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LIPIDES ET CERVEAU

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Why lutein is important for the eye and the brain

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Abstract – Lutein and zeaxanthin are carotenoids that accumulate in the macula. The macula is a yellow spot near the center of the retina that is responsible of high resolution vision. Macular pigment acts as a natural blue light filter and protects the eye from damage. Macular pigment optical density (MPOD) increases with lutein administration and is related to visual function and to the prevention of age-related macular degeneration. MOPD can be measured non-invasively and has been related to better cognitive performance. Moreover, compositional analyses of centenarian brains have shown that lutein is the main carotenoid in the brain although not in plasma, indicating a preferential accumulation in neural tissues, and that carotenoids status is correlated with some functional outcomes. Carotenoids are present in human milk with higher concentration in colostrum than in transitional and mature milk. Formula fed-infants have less plasma lutein concentration than breast fed infants. Analyses of brain from infants who died during the first year of life showed that lutein is also the predominant carotenoid of brain. Studies in non-human primates revealed that carotenoids are determinant in the formation of the retinal epithelia. *In vitro* studies showed that lutein stimulates the differentiation of human stem cells to neural progenitor cells. All this findings together, mostly the presence of lutein in breast milk, plasma concentration in breast-fed infants *vs*. formula fed infants, preferential accumulation in the brain and evidences of influence on the retina and the functionality of the brain signal the importance of the role of lutein and zeaxanthin on visual maturation and brain development.

Keywords: Lutein / zeaxanthin / brain / infant / nutrition

Résumé – Importance de la lutéine pour l'œil et le cerveau. La lutéine et la zéaxanthine sont des caroténoïdes qui s'accumulent dans la macula. La macula est une tache jaune, située près du centre de la rétine, qui est responsable de la vision fine. Le pigment maculaire agit comme un filtre naturel de la lumière bleue nocive et protège l'œil contre d'éventuels dommages. La densité optique du pigment maculaire (ou MPOD, acronyme de *Macular pigment optical density*) augmente avec l'administration de lutéine et est liée à la qualité de la fonction visuelle et à la prévention de la dégénérescence maculaire liée à l'âge. La MOPD peut être mesurée de manière non invasive et a été associée à de meilleures performances cognitives. En outre, les analyses de composition de cerveaux de centenaires ont montré que la lutéine est le caroténoïde principal du cerveau mais pas du plasma, ce qui indique une accumulation préférentielle dans les tissus neuronaux et que le statut en caroténoïdes est corrélé avec quelques données fonctionnelles. Les caroténoïdes sont présents dans le lait maternel avec une concentration plus élevée dans le colostrum que dans lait de transition ou mature. Les enfants nourris avec des formules infantiles (végétales) présentent des diminutions de concentrations plasmatiques en lutéine comparativement aux valeurs observées à la naissance ainsi qu'à celles d'enfants nourris au lait maternel qui à l'inverse, sont augmentées. Les analyses de cerveau de nourrissons décédés au cours de leur première année de vie ont montré que la lutéine est également le caroténoïde prédominant du cerveau. Des études menées chez des primates non-humains ont démontré que les caroténoïdes sont déterminants dans la formation de l'épithélium de la rétine. Des études *in vitro* ont également montré que la lutéine stimule la différenciation de cellules souches humaines en cellules précurseurs neurales. L'ensemble de ces résultats – et surtout la présence de lutéine dans le lait maternel, les concentrations plasmatiques élevées chez les nourrissons allaités *vs.* enfants nourris au biberon, l'accumulation préférentielle dans le cerveau et les preuves de l'influence sur la rétine et la fonction cérébrale convergent pour souligner l'importance du rôle de la lutéine et de la zéaxanthine dans la maturation visuelle et le développement cérébral.

Mots clés : Lutéine / zéaxanthine / cerveau / nourrisson / nutrition

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1 Introduction

Carotenoids are a class of naturally occurring pigments that are synthesized by plants and produce the red, orange, and yellow colors of fruits and vegetables.

Carotenoids share a 40 carbon atom backbone and are classified into two subclasses depending on the presence of oxygen in the molecule: xanthophylls (lutein, zeaxanthin ($C_{40}H_{56}O_2$), and β-cryptoxanthin ($C_{40}H_{56}O$) and carotenes (α-carotene, β-carotene, and lycopene ($C_{40}H_{56}$)) (see Fig. 1 in Krinsky and Johnson, 2005). The structure of zeaxanthin derives from β-carotene ((3R,3′R)-β,β-carotene-3,3′-diol. A shift of one double bond in one ionone ring system leads to the structure of lutein ((3R,3′R,6′R)-β,ε-carotene-3,3′-diol) (Dachtler *et al.*, 2001).

They are found in green leafy vegetables and brightly colored fruits. Green vegetables have the highest concentration of lutein particularly kale, spinach parsley, and collards (Alisa Perry and Johnson, 2009; Humphries and Khachik, 2003). Yellow-orange vegetables and fruits are less enriched in xanthophylls and some of them may contain both lutein and zeaxanthin at a ratio close to 1 (Humphries and Khachik, 2003). Some foods increase the amount of carotenoids after cooking. In fact, compared to raw spinach, cooked spinach contained considerably more carotenoids (Alisa Perry and Johnson, 2009). Egg yolk contains lower concentration of xanthophylls than green vegetables but with a higher bioavailability and equal concentrations of lutein and zeaxanthin (Alisa Perry and Johnson, 2009).

From the more than 750 carotenoids in nature, there are only about 40 present in the typical human diet, of which only 20 are found in blood, and from all of them only two accumulate specifically in the retina (Widomska and Subczynski, 2014) and just five in the brain (Johnson *et al.*, 2013; Vishwanathan *et al.*, 2014b). There seems to be a bioselection process of carotenoids.

The absorption of carotenoid like other lipophilic substances is not an easy process. It occurs through the classical pathway of lipid-soluble compounds through the lymph and lipoprotein distribution. A few features of carotenoid absorption process are: (1) mucosal uptake occurs by passive diffusion at pharmacological doses but at dietary doses the preferential route is mediated by cholesterol transporters (Borel, 2012), (2) HDL play an important role in the transport to the retina (Connor *et al.*, 2007) (3) several proteins are involved in carotenoid metabolism in humans, namely carotene oxygenases β,β-carotene-15,15′-monooxygenase (BCMO1) and β,β-carotene-9′,10′-oxygenase (BCDO2), which are involved in carotenoid cleavage; scavenger receptor class B type I (SR-BI), cluster determinant 36 (CD36), and Niemann Pick C1-like 1 (NPC1L1), which are involved in carotenoid uptake by cells; and glutathione S-transferase Pi 1 (GSTP1) and human retinal lutein-binding protein (HR-LBP), which are involved in the transport of xanthophylls in the retina (Borel, 2012). The different nucleotide polymorphisms exhibited by those enzymes condition interindividual differences on the carotenoid metabolism and explain the variability of carotenoid concentration in blood and tissues.

2 What is the function of carotenoids in the eye?

Carotenoids accumulate in the macula. The macula is a yellow spot of about 5 millimetres diameter near the centre of the retina. In its centre is the fovea, a small pit that contains the largest concentration of cone cells in the eye which is responsible for central, high resolution vision. When you look directly at something, the centre part of the image falls on the fovea.

The macular pigment (MP) is composed principally of three isomeric carotenoids, lutein, zeaxanthin, and meso-zeaxanthin. They represent roughly 36, 18, and 18% of the total carotenoid content of the retina. Meso-zeaxanthin, an stereoisomer of zeaxanthin, is not present in the diet or in the blood and it is supposed to be produced from lutein in the retina. Those compounds are not homogenously distributed within the macula: lutein/zeaxanthin ratio reaches a minimum in the central macula where meso-zeaxanthin reaches its highest levels which is approximately 50% of the total zeaxanthin present (Landrum and Bone, 2001).

MPOD has been related to a number of visual performance parameters. Namely, MP acts as a natural blue light filter that protects the eye from oxidative damage (Snodderly, 1995). It is also capable of enhancing contrast by adding luminance contrast information to an edge (Liu *et al.*, 2015; Renzi and Hammond, 2010a). It has been related to visual performance and temporal vision (Renzi and Hammond, 2010b) and it is strongly related to improvements in glare disability and photo stress recovery (Stringham and Hammond, 2007).

MPOD can be measured non-invasively by using heterochromatic flicker photometry which is the most widely used MPOD measurement to date and has been validated in elderly subjects. By using this technique, it has been shown that serum lutein response and MPOD response were linearly correlated with lutein doses in healthy subjects (Bone and Landrum, 2010).

Age-related macular degeneration (AMD) is the leading cause of irreversible visual dysfunction in individuals over 65 in Western Societies and it is a multifactorial and complex disease. Early AMD is characterized by a deterioration of the retina that is associated with extracellular deposits forming yellow spots (drusen) and or irregular focal hypopigmentation or hyperpigmentation. The aging retina gradually accumulates fluorescent phototoxic chromophores, generally known as lipofuscin, which leads to apoptosis of retinal pigment epithelial (RPE) cells and the formation of drusen. These changes in turn lead to RPE cellular dysfunction and eventually result in the loss of central vision (Gehrs *et al.*, 2006).

Some epidemiological studies suggest that higher consumption of lutein and zeaxanthin is associated with lower risk of AMD (Whitehead *et al.*, 2006). A recent meta-analysis including 8 randomized clinical trials involving 1176 AMD patients concluded that lutein and zeaxanthin supplementation was a safe strategy to improve visual performance of AMD patients (Liu *et al.*, 2015). In fact, the study by Ma *et al.* (2012) showed that electroretinogram responses increased after lutein supplementation alone or lutein + zeaxanthin supplementation for up to 6 or 12 months in early AMD patients.

Two recent papers have adressed the question why only human and primates acumulate lutein in the retina (Li *et al*., 2014; Widomska and Subczynski, 2014). The first one discovered that the enzyme BCO2, also known as BCDO2, the only known mammalian xanthophyll cleavage enzyme, is expressed in both mouse and primate retinas, but that the primate enzyme is not able to cleavage xanthophyll carotenoids (Li *et al*., 2014). The second paper is a review that indicates the specific properties of macular xanthophylls that could help explain their selective accumulation in the primate retina, namely: (1) high membrane solubility than other carotenoids, (2) transmembrane orientation that enhances their stability in retina membranes, and maximizes their protective action in the eye, (3) location in the most vulnerable regions of photoreceptor outer segment membranes, which play a significant role in enhancing protection of retina against oxidative damage, and (4) high chemical stability (Widomska and Subczynski, 2014).

3 Lutein and zeaxanthin: the function in the brain

The study by Vishwanathan *et al*. in non-human primates was the first to report that lutein and zeaxanthin in the macular region of the retina are related to brain lutein and zeaxanthin levels. This association was found in the occipital cortex, the primary visual processing area of the brain, in the cerebellum, which is crucial for motor control and some types of learning, and in the pons, a region not associated with visual processing or cognitive function. A significant relationship was found after bivariate analysis that was maintained after adjustment by sex and age, and by sex, age and n-3 fatty acid status. This association also existed in the frontal frontal cortex, which is responsible for several aspects of higher cognitive function, although was only significant after adjusment of the three factors (Vishwanathan *et al*., 2013).

There have been a number of articles linking lutein in neural tissues to better cognitive performance. Johnson *et al.* performed a small clinical trial in 60–80 year-old women that were randomized to receive DHA (800 mg/day), lutein (12 mg/day), or a combination of DHA and lutein. Each treatment alone or in combination improved performance in a Verbal fluency test and only the combination of lutein and DHA improved performance in other tests such as Word list, Shopping list and MIR apartment tests sugesting a potential synergistic effect of both nutrients (Johnson *et al*., 2008).

Of note is the Georgia Centenarian Study, a population-based multidisciplinary study conducted in 44 counties in northern Georgia (USA) from 2001 to 2009. It was designed to identify and isolate longevity genes, neuropathology, functional capacity, and adaptational characteristics of centenarians. It represents a unique opportunity to link cognitive findings with compositional analyses of the brain in humans. We can realize that while β-carotene was the major carotenoid in serum, lutein and zeaxanthin account for almost 50% of carotenoids in the brain. If serum represents the actual intake, this means that there is a preferential uptake of lutein and zeaxanthin in the brain as it happens in the retina (Johnson *et al*., 2013). Moreover, total carotenoids content was inversely associated to a global cognitive deterioration scale (Johnson *et al*., 2013) and particularly lutein and/or zeaxanthin levels in several areas of the brain, such as temporal, occipital, and frontal cortices as well as cerebellum were correlated to different cognition measures such as retention, global cognition or intelligence quotient (Johnson, 2012).

Other studies have correlated MOPD with cognitive outcomes in aging. Fenney *et al*. studied the relationship between MP and cognitive function in 4453 adults aged $\geqslant$ 50 years as part of the Irish Longitudinal Study on Aging. Lower MPOD was associated with poorer performance on the mini-mental state examination and on the Montreal cognitive assessment. Individuals with lower MPOD also had poorer prospective memory, took longer time to complete a trail-making task, and had slower and more variable reaction times on a choice reaction time task (Feeney *et al*., 2013). MPOD levels were significantly associated with better global cognition, verbal learning and fluency, recall, processing speed and perceptual speed in older adults from the age-related maculopathy ancillary study of the Health Aging and Body Composition Study (Vishwanathan *et al*., 2014a). Finally, in subjects with mild cognitive impairment, MPOD was related to cognition including the composite score on the mini-mental state examination, visual-spatial and constructional abilities, language ability, attention, and the total scale on the repeatable battery for the assessment of neuropsychological status (Renzi *et al*., 2014).

4 The role of lutein on infant nutrition

According to Horton *et al.* and in contrast to the carotenoid composition of plasma in other studies, where β-carotene was the most abundant, lutein + zeaxanthin and beta-cryptoxanthin were the major carotenoid in maternal plasma during gestation. The concentration of total carotenoid in mother plasma tended to increase during gestation, and after birth, carotenoid in cord plasma decreased sharply (Horton *et al*., 2013).

Although the fovea started to develop in the utero, it begins postnatal life at a relatively immature stage and develops more rapidly after birth. In fact, the future fovea is identifiable at 22 weeks of gestation and 1 week after birth, there is only a shallow foveal depression (Hendrickson and Yuodelis, 1984). Both pigments lutein and zeaxhanthin were detected in prenatal eyes (approximately at 20 weeks of gestation) but did not form a visible yellow spot. Generally they were not easily discernible until about 6 months after birth (Bone *et al*., 1988) but the human fovea reaches maturity between 15 and 45 months of age (Hendrickson and Yuodelis, 1984). However, cone density probably increases further with age until 13 years of age (Hendrickson, 1992). Moreover, lutein and zeaxanthin are transfer from vitreous to retina and lens during fetal development (Panova *et al*., 2007). The lutein/zeaxanthin ratio change with age being lutein the predominant in infants and zeaxanthin the predominant in adults (Bone *et al*., 1988).

Carotenoids are present in human milk with higher concentration in colostrum than in transitional and mature milk. The most important ones are β-carotene and lycopene. Lutein concentrations in human milk range from approximately 3–237 mg/L (Bettler *et al*., 2010; Canfield *et al*., 2003; Jewell *et al*., 2004; Tacken *et al*., 2009). Taken together lutein and zeaxanthin account for 28% of total (Song *et al*., 2012).

In colostrum the carotenoid pattern resembled those of plasma and the low-density lipoprotein fraction. In mature milk it was similar to the pattern found in the high density lipoprotein fraction. Based on these observations a selective mechanism might be responsible for the transfer of these components in milk involving different lipoprotein fractions at specific times of lactation (Schweigert *et al*., 2004).

At birth, infants might have around 50 μg/L of lutein and zeaxanthin in plasma. After one month of formula feeding the level decreased while in breast-fed infant increased (Bettler *et al*., 2010).

With regards to the level of carotenoids in the brain, there was an interesting study by Vishwanathan *et al*. (2014b) that provided the first data on the distribution of carotenoids in the infant brain and compare concentrations in preterm and term infant. The study was done on pre-existing voluntarily donated samples that were obtained from a federally-funded brain tissue bank. Brain tissue samples were from healthy infants who died during the first year of life from SIDS (sudden infant death symdrome) or other conditions. There were 30 subjects, 22 term and 8 preterms. The results showed that the major carotenoids detected in the infant brain were lutein (0–181.7 pmol/g), zeaxanthin (0–33.94 pmol/g), cryptoxanthin (0–35.29 pmol/g), and β-carotene (0–88.19 pmol/g). Lutein was the predominant carotenoid in all the brain areas evaluated being the higher content in auditory and occipital cortex. Infants born preterm had significantly lower concentrations of lutein and zeaxanthin compared with term infants in most of the brain regions analyzed. If on average the total content of carotenoids in term infants was between 50–60 pmol/g, in preterm infant was about 20 pmol/g, sugesting a potential deficiency in infant born before term.

Moreover, if the average of the 5 regions is considered, lutein account for more than 59% of total carotenoids in the brain, followed by β-carotene (16%), zeaxanthin (13%), β-criptoxanthin (7%), and lycopene (5%). If this distribution is compared to the dietary intake pattern, which predominantly was enriched in β-carotene (43%) and lycopene (23%), according to the National Health and Nutrition Examination Survey (NHANES, 1988–1994), it seems that there is a preferential accumulation of xanthophylls on the brain likely due to their chemical properties mentioned above (Widomska and Subczynski, 2014). If the percentual composition of carotenoids in infant brains is compared to that found in the Georgia centenarian study, the percentage of lutein decreases with age (from 59 to 34%).

5 Is there a translation to functionality?

There have been a number of clinical studies testing lutein supplementation in infants. One of them dealed with serum concentration of lutein supplemented infants in comparison to breast fed infants (Bettler *et al*., 2010). Another one was focus on the supplementation of the mother throught lactation and how it affected breast milk levels and maternal and infant plasma levels (Sherry *et al*., 2014). Capeding *et al.* addressed safety, tolerance and growth (Capeding *et al*., 2010). There have been three papers suggesting a potential influence of lutein supplementation on the prevention on the retinopathy of prematurity (Dani *et al*., 2012; Manzoni *et al*., 2013; Romagnoli *et al*., 2011). The first one did not showed any effect of lutein/zeaxanthin supplementation. The second one found lower incidence of necrotizong enterocholitis, bronchopulmonary dysplasia and retinopathy of prematurity (ROP) in the carotenoid supplemented group although the differences did not reach statistical significance. Noteworthy, the progression rate from early ROP stages to threshold ROP was decreased by 50%. Romagnoli *et al*. did not find conclusive results but pointed out that supplementation with antioxidant substances might have beneficial effects noticeable only on larger samples of high risk neonates or at very high dosages.

The study by Henriksen *et al.* showed that infant serum zeaxanthin levels but not lutein correlated with MPOD and that mother serum zeaxanthin levels correlated with infant MPOD (Henriksen *et al*., 2013). A randomized controlled multicenter study in preterm infants fed diets with and without added lutein, lycopene and beta-carotene showed that supplemented infants had lower plasma C-reactive protein pointing out that carotenoid supplementation may decrease inflammation. Moreover, the supplemented group showed greater rod photoreceptor sensitivity and plasma lutein levels correlated with full field electroretinogram-saturated response amplitude in rod photoreceptors suggesting protective effects of lutein on the health and maturation of preterm retina (Rubin *et al*., 2011). There was another study in which infants were supplemented at birth with only two doses of lutein (0.28 mg) within 6 h after birth and at 36 h of life and the generation of free radical-induced damage at birth was reduced by lutein (Perrone *et al*., 2014).

Despite those studies showing a beneficial effect on different outcomes after birth, so far there have not been any randomized clinical trials testing the effect of lutein supplementation on cognitive development in infants. There was only one showing that an intervention with lutein and zeaxanthin increased temporal processing speed in young healthy subjects (18–32 years) showing that carotenoid supplementation not only prevents diseases but it also optimizes function throughout life (Bovier and Hammond, 2014). Nonetheless, the potential role of lutein on the functionality of the brain during this stage of life comes from indirect evidences. For instance, lutein has also been shown to enhance gap junctional communication (Stahl and Sies, 2001), which may be important for the development of the brain and visual proceesing (Johnson, 2014).

Recently, our group has shown that lutein was able to stimulate the differentiation of human stem cells into neural cells in vitro simulating the process of brain development and maturation (Kuchan *et al*., 2013). In particular, treatment of human stem cells with lutein (1 μM) alone for 6–9 days resulted in increased SOX1 and PAX6 expression compared with vehicle (3.8- and 3.1-fold, respectively). PAX6 and SOX1 are neuroepithelial transcription factors and well-accepted protein markers for neural progenitor cells. PAX6 (paired-box protein) is a transcription factor that acts at the molecular level in the signaling and formation of the central nervous system (Manuel *et al*., 2015). SOX1 (sex-determining region Y-box 1) is another transcription factor involved in the early central nervous

system development and maintenance of neural progenitor cells identity (Pevny *et al*., 1998).

6 Conclusions and final remarks

It seems like the research around the influence of xanthophylls, particularly lutein, follows a paralelism with the research supporting the foundation for the addition of docosahexaenoic acid (DHA) to infant formulas. Firstly, in the eighties it was extensively described that DHA was present in human milk (Harris *et al*., 1984). Concomitantly, the importance of this fatty acid for the retina and the brain was also shown (Connor and Neuringer, 1988; Connor *et al*., 1990). As it happens with lutein, it was reported that plasma DHA levels of formula fed infants were lower than breast-fed infants (Innis *et al*., 1997) and thereafter in postmortem analyses, that formula fed infants had lowers level of DHA in the brain (Farquharson *et al*., 1995). Currently, there are many evidences of the role of DHA on the retina and on the brain at molecular and signaling levels (Bazan *et al*., 2011). Despite this, there are two differences: on the one hand, there is always some DHA in tissues however it was reported that a few infants had no detectable levels of carotenoids (Vishwanathan *et al*., 2014b). On the other hand, DHA can be synthetized from alpha-linolenic acid while lutein can not be synthetized and must be taken with the diet.

All these scientific evidences and reasoning point out a potential conditionally essential role of lutein in infant nutrition and may support its inclusion on infant formula composition.

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