



Emerging Science on Lutein in the Brain

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Lutein and its isomer zeaxanthin are dietary carotenoids that are preferentially taken up into the central region of the retina, referred to as the macula.¹ In the macula, lutein and zeaxanthin are referred to as macular pigment and are believed to prevent damage that leads to age-related macular degeneration,² a leading cause of visual impairment and blindness in the United States.^{3,4} The mechanisms by which lutein is thought to be protective are as an antioxidant and blue (visual) light filter.² Recently it has been suggested that lutein also may play a role in age-related cognitive function and early neural development.⁵ The rationale behind this comes from the following observations: 1) lutein is the predominant carotenoid in human brain tissue,^{6,7} 2) primate retinal lutein concentrations—ie, macular pigment—are related to brain lutein concentrations,⁸ 3) macular pigment is related to cognitive function in adults,⁹ and 4) lutein supplementation in adults improves cognitive function.¹⁰

Lutein as a Component of Neural Tissue

Lutein and zeaxanthin are xanthophyll carotenoids commonly found in green, leafy vegetables and brightly colored fruits. These plant pigments are distributed ubiquitously in body tissues but tend to be the dominant carotenoids in central nervous tissues. For example, lutein and zeaxanthin are the sole carotenoids in the macula of the primate retina (macular pigment), where they exist in approximately 500-fold higher concentrations than in other body tissues such as serum and are believed to be protective through their roles as blue light filters and antioxidants.²

Lutein is also among the dominant carotenoids in human brain tissue, where it accounts for 30%–60% of total carotenoid concentration.^{6,7,11,12} Cortical lutein and zeaxanthin are likely protective in nature and also may influence interneuronal communication and function via multiple mechanisms. Although the molecular basis of these neuroprotective effects of lutein remains unknown, several mechanisms have been proposed such as decreased oxidative stress, activation of anti-inflammatory pathways,^{13–16} and modulation of functional properties of synaptic membranes along with changes in their physicochemical and structural features.¹⁷ Lutein also has been shown to enhance gap junctional communication,¹⁸ which in the retina is important for light processing and may be important for the development of neural circuitry in the visual system. Lutein, as macular pigment,

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increases visual processing speed and reduces scotopic noise (noise associated with vision under dim light conditions).¹⁹⁻²¹

Adults

Lutein plays a role in human health through its actions as an antioxidant, anti-inflammatory, and blue light filter. These characteristics provide biological plausibility to a relationship with many age-related diseases. The strongest evidence is in support of visual health. Given that the eye is an extension of the neural system, lutein may have a role in cognitive function.

Epidemiological studies indicate that dietary lutein and zeaxanthin may be of benefit in maintaining cognitive health. As stated previously, among the carotenoids lutein and zeaxanthin are the only two that cross the blood-retina barrier to form macular pigment in the eye.¹ They also preferentially accumulate in human brain.^{6,7,11,12} Lutein and zeaxanthin in the macula were found to be significantly correlated with their levels in matched brain tissue.⁸ Therefore, macular pigment can be used as a biomarker in brain tissue. This is of interest given that a significant correlation was found between macular pigment density and global cognitive function in healthy older adults.⁹ Examination of the relationship between cognition and lutein levels in brain tissue of decedents from a population-based study of adults found that among the carotenoids, only lutein was consistently associated with a wide range of cognitive measures.¹¹ Furthermore, in a double-blinded, placebo-controlled trial of 4 months in women involving lutein supplementation (12 mg/d), alone or in combination with docosahexaenoic acid (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 those in the combined treatment group, who also displayed a trend toward more efficient learning.¹⁰ Given these observations, the idea that lutein can influence cognitive function is feasible.

Infants

Current evidence supports a role for lutein in neural health (visual and cognitive function) in the adult. While it is unknown whether this role is specific to the adult, the proposed mechanisms by which lutein may exert its effect (antioxidant, anti-inflammatory, and structural) would apply to the infant. In fact, in a randomized, double-blind, placebo-controlled study of healthy term newborns, supplemental lutein was found to significantly increase serum measures of antioxidant activity.²² This is particularly important in the early neonatal period when oxidative stress



plays a crucial role in pathological conditions. Antioxidants are essential to the retina and brain, particularly because of the high metabolic rate of these organs. The human newborn brain has a relative deficiency of endogenous antioxidant enzymes.²³ In addition, neuronal membranes are rich in polyunsaturated fatty acids, which are highly oxidizable. Thus, the placement of an antioxidant in a highly oxidizable environment would be of benefit.

Studies in adults strongly suggest that macular pigment improves visual performance.²⁴⁻²⁸ Optimal visual performance in early life could influence brain development, which is rapid in the 1st year.²⁹ Environmental enrichment, as would occur with visual cues, has long been investigated as an influence on brain structure and function. Morphological and functional effects elicited by environmental enrichment at the neuronal level have been reported to be accompanied by improvements in cognitive performance.³⁰ Lutein's role in early neural development has been a focus of recent research. The first step in addressing such a role is an assessment of infant brain concentrations.

Distribution of Carotenoids in Pediatric Brain Tissue

To assess brain concentrations of carotenoids, brain tissue from 30 subjects who died during the 1st year of life was assessed for carotenoids using standard methods.⁶ Brain tissues (hippocampus, frontal, auditory, and occipital cortices) were obtained from a federally funded tissue bank. The cause of death was sudden infant death syndrome or another condition. There was significantly greater accumulation of xanthophylls (lutein, zeaxanthin, and cryptoxanthin) compared to carotenes (β -carotene and lycopene) in all four regions of the brain ($P<0.05$). Lycopene was detected in only two decedents. Alpha-carotene was not detected in any tissues. The average concentration of lutein in all four brain regions was significantly greater than that of the other dietary carotenoids (zeaxanthin, cryptoxanthin, β -carotene, and lycopene) (Fig 1).⁶

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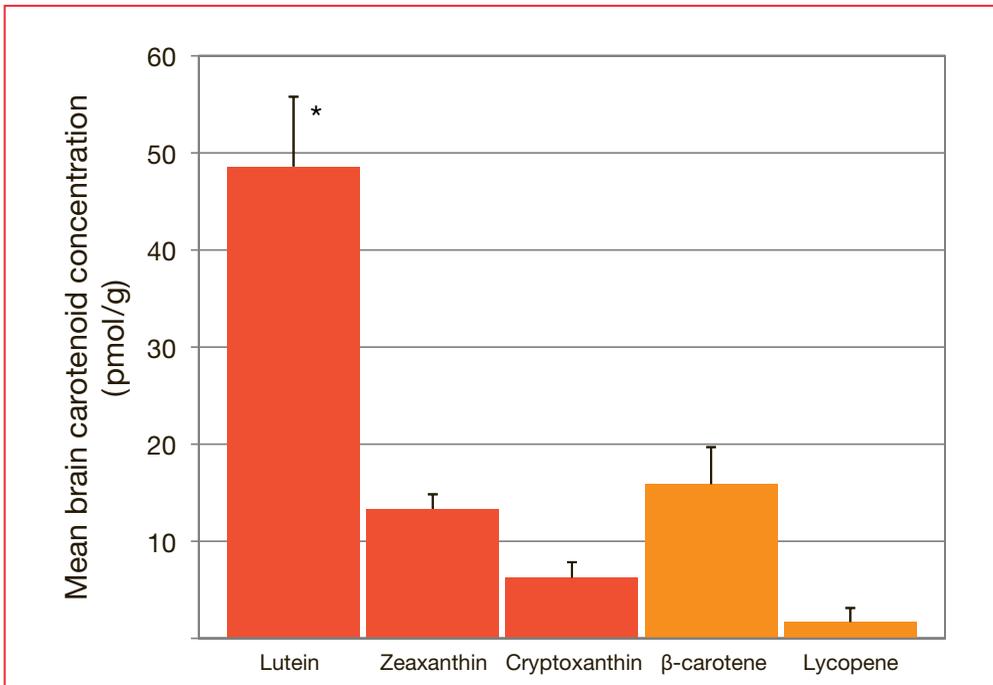


Fig 1. Carotenoid concentration in the brain (mean of the four regions) from 30 infant decedents.⁶ *Significantly different from all other carotenoids at $P < 0.05$. No α -carotene was detected. Lycopene was detected in only two decedents.

As in the adult brain,¹¹ lutein was the major carotenoid in infant brains. However, the relative contribution of lutein to total carotenoids was approximately twice that of the adult (58% vs 31%, respectively), indicating a possible additional role of lutein in early neural development. Evaluation of dietary carotenoids in infants 2-11 months (National Health and Nutrition Examination Survey [NHANES] 1988-1994) shows a much different pattern, with β -carotene being the major dietary carotenoid (43% total) followed by lycopene (28%), α -carotene (13%), and lutein (12%).³¹ The respective values in infant brain tissue were 15%, 3%, 0%, and 58% (Fig 2) (Vishwanathan et al, unpublished data, 2013).

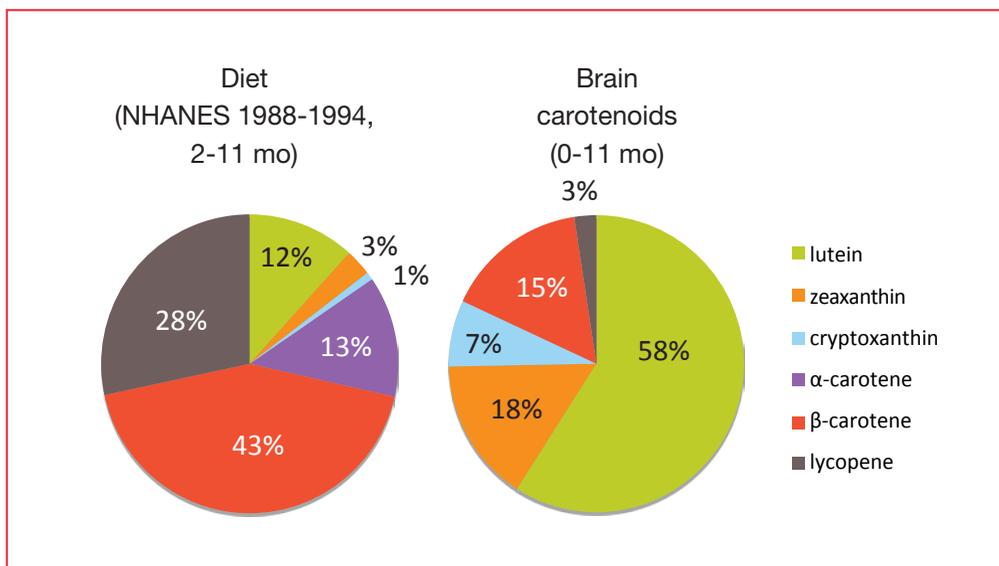


Fig 2. Dietary carotenoid intake versus brain carotenoids (percent total carotenoids).³¹

NHANES=National Health and Nutrition Examination Survey

Source: Vishwanathan R et al, unpublished data, 2013.

These data strongly suggest a preferential uptake of lutein into infant neural tissue. In part, this may be due to a preferential uptake of lutein into breast milk.^{32,33} Further substantiating a preferential uptake of lutein into the infant brain is the observation that in two decedents lutein and zeaxanthin were the only carotenoids in brain tissue. None of the decedent brain tissues that had other carotenoids lacked lutein.

Conclusion

Lutein is the predominant carotenoid in pediatric and adult brain tissue. Lutein in neural tissue has biological effects including antioxidant, anti-inflammatory, and structural actions. In infants' brains, the contribution of lutein to the total carotenoids is twice that found in adults, accounting for more than half the concentration of total carotenoids. In the adult, a variety of evidence supports a role for lutein in cognition. Therefore, the greater proportion of lutein in the pediatric brain suggests a need for lutein during neural development. Infant formula is not routinely supplemented with lutein, whereas breast milk is a highly bioavailable source of lutein.³⁴ The significantly higher scores for cognitive development in breastfed infants compared with formula-fed infants, as reported in a meta-analysis

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of 11 studies, may be attributable in some part to the differential in carotenoid uptakes, including lutein uptakes, between the two groups.³⁵ Consequently, further investigation of the impact of lutein intake on neural development is warranted. Given that the 1st year of life is a time of neural growth and development for which nutrition can have significant consequences, the addition of this dietary plant pigment to infant formulas could be an important strategy toward long-term health outcomes.

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