4 Lutein in Neural Health and Disease

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4.1 INTRODUCTION

Carotenoids are a large class of naturally occurring pigments that are ubiquitous in nature. They are synthesized by plants and some microorganisms, as well as some non-photosynthetic bacteria and fungi. Carotenoids are an important and obligatory dietary constituent for many species.¹ In higher plants, carotenoids are present in plastids, in the chloroplasts of photosynthetic tissues and the chromoplasts of fruits and flowers.¹,² The roles that carotenoids play in photosynthesis give important clues to their functions in humans. As accessory light-harvesting compounds, carotenoids transfer absorbed energy to chlorophylls to help fuel photosynthesis. This absorbed energy comes specifically from the 450–550 nm region of the light spectrum, the blue light region. Carotenoids also prevent damage from singlet oxygen, a free radical generated in plants as chlorophyll enters an energetic “triplet state” and reacts with molecular oxygen in the presence of light. The subsequent
formation of excited triplet states of carotenoids results in the dissipation of excess heat as carotenoids relax to a ground state. Photosynthetic organisms also benefit from the ability of carotenoids to stabilize pigment-protein complexes. Such complexes form the basic architecture of photosynthetic systems. These systems, although diverse among different organisms, follow a basic pattern of a light harvesting complex (LHC) coupled to a reaction center (RC). It appears that higher plants require lutein in order to establish stable LHCII complexes, alluding to the importance of lutein as a structural component in these assemblies. The carotenoids relative to humans are distinctly different in number from those that occur in nature: from a family of over 750 identified compounds, only about 40 carotenoids are present in the typical human diet, only about 20 are found in human blood, only 5 have been reported in the human infant brain, and only 3 (lutein, zeaxanthin, and meso-zeaxanthin; Figure 4.1) accumulate specifically in the human retina. Bioselection of carotenoids therefore seems evident in the human body. Major roles of carotenoids in human health derive from their varying degrees of vitamin A and antioxidant activity. As one of the main carotenoids in human tissue and serum, lutein has many applications to human health. This chapter will focus on the chemical and biological properties of lutein in relation to human health.

### 4.2 CHEMISTRY

Carotenoids are hydrocarbon molecules consisting of linked isoprene units, joined head to tail. The majority are derived from a C-40 backbone, containing 3 to 15 conjugated double bonds, whose structure determines the absorptive and antioxidant characteristics of the molecule. Modifications to the basic structure include chain elongation, isomerization, or degradation. Carotenoids are divided into two main classes: carotenes and xanthophylls, the latter containing at least one oxygen atom. The carotene family members are non-polar molecules, containing carbon and hydrogen only, and include α-carotene, β-carotene, and β-cryptoxanthin. Xanthophylls are oxygenated carotenoids, structurally characterized by the presence of hydroxyl groups attached to each of the two terminal β ionone rings in the molecule. Lutein and zeaxanthin are examples of xanthophylls. Zeaxanthin is a close structural isomer of lutein, and typically occurs in similar foods as lutein. The presence of
hydroxyl groups increases the polarity and hydrophilicity of these compounds, facilitating reaction with singlet oxygen more readily than nonpolar carotenoids. An additional benefit to this polarity is the ability to modulate cell membrane dynamics. Polar carotenoids restrict the molecular motion of lipids, thereby increasing membrane rigidity.

4.3 DIETARY SOURCES AND BIOAVAILABILITY

Humans must obtain lutein from the diet, since it cannot be synthesized endogenously. Many commonly consumed fruits and vegetables contain lutein and zeaxanthin, with lutein content usually but not always exceeding zeaxanthin content. The highest concentrations of lutein are found in dark-green leafy vegetables such as kale, spinach, turnip greens, and collards. It has been reported that the bioavailability of lutein from a high-vegetable diet exceeds that of β-carotene, perhaps due to β-carotene conversion to vitamin A or the enhanced availability of a more polar carotenoid such as lutein in the aqueous environment of digestion. Lutein is highly bioavailable from egg yolks, owing to the lipid matrix of this food.

Serum and tissue levels of lutein can be increased over time, indicating that lutein can be accumulated in the human body. Reported half-lives of lutein can vary from days, weeks, and months depending on the population, diet, dosing regimen, and design of the study. A relatively short half-life of 5.6 days has been reported, contrasting with other reports of much longer half-lives ranging from 33 to 76 days. Lutein occurs in a variety of tissues in the human body including lung, liver, and eye, although exactly how lutein is deposited and metabolized in various tissues is not fully understood. The concentration of lutein and zeaxanthin seems to be preferential to some tissues such as the human eye, where levels of these carotenoids can reach millimolar concentrations as they collectively form the macular pigment (MP). Evidence from a novel approach utilizing a plant biofactory suggests that sufficient quantities of pure lutein isotope can be produced, potentially providing an important avenue by which lutein’s distribution, metabolism, and function can be better understood.

The current focus on healthy eating, along with multiple recommendations to consume a diet rich in fruits and vegetables, likely helps to bolster lutein intake in populations adhering to such recommendations. As such, however, studying the effects of lutein-depleted diets is difficult in humans adhering to these recommendations. Although some studies have reported success in administering low-carotenoid diets, compliance is an issue and in some populations, such as infants, consumption of a carotenoid-free diet may be viewed as unethical and oppositional to feeding breastmilk, which contains lutein. A well-studied primate animal model has provided data on the study of short- and long-term effects of lutein depletion across the lifespan. This model has been particularly important for the study of lutein in ocular disease, as nonhuman primates are the only animals with a macular structure closely resembling that in humans. The earliest use of this model described the basic model and study design, where monkeys were raised on normal or xanthophyll-free diets. In this early study, primates consuming the xanthophyll-free diet lacked MP and exhibited multiple abnormalities in the retina, including increased drusen-like bodies within the retinal pigment epithelium (RPE). Subsequent reports utilizing this model confirmed no detectable MP in subjects following a xanthophyll-free diet, but also showed that supplementing a portion of the initial subjects with pure lutein and or zeaxanthin (2.2 mg/kg per day) for 24 to 56 weeks resulted in a rapid increase in both serum lutein and zeaxanthin over the first 4 weeks, followed by a leveling off from 16 weeks onward. Peak MP optical density in these supplemented primates is suggested that MP density may reach a plateau after a period of supplementation. A portion of the supplemented monkeys in this study received acute short-wavelength light exposures in the fovea and parafovea, with results showing that primates fed xanthophyll-free diets had a dip in the RPE cell density profile at the foveal center, rather than exhibiting a normal peak. Supplementation with xanthophylls reversed this abnormality to a more symmetric profile, indicating that RPEs are
sensitive to depletion of xanthophylls. Utilizing a longer-term supplementation of xanthophylls from 24 to 101 weeks, an isomer of lutein, meso-zeaxanthin, was found to be deposited in the retinas of monkeys supplemented with lutein, although the diet did not contain meso-zeaxanthin. Thus, the discovery of lutein as the precursor of meso-zeaxanthin in the retina was an important finding. After long-term xanthophyll deficiency, lutein or zeaxanthin supplementation protected the fovea from blue light–induced damage. Lipofuscin accumulation, a marker of RPE cell damage, aging, and retinal disease, was higher in animals fed diets deficient in lutein and zeaxanthin, as well as omega-3 fatty acids. The increase corresponded to a mathematically calculated 12–20 year acceleration in lipofuscin accumulation compared to animals fed a standard diet.

4.4 SAFETY OF LUTEIN

Exposure to carotenoids primarily occurs through consumption of fruits and vegetables. Plasma levels of lutein/zeaxanthin increase following consumption of concentrated dietary sources of the carotenoids or supplements, and plasma levels of lutein/zeaxanthin are positively associated with fruit and vegetable consumption. Carotenoid intake from foods, even when ingested in large amounts (e.g., >30 mg carotenoid) are not known to be toxic. The Institute of Medicine evaluated the safety of lutein and zeaxanthin and concluded that no adverse effects, other than carotenodermia, have been reported from the consumption of carotenoids in foods, including lutein and zeaxanthin. No tolerable upper intake levels for lutein or zeaxanthin have been established. Lutein was recently cited as a case study for the re-examination of establishing dietary upper intake levels for bioactive nutrients. Although not determined to meet the classical definition of an essential nutrient in 2000, there is accumulating evidence that a Dietary Reference Intake should be established for lutein because of its role in eye health.

In 2004, Alves-Rodrigues and Shao published a summary of the role of lutein in human health, reviewed lutein absorption and deposition, and presented information on safety of lutein intake. Based upon their review of the literature, the authors report that doses of 20 mg lutein per day for up to 6 months, or doses of 40 mg per day for over 2 months, were not associated with adverse effects in humans. The only side effect noted in human studies was carotenodermia, a reversible and harmless condition. The authors also review the oral animal toxicity studies conducted in rats and monkeys and the mutagenicity studies that were used to complete the GRAS determination for crystalline lutein. Similarly, Shao and Hatchcock found no adverse events in over 30 peer-reviewed studies involving lutein.

4.4.1 United States

Lutein is generally recognized as safe for use as an ingredient in a variety of food and beverage products, including baked goods and baking mixes, beverages and beverage bases, breakfast cereals, chewing gum, dairy product analogs, egg products, fats and oils, frozen dairy desserts and mixes, gravies and sauces, hard candy, infant and toddler foods (other than infant formula, at levels up to 1 mg/serving), milk products, processed fruit and vegetable products, soft candy, soups and soup mixes, medical foods intended as the sole item of the diet at levels up to 3 mg/serving, and as an ingredient in term infant formula at a maximum level of 250 µg/L.

4.4.2 Europe

In 2008, the European Food Safety Authority (EFSA) released a scientific opinion on the suitability of lutein in infant formula and follow-on formula; in the opinion, EFSA stated that the proposed use of 250 µg lutein/L in infant formula products raised no safety concerns. In 2010, EFSA re-evaluated lutein as a food additive and derived an acceptable daily intake (ADI) of 1 mg/kg body weight/day, based on a no-observed-adverse-effect-level (NOAEL) of 200 mg/kg body weight/day in a 90-day study in rats, with an additional 200-fold safety factor.
4.4.3 **Australia and New Zealand**

In July 2008, the Food Standards Australia New Zealand (FSANZ) approved the addition of up to 250 μg lutein/L in infant formula products. In March 2009, FSANZ completed a First Review in which they recommended that use of up to 250 μg lutein/L be reduced to a level of up to 143 μg lutein/L (5 μg/100 kJ) in infant formula products. It was indicated that the evidence submitted to support the higher proposed levels of use in the original application did not demonstrate that lutein bioavailability from breast milk is higher than that from infant formula products. Given that there was no justification for the addition of greater amounts of lutein in infant formula, FSANZ adopted a conservative approach and reduced the permitted use levels of lutein in infant formula to reflect concentrations within the range present in breast milk. In 2009, FSANZ also recommended amending standards to permit the voluntary addition of lutein as a nutritive substance to formulated supplementary foods for young children up to a potential maximum concentration of 100 μg lutein/serving, or 500 μg lutein/L.

4.4.4 **Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives**

The Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (JECFA) established a group Acceptable Daily Intake (ADI) for lutein from *Tagetes erecta* L. and synthetic zeaxanthin of up to 2 mg/kg body weight. In conjunction with dietary intake data from the U.S. Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III), the Institute of Medicine (IOM) used an expanded carotenoid database for foods reported in NHANES III to estimate the usual consumption of lutein and zeaxanthin by the total U.S. population greater than 2 months of age (29,015 individuals). The estimated mean and 90th percentile consumption of total lutein and zeaxanthin by the surveyed sample were 1.71 and 3.01 mg/person/day, respectively. Slightly higher mean intakes of 2.2 and 1.9 mg/person/day of total lutein and zeaxanthin, for men and women, respectively, were estimated from food frequency data obtained from 8341 adults in the 1992 National Health and Interview Survey using the USDA National Cancer Institute carotenoid food composition database.

Kruger et al. estimated the intake of lutein and zeaxanthin using the dietary records for only those respondents to NHANES III who met their recommended daily intake of vegetables, as described in the Dietary Guidelines for Americans, and the carotenoid database employed by the IOM. The mean and 90th percentile for total lutein and zeaxanthin intakes for these individuals (5708 participants, approximately 25% of the total surveyed sample) were determined to be 3.83 and 7.29 mg/person/day, respectively. Therefore, estimated intakes of lutein and zeaxanthin based on recommended levels of vegetable consumption appear to be greater than twice the estimated actual intakes for the total U.S. population.

Johnson et al. estimated the individual intakes of lutein and zeaxanthin using lutein and zeaxanthin values in major dietary sources, applied to data from the NHANES 2003–2004 survey. Lutein intakes were reported to be significantly greater than zeaxanthin intakes among all age groups, both sexes, and all ethnicities.

4.5 **Absorption and Digestion of Lutein**

Lutein and other carotenoids are digested and absorbed similarly to dietary lipids. As a fat-soluble compound, dietary fat facilitates lutein absorption, although exact requirements for optimal absorption are varied. Relatively low levels of dietary fat in a meal are enough to enhance the carotenoid concentration in human plasma and increase the plasma response from carotenoids in raw salads. Carotenoids released from the food matrix are available for absorption by the intestinal epithelium via steps common to other lipid soluble compounds such as transfer to lipid droplets, incorporation into mixed bile salt micelles, uptake by enterocytes, and incorporation into
chylomicrons for secretion into lymph. Release from the food matrix and pre-intestinal digestion are followed by transfer to mixed micelles during typical dietary lipid lipolysis. Once incorporated into mixed micelles in the intestinal lumen, the carotenoids are shuttled across the unstirred water layer and contact the brush border epithelium (enterocytes). Micelle dissociation occurs near the brush border, releasing carotenoids for uptake by the enterocyte, although the exact steps involved in this process are not always completely understood. An important step for the absorption of carotenoids and other lipophilic compounds appears to be cleavage of phospholipids by phospholipase A2 (PLA2). The phospholipid content of micelles affects the cellular uptake of carotenoids. Uptake of micellar beta-carotene and lutein is suppressed by phosphatidylcholine in a dose-dependent manner, and the addition of PLA2 from porcine pancreas to the medium enhances the uptake of carotenoids from micelles containing phosphatidylcholine. Carotenoid uptake by enterocytes was previously thought to occur by simple diffusion; however, several studies support the existence of receptor-mediated transport of carotenoids in the apical membrane of enterocytes. Membrane proteins of intestinal cells, such as CD36 (cluster determinant 36), FAT (fatty acid translocase), NPC1L (Nieman Pick C1-like 1), and the ABCG5/G8 from the ABC transporters superfamily have been associated with the absorption of carotenoids. There is considerable interindividual variability in the absorption and tissue response to dietary carotenoids. It would follow that genetic variation in the expression of proteins involved in carotenoid metabolism could explain these biological effects in humans, and indeed such variants have been reported to affect carotenoid metabolism and carotenoid status. Once within enterocytes, the carotenoids are transported to the Golgi apparatus and assembled in nascent chylomicrons, which are secreted into the lymphatic system for their transport in the bloodstream. In the bloodstream, carotenoids are carried via lipoproteins. The degree to which each carotenoid is transported by specific lipoproteins can vary. Lutein and zeaxanthin are reported to be primarily associated with high-density lipoprotein HDL, consistent with their less hydrophobic nature relative to the carotenes. The specific components of HDL responsible for carotenoid binding remain to be identified. Low circulating levels of HDL can result in a mutation in the ABCA1 transporter gene are characteristic of the Wisconsin hypoalpha mutant (WHAM) chicken. When these animals are fed a high-lutein diet, lutein levels increase in several organs, but not in retina, suggesting that HDL is critical for delivery of carotenoids to retinal tissue. Data suggests that the uptake of carotenoids is similar to that of cholesterol, and that HDL and the receptors of HDL such as SR-BI (scavenger receptor class B type 1) may be involved in this process. SR-BI, a member of the ATP-binding cassette (ABC) transporter super-family, mediates the selective uptake of cholesterol and cholesteryl esters by the liver and other steroidogenic tissues from HDL particles. Carotenoid transport in Caco-2 cells is shown to be decreased by ezetimibe, an inhibitor of cholesterol transport. This effect decreased with increasing polarity of the carotenoid molecule and required SR-B1. Zeaxanthin is exclusively dependent upon SR-BI for uptake in RPE cells, yet this mechanism only partly explains uptake of beta carotene. HDL-mediated transport of lutein is challenged by recent data showing that lutein is delivered in LDL despite its greater extent of association with HDL in serum. It is suggested that HDL-dependent uptake of zeaxanthin occurs via SR-B1, while LDL-dependent uptake of lutein occurs via the LDL receptor. By creating competition for cellular uptake by increasing the amounts of unenriched LDL, the authors showed that lutein uptake decreased by 27%. This finding is supported by other evidence that LDL complexes of lutein and HDL complexes of zeaxanthin and meso-zeaxanthin are taken up better by cells in culture. This group has also reported that all three scavenger receptor proteins (SRB1, SRB2, and CD36) are capable of binding and transporting macular carotenoids. Interesting data exists for how lutein might be transported to individual tissues, especially the human eye. Nature provides an example by which silkworms deliver lutein to the silk gland by both a specific cell-surface uptake protein and a specific binding protein. In the human macula, a similar process appears to involve the following binding proteins: (1) a lutein-binding protein, stereoidogenic acute regulatory domain 3 (StARD3); (2) a zeaxanthin-binding protein, glutathione S-transferase P1; and (3) tubulin, which serves as a site for high-capacity, less specific binding protein of carotenoids in retina.
Polar lipid nutrients such as carotenoids may be less bioavailable than desired in supplements and are thus typically over-fortified in the product to ensure adequate delivery. Animal data using a lymph fistula model reported that the solubility of lutein can be significantly increased by mixing lutein in a specific combination of mono- and diglycerides (MDG) compared with standard triglyceride-based oils. This work was further corroborated in humans, where a single dose of MDG lutein resulted in a 129% increase in plasma lutein within the first 12 h compared with control.29

4.6 BIOLOGY AND BIOACCUMULATION

4.6.1 LUTEIN IN EYE HEALTH

Lutein and zeaxanthin have suggested roles in modulating several diseases including cancer, heart disease, and stroke, as well as the eye-related disorders age-related macular degeneration (AMD) and cataract.72 Of all dietary carotenoids, only lutein and zeaxanthin concentrate within the lens17,73,74 and are predominant in the human retina. Lutein concentrates in the eye 1000 times greater than in the blood, and more specifically in the macula, a small, highly specialized area of the retina involved in relaying information to the visual cortex of the brain.75,76 In the primate macula, lutein, zeaxanthin, and meso-zeaxanthin compose the MP, often measured as macular pigment optical density (MPOD). MPOD has a multifunctional role in the retina, including improving visual performance and protecting against damaging light. As such, levels of MP in the eye are considered a “proxy” for overall health of the macula.

There are several mechanisms by which lutein may protect against ocular diseases. Lutein has been shown to prevent oxidative damage to lipid membranes,77 and lutein molecules tend to orient themselves in membranes such that they maximize interactions to reduce oxidative stress and lend stability.78 The ability of supplemental lutein to accumulate in ocular tissues is a key aspect of its ability to prevent or deter ocular disease. Dietary or supplemental lutein intake in a variety of age groups is associated with an increase in both serum concentration and MP density.28,79,80 Population studies have shown positive relationships of varying strength among dietary lutein and zeaxanthin, their concentrations in blood, and MP density.81–83

As is true of many carotenoids, lutein absorbs light. The particular wavelengths of absorption correspond to approximately 450 nm, or the blue light region. Due to its high energy, blue light can penetrate tissues and cause cellular damage. Blue light is common in the environment and a constituent of the visible light spectrum: sources include sunlight and some forms of artificial lighting. Accordingly, lutein’s protective qualities on health of the eye fall into two major categories: (1) absorption or “filtering” of damaging light75 and (2) antioxidant ability.84 Lutein supplementation in healthy term newborns has been shown to increase antioxidant activity and decrease oxidative stress as compared to newborns who did not receive lutein supplementation.85 The selective accumulation of lutein in the retina may also be due to specific properties that afford membrane stability. Properties of lutein that may support membrane integrity include a high membrane solubility, transmembrane orientation, high chemical stability, and location in the most vulnerable regions of photoreceptors.4

4.6.2 LUTEIN AND EYE DEVELOPMENT

The human eye is embryologically derived from surface ectoderm, neural ectoderm, and mesoderm by the end of 3 weeks gestation. The neural ectoderm is the same tissue from which the neural plate and other brain tissues are derived. All the basic structures of the eyes are present by the sixth week of gestation.86 Lutein is present in infant eyes during early gestation and predominates in the macula up to ∼2 years of life.87,88 The developing newborn eye may be vulnerable to damaging blue light and oxidative damage,89,90 partly due to the relatively transparent lens of an infant, which can allow more damaging blue light to reach the retina.91 The central portion of the retina, the fovea, changes dramatically after birth and evidence has shown that the infant retina “ages” rapidly due to increased
oxidative stress. For example, the accumulation of lipofuscin is most rapid in the first years of life.92,93 The photoreceptors of the retina, rods and cones, are important for visual transmission and may be particularly vulnerable to damage due to their high concentrations of polyunsaturated fatty acids, particularly docosahexaenoic acid.

4.6.3 Lutein and the Brain

The close anatomical and embryological relationship between the eye and the brain makes it logical that lutein’s proposed functions could extend to the human brain. Lutein is present in the adult brain and is the predominant carotenoid in the infant brain, including multiple anatomical areas important to memory and learning.5,94 In an infant primate model, feeding of a carotenoid-supplemented formula was found to enhance deposition of lutein in both serum and brain tissue of monkeys.95 Both MPOD and processing speed can be improved with lutein and zeaxanthin supplementation, demonstrating the beneficial effect of these dietary components on neural health.96 In older subjects with mild cognitive impairment, MPOD is shown to be significantly related to several cognitive attributes, including attention, language, and visual-spatial abilities. Fitting with its antioxidant role, lutein may ameliorate oxidative stress in neural tissues, as demonstrated by its ability to reduce malondialdehyde (MDA) levels in primary neuronal cell membranes.97

4.6.4 Lutein in Neural Cell Membranes

The cell membrane is a dynamic array of molecules. Previous descriptions of the membrane as a “fluid mosaic” have been modified in recent years to incorporate data that suggests that membranes can segregate into regions. These regions are often characterized as “raft domains” and non-raft “bulk lipid” domains. Highly unsaturated lipids such as DHA seem to prefer an orientation close to non-raft proteins. Lutein, while an excellent antioxidant, may play a separate yet very important role in membrane physiology. The fact that lutein has two polar end groups that span the entire membrane means that it may afford structure and stability to the membrane, in addition to its important antioxidant role.7 In this way, each end of the lutein molecule “anchors” to the membrane bilayer, affording order and structure to that area of the membrane. The significance of lutein being found in similar areas of the membrane as DHA means that these nutrients can functionally interact in optimal ways to preserve DHA stability and, subsequently, membrane integrity and function. The membrane distribution of lutein in brain regions and its role as a neural antioxidant was recently evaluated in primates fed a stock diet containing ~2 mg/day lutein or the stock diet plus a daily supplement of lutein (~4.5 mg/day) and zeaxanthin (~0.5 mg/day) for 6–12 months. Nuclear, myelin, mitochondrial, and neuronal plasma membranes were isolated from several brain regions, including prefrontal cortex, cerebellum, striatum, and hippocampus. Lutein was detected in all regions and membranes studied and lutein/zeaxanthin supplementation significantly increased total concentrations of lutein in serum, prefrontal cortex, and cerebellum. In the prefrontal cortex and striatum, mitochondrial lutein was inversely related to DHA oxidation products, supporting lutein’s potential role as an antioxidant in the brain.98

4.6.5 Other Roles

Carotenoids, in addition to their antioxidant potential, have important non-antioxidant roles in biology. Apocarotenoids, molecules resulting from the oxidative cleavage of double bonds in the carotenoid molecule, serve as signaling molecules and assist plants in their interactions with the environment.99,100 Apocarotenoids are formed by chemical reactions in foods that contain carotenoids or by enzymatic cleavage of intact carotenoids. A member of the β-carotene oxygenase family, BCO2, has been found to catalyze the eccentric cleavage of xanthophylls, such as zeaxanthin and lutein and the acyclic carotenoid lycopene.101 Nature provides evidence that carotenoids may function
in gene regulation. As plants are often exposed to far more light than they can use for photosynthesis, they have adapted by down-regulating their light harvesting systems in a mechanism termed non-photochemical quenching (NPQ). Carotenoids participate in NPQ by regulating gene expression of proteins involved in light harvesting. Lastly, the stimulation of gap junction communication by carotenoids is not related to their antioxidant ability or their pro-vitamin A ability. In fact, there seems to be little correlation between the effects of carotenoids on gap junction communication and their ability to quench singlet oxygen. Metabolites of carotenoids often have similar or increased activity as the parent compound, as decomposition products of retinoic acid have been shown to enhance gap junction communication.

4.7 LUTEIN ACROSS THE LIFESPAN IN RELATIONSHIP TO HEALTH AND DISEASE

4.7.1 Lutein in Infancy and Childhood

Carotenoid status in the newborn depends on the nutritional status of the mother, but little is known about the transfer of carotenoids from the mother to the fetus. There is evidence that preterm birth is associated with almost absent MP. As lutein cannot be synthesized by humans, the nutritional status of the newborn will depend directly on its diet.

Important dietary sources of this nutrient prior to food introduction are colostrum, human milk, and infant formula (Table 4.1). Lutein is ~50% more concentrated in colostrum than in mature human milk. Levels of lutein in human milk are variable and generally reflective of maternal dietary intake. Mean concentrations of lutein/zeaxanthin in human milk from women in China and Japan (44 and 43 µg/L, respectively) are reported to be higher than those in the United States, perhaps due to different dietary habits. Lutein content in human milk decreases with lactation stage but appears to level off at approximately 2 months. Lipkie and colleagues report a similar decrease in lutein content with stage of lactation, and a median lutein content of samples from China, Mexico, and the U.S. across all stages as 114.4 nmol/L (~65 µg/L). A selection of reported human milk levels are included in Table 4.1. Dietary carotenoid intake appears to have an impact on milk carotenoid levels, as consumption of carotenoid-rich vegetables or supplements by lactating women increased milk levels of these nutrients. Plasma concentrations of lutein are significantly correlated with intake and are similar to the breastfed infant for select supplemental concentrations studied in infant formula.

A contemporary challenge facing many children today is the cumulative risk to ocular health from exposure to electronic devices with screens, such as smart phones or tablets that emit blue light. Data from a sample of individuals in developed countries born between the years of 1965 and 1996 show that an estimated 35% of this sample spends at least 9 hours a day on devices such as smartphones, tablets, and computers. An American Optometric Association (AOA) survey reports that 83% of children between the ages of 10 and 17 estimate that they use electronic devices 3 or more hours each day. A 2015 CHILDWISE Monitor survey conducted in the UK estimates that this number is actually much higher, at around 6 or more hours per day on screens and also highlights the concept of “multiscreening,” where children are viewing multiple screens at once without adequate breaks. Early behavioral and nutritional measures to ensure eye health will be important to combat later damage from such environmental stresses.

Few studies have quantitatively examined lutein intake in young children. Johnson and colleagues report that intakes for all age groups from 1 to 18 years were significantly less than all older age groups. The average lutein intake reported was 279±21 µg/day, which is quite low. Given the unique ability of lutein to accumulate in the retina and brain, such a low early intake may hold later consequences for age-related cognitive and visual abnormalities. Various nutritional products for children now contain added lutein, such as kids’ growing-up milk beverages and various dietary supplements.
4.7.2 LUTEIN AND VISUAL OR COGNITIVE HEALTH OF INFANTS AND CHILDREN

The benefit of lutein on visual and cognitive function in young people is difficult to detect due to the subject age and sensitivity of measurement. It is also somewhat difficult to detect improvement in such parameters in subjects already exhibiting normal or optimal visual and cognitive function, as is common in young people. However, several studies point to a benefit. MPOD measured in young children between the ages of 7 and 10 was positively and significantly associated with hippocampal-dependent memory performance.\(^{118}\) Using a modified test of inhibitory control paired with a neuroelectric measurement, Walk and colleagues report that MPOD in preadolescent children (mean age ~9 years) was associated with better performance on the behavioral task and neuroelectric indications of improved cognitive efficiency as exhibited by lower cognitive load.\(^{119}\)
4.7.3 **Lutein in Adulthood**

The National Health and Nutrition Examination Survey (2003–2004) indicates that, on average, American adults consume only about 1.5 mg of lutein per day. For reference, a 0.5-cup serving of spinach contains approximately 11 mg of lutein.9 Recommended dark green vegetable intake in the Dietary Guidelines for Americans 2015 are 0.5 cups per week for a 1000 kcal level and up to 2 cups per week on a 2200 kcal diet. Over the course of a week, then, if one were aiming to achieve the recommended intake of dark green vegetables through spinach alone, the lutein intake per day (at a 0.5–2.0 cups per week recommendation) would range from 1.6 to 6.3 mg/day. Thus, an average intake of 1.5 mg/day demonstrates that the average American diet appears woefully lacking in lutein.

Human adult brain carotenoid content reported by Craft and colleagues indicated that xanthophyll content exceeded carotene content, although \(\beta\)-cryptoxanthin was in the greatest concentration, regardless of region.94 Lutein tended to be higher in the frontal lobe compared with the occipital and was also higher in the gray matter than in the white matter. Additional and more recent evidence that lutein concentrates in brain tissue despite not being the major carotenoid in matched serum suggests preferential uptake of lutein in the brain.120 The content of lutein and zeaxanthin in the macula is significantly correlated with their levels in matched brain tissue, supporting that MPOD could be considered a biomarker of brain lutein concentrations, and related to the observation that MPOD is related to global cognitive function in adults.5,121,122 A larger study analyzing multiple regions determined that lutein was present in samples at higher concentrations than all other carotenoids, regardless of region.120 In adults, supplementation with both DHA and lutein significantly improved global cognitive function.123 Older adults with higher levels of MPOD are reported to have significantly better global cognition, verbal learning and fluency, recall, processing speed, and perceptual speed than those with lower levels.124 Supplementation with lutein and zeaxanthin in young healthy adults increased MPOD significantly over the course of a year and resulted in significant improvements in spatial memory, reasoning ability and complex attention, above and beyond improvements due to practice effects.125 In a unique study using neuroimaging to measure the relationship of lutein and zeaxanthin to brain structure in community-dwelling older adults, serum lutein and zeaxanthin and MPOD were related to brain white matter integrity, particularly in regions vulnerable to age-related decline.126

4.7.4 **Lutein and Visual Performance**

Visual perception and cognition are highly related.127 Both visual dysfunction and poor cognition can occur with increasing age, although the relationship between the two is not well defined. In a cross-sectional analysis of two national data sets, NHANES (1999–2002) and the National Health and Aging Trends Study (NHATS, 2011–2015), vision dysfunction at distance and based on self-reports was associated with poor cognitive function.128 This underlies the importance of visual function in the maintenance of cognition. Indeed, MPOD is related to a number of visual performance parameters.129,130 Lutein supplementation in cataract patients was associated with improvements in visual acuity and reductions in glare sensitivity after a 2-year supplement.33 Stringham and Hammond measured changes in photostress recovery and glare disability after supplementing young healthy subjects with 12 mg of lutein and zeaxanthin per day for 6 months. Supplementation led to direct improvements in glare disability and photostress.130 A detailed analysis of how MP improves visibility reports a likely reduction in the veiling effects of blue haze, leading to the potential to see about 30% farther through the atmosphere compared to someone with little or no MP.131

4.7.5 **Lutein and Alzheimer’s Disease**

The brain is particularly susceptible to oxidation due to its high metabolic activity, oxygen demand, and polyunsaturated fatty acid content.132 Indicators of both oxidative stress and low levels of antioxidants have been reported in Alzheimer’s disease patients,132,133 with demonstration that lutein can modulate
interactions of amyloid beta with healthy cells. Lutein has also been shown to modulate the toxicity of amyloid beta by blocking nuclear factor kappa B (NF-κB) expression and upregulating the protective NF-E2-related factor 2 (NRF2) pathway in cerebrovascular endothelial cells. Lutein is an effective antioxidant and scavenger of nitric oxide, a compound with known relationship to cognitive disease. Due to its local concentration in areas of the eye and brain that can reach very high metabolic demand, lutein seems optimally positioned to exert a protective antioxidant effect in the brain. Min and colleagues have reported that high serum levels of lutein and zeaxanthin are associated with a lower risk of Alzheimer’s disease mortality in adults, suggesting that dietary intake of these xanthophylls may be an important and simple lifestyle habit for reducing mortality risk.

### 4.7.6 Age-Related Macular Degeneration

Age-related macular degeneration is the leading cause of blindness in the United States in the population over the age of 40; however, the incidence of AMD has declined in recent years. As reviewed by Mares, lutein and zeaxanthin intake are associated with a lower risk of developing AMD, presumably by reinforcing the concentrations of lutein and zeaxanthin in the macular pigment; however, there are other proposed mechanisms by which lutein and zeaxanthin modulate ocular diseases. Two large randomized controlled trial (RCT) intervention trials supported by the National Eye Institute, AREDS and AREDS2, investigated the effect of supplementation of select vitamins, minerals, and fatty acids on the development and progression of AMD. The original AREDS intervention used four different supplements containing (1) zinc, (2) antioxidants: Vitamins C, E, and beta-carotene, (3) zinc + antioxidants, or (4) placebo. The supplement containing the combined zinc and antioxidants yielded a significant OR of 0.72 for progression to advanced AMD compared to placebo. Following the relative success of the first AREDS trial, a second trial was undertaken to improve safety and efficacy of the zinc + antioxidants supplement. The AREDS2 trial included interventions that substituted lutein + zeaxanthin for beta-carotene and supplements including fish oil containing DHA and EPA. Although there was no statistical improvement in reducing further progression of AMD with any of the AREDS2 supplements compared to the original AREDS supplements, secondary analyses of the cohort revealed that subjects given lutein + zeaxanthin had a significant reduction in progression to advanced AMD (HR = 0.87, p = 0.04), demonstrating the AREDS2 supplement was an appropriate alternative to the original AREDS supplement in individuals with concerns about beta-carotene (smokers).

### 4.7.7 Cataract

Another leading cause of blindness globally is cataract. Cataract is a disease that clouds the lens and eventually blocks light from entering the eye. Cataract is successfully managed and treated with surgery; however, prevention of cataract development in both developed and developing countries would be far more cost effective. There is evidence to suggest a beneficial role of lutein and zeaxanthin in the protection against cataract development to help protect against oxidative damage to the lens. Recent evidence also suggests the effectiveness of lutein supplementation on cataract development was better in males compared to females.

### 4.8 SUMMARY

Lutein is an important nutrient for human health. It is a dihydroxy carotenoid with important functions in both plants and humans that center around its ability to absorb light and provide antioxidant protection. Novel roles for lutein include its ability to regulate gene expression and modulate cell membrane dynamics. Lutein specifically accumulates in the human macula and gives this structure its characteristic yellow pigmentation. It is this specific accumulation that makes lutein a promising nutrient for prevention and/or treatment of the age-related disease AMD.
evidence shows that lutein also accumulates in the brain, and more research is needed to determine the exact role it plays in this organ. Lutein is absorbed from the diet and is transferred to specific tissues by plasma lipoproteins and specific binding proteins. Many studies have established that the MP is related to dietary and plasma lutein levels, with higher intakes leading to higher pigment density. Lutein levels from a variety of regulatory bodies do not raise concern about the safety of lutein in various products. Studies in non-human primates have given us a unique understanding of the consequences of a diet lacking or devoid in xanthophylls. Such diets lead to lack of development of MP and disturbances in retinal development and function. While the relationship among eye function, MPOD, and plasma lutein is still a complex one, a case can be made that the average Westernized diet is low in lutein. The consequences of this modest intake may be more deleterious than previously thought, especially given the lifestyle changes in recent generations that include increased reliance on blue light–emitting devices. Although there is no requirement for lutein and no nutritional reference value or dietary recommendation has been established, the available data demonstrate that lutein may offer long-term benefits on neural function and development. Thus, its incorporation into a healthy diet is encouraged.

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