</td>
</tr>
<tr>
<td></td>
<td>(Baseline)</td>
<td>(Final)</td>
<td>(Baseline)</td>
<td>(Final)</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shopping list memory test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1: items recalled (max 10)</td>
<td>6.5 ± 1.2</td>
<td>7.7 ± 1.5</td>
<td>7.2 ± 1.4</td>
<td>7.7 ± 1.7</td>
</tr>
<tr>
<td>Trials to learn (max 6)</td>
<td>3.0 ± 0.8</td>
<td>2.8 ± 0.9</td>
<td>3.1 ± 1.3</td>
<td>2.6 ± 1.3</td>
</tr>
<tr>
<td>Delayed recall (max 10)</td>
<td>9.5 ± 0.9</td>
<td>9.5 ± 0.7</td>
<td>9.0 ± 0.9</td>
<td>8.7 ± 1.7</td>
</tr>
<tr>
<td>Word list memory test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1: items recalled (max 10)</td>
<td>6.2 ± 1.3</td>
<td>6.6 ± 1.8</td>
<td>6.3 ± 1.7</td>
<td>5.9 ± 1.5</td>
</tr>
<tr>
<td>Trials to learn (max 4)</td>
<td>3.1 ± 0.9</td>
<td>2.8 ± 0.9</td>
<td>3.0 ± 1.0</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>Delayed recall (max 10)</td>
<td>8.1 ± 1.1</td>
<td>8.3 ± 1.8</td>
<td>8.1 ± 1.1</td>
<td>8.6 ± 1.3</td>
</tr>
<tr>
<td>MIR apartment test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed recall (max 10)</td>
<td>9.7 ± 0.8</td>
<td>9.4 ± 0.7</td>
<td>9.4 ± 0.9</td>
<td>9.4 ± 0.8</td>
</tr>
<tr>
<td>Location recall (max 10)</td>
<td>9.7 ± 0.7</td>
<td>9.7 ± 0.7</td>
<td>9.9 ± 0.3</td>
<td>10.0 ± 0.0</td>
</tr>
</tbody>
</table>

*Values are means ± SDs. Adapted from reference 55. *P < 0.05, **P ≤ 0.10. max, maximum; MIR, Memory in Reality.
48. Vishwanathan R, Neuringer M, Schalch W, Wittjer J, Johnson EJ. Lutein (L) and zeaxanthin (Z) levels in retina are related to levels in the brain. FASEB J 2011;25 (abstr. 344.1).