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Review

Lutein as protective agent against neonatal oxidative stress

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Abstract

Free radicals (FR) are important for a correct development of neonatal organs and tissues. However, newborn and fetus have profoundly impaired antioxidant system. In these subjects, oxidative stress (OS) may be detrimental by activating deleterious cellular processes. Decreasing FR and restoring oxidative imbalance certainly appear to be beneficial in perinatal period. Among the therapeutic antioxidant approaches in newborns, lutein, a compound belonging to the xanthophyll family of carotenoids, is one of the emerging strategies. Humans cannot synthesize lutein, hence the intake primarily depends on diet. In the neonatal period, fresh, non-processed human milk is the main dietary source of lutein, while infant formula is lacking it. Lutein has antioxidant and anti-inflammatory properties.

Lutein supplementation in human newborns during the first days of life has been demonstrated to decrease plasma biomarkers of OS and increase antioxidant capacities. Numerous experimental study have demonstrated that lutein effectively neutralizes oxidants and modulates inflammatory processes, showing particular protective effects on macula and photoreceptors against phototoxicity and oxidative injury. Only few clinical studies evaluated the effectiveness of lutein in reducing preterm and term infant morbidity, reporting no definitive results. The challenge for the future is to better clarify the timing, the optimal dose and the duration of lutein intervention in perinatal period and to verify its impact on infants' health.

Keywords

Lutein, oxidative stress, antioxidant, free radicals, inflammation, newborn infant.

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Introduction

During fetal period, a balance between the levels of oxidants and antioxidants is essential for survival and growth of the embryo and fetus. Thus free radicals (FR) production is of pivotal importance for a correct development of neonatal organs and tissues. The overproduction of FR and the deficiency of antioxidant mechanisms result in oxidative stress (OS), a deleterious process and important mechanism of cellular damage. The newborn and particularly the fetus are highly prone to OS because of their organs' structural and functional immaturity, the overloading of aerobic metabolism with rapidly growing energy demand, and conditions leading to an increase in free iron levels with excessive FR production (i.e. chorioamnionitis or placental hypoperfusion, neonatal hypoxia or inflammation, blood transfusions). Moreover, neonatal plasma has profoundly disturbed antioxidant profiles with low levels of gluthatione peroxidase activity, superoxide dismutase, β-carotene, riboflavin, α-proteinase, vitamin E, selenium, copper, zinc, caeruloplasmin, transferrin and other plasma factors [1]. The impairment in the oxidative balance has been thought to be the common link among different neonatal diseases grouped together as "free radical disease of the neonate", including retinopathy of prematurity (ROP), bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy (HIE), renal failure, and necrotizing enterocolitis [2].

Several evidences correlated free radical diseases of the newborn to OS caused by the harmful effect of FR on developing tissues [3-7]. FR are very unstable molecules due to the presence of one or more unpaired electrons, and they react with other molecules through reactions of oxidation-reduction, donating or receiving electrons, in order to reach chemical stability. Considering the growing role of OS in preterm newborn morbidity, one of the goals of the modern neonatology is to minimize FR production or promote the development of adequate antioxidant systems.

Vitamins, oxygen-free radical inhibitors and scavengers have been used as antioxidant drugs in clinical and experimental approaches to reduce OS in free radical related neonatal diseases, with still uncertain results. Decreasing FR and restoring oxidative imbalance certainly appear to be beneficial in response to hypoxia, reperfusion, inflammation, but to date studies have not adequately addressed the consequences of altering oxidative or immune balance when OS is not present. The administration of antioxidants when OS is suspected is not yet ready to enter clinical practice. The challenge for the future is to better clarify the benefits and risks of antioxidant intervention strategies and to verify their impact on infants' health.

Among the therapeutic antioxidant approaches, lutein, a compound belonging to the xanthophyll family of carotenoids, is one of the emerging strategies applied in newborns. Xanthophyll biosynthesis only takes place in plants, algae, bacteria and certain fungi [8]. Humans cannot synthesize lutein hence the intake primarily depends on diet [9], i.e. eggs, dark green leafy vegetables, such as kale and spinach [10, 11]. Particularly, in the neonatal period, fresh, non-processed human milk is the main dietary source of lutein and zeaxanthin, its stereoisomer [12, 13], while infant formula is lacking it.

Neonatal lutein supplementation has been demonstrated to decrease plasma biomarkers of OS and increase antioxidant capacities in the first days of life in human newborns [14, 15].

Lutein biochemistry

Lutein ($C_{40}H_{56}O_2$) is one of the approximately 700 carotenoids isolated and identified in nature, with in excess of 40 found in fruits and vegetables [16, 17]. Despite this, only 14 of these dietary carotenoids may be absorbed, modified, and/or used by the human body [18] and yet lutein is found at the macula, reflecting an exquisite degree of biological selectivity.

The biochemical structure of lutein contains 40 carbon atoms, hence known as tetraterpenoids, with alternating single and double carbon-carbon bonds with attached methyl side groups. At both ends of the conjugated polyene chain, the molecule contains a cyclic hexenyl structure with an attached hydroxyl group responsible for the high chemical reactivity.

This electron-rich system makes the molecule reacting more easily with singlet oxygen than other carotenoids [19-21] and neutralizing reactive oxygen species [22]. The most striking characteristic is p-electrons which efficiently delocalized over the entire length of the polyene chain. Upon oxidation the resultant lutein degradation products have the polyene chain with a varied length and end group such as aldehyde, ketone, etc., which might render these products as highly reactive compounds [23]. Such products have been identified in the human as well as the monkey retina [24].

The presence of a hydroxyl group at both ends of the molecule distinguishes lutein and zeaxanthin from other carotenoids. The characteristic structure with nine double bonds is responsible for the absorbance of certain wavelengths of light and the emission of other wavelengths, leading to the characteristic chromatic properties of these molecules. The yellow color of lutein is directly linked to its structure and as a result gives yellow color to egg yolk, animal fat and human eye retinal macula.

Lutein actions and experimental studies

The *macula lutea* is located in the central and posterior portion of the primate retina and it possesses the highest concentration of photoreceptors, which are responsible for central vision and high-resolution visual acuity. It is a circular area 5-6 mm in diameter, that possesses a characteristic yellow pigment, that is made up entirely of lutein and zeaxanthin. The presence of carotenoids in the macula capable of absorbing light of the blue range wavelength may protect against light-induced retinal damage. Specifically, lutein appears to play a specific role as a photoprotective agent, effectively screening out the damaging blue light from causing excessive damage on the photoreceptors [25]. Moreover, lutein is known to be one of the major antioxidant molecule in the retina, acting as an oxygen free radical scavenger during OS conditions. It prevents the accumulation of oxygen radicals and lipid peroxidation, resulting from increased retinal oxygen utilization which is responsible for photoreceptor apoptosis [25].

Retinal ischemia is a common feature in ischemic retinopathy such as diabetic retinopathy and ROP. In both ocular diseases, there is initially an impairment in the normal retinal blood supply while the subsequent formation of abnormal new blood vessels (retinal neovascularization) further worsens the condition. The presence of ischemia and consequently OS makes the already vulnerable retina more susceptible to oxidative damage [26]. Lutein has been shown to be able to block paraquat and hydrogen peroxide-induced apoptosis in cultured retina photoreceptors promoting photoreceptor survival and differentiation [27]. The lipid-soluble carotenoids zeaxanthin and lutein are demonstrated to be potential sources of protection against the photooxidation of A2-PE [28]. A2-PE is deposited in retinal pigment epithelial (RPE) cells secondary to phagocytosis of shed outer segment membrane and it can initiate photochemical processes leading to the formation of reactive moieties. Moreover, lutein modulates inflammatory responses in cultured RPE cells in response to photooxidation, protecting the proteasome from oxidative inactivation [29]. In a model of lipopolysaccharide (LPS) stimulated macrophages, it has been found that intracellular lutein can reduce the intracellular H_2O_2 accumulation by scavenging H_2O_2 and superoxide anion [30].

Lutein inhibits arachidonic acid release from a macrophage cell line, blocking cytosolic phospholipase A2 activity [31]. Intracellular FR production induced by platelet-derived growth factor (PDGF) is limited by lutein, which may also lower the concentration of H_2O_2-induced PDGF-receptor signaling, through an oxidative inhibition of protein tyrosine phosphatase [32]. Consequently, FR-induced ERK1/2 and p38 MAPK activation is attenuated.

Supplementation with lutein increases reduced glutathione (GSH) levels and reduced/oxidized GSH ratio (GSH/GSSG), particularly in response to OS [33]. Supplementation with lutein decreases vascular endothelial growth factor expression in the retinas of mice [34]. Lutein significantly elevates the ratio of GSH/GSSG as well as activities of superoxide dismutase, GSH peroxidase, and catalase and decreases malondialdehyde, brain carbonyl, the expression of oxidated proteins, the number of apoptotic cells, and neurological deficit scores in mice undergoing transient cerebral ischemic injury [35].

Lutein contributes to the prevention of early atherosclerosis development by reducing cholesterol accumulation and features of atherosclerosis in aorta. Further, lutein attenuates the inflammatory state in aorta by decreasing malondialdehyde and oxidized low density lipoprotein levels and reducing inflammatory cytokines such as interleukin (IL)-10 [36].

Lutein inhibits the expression of inflammatory genes through suppression of nuclear factor

NF-kappa-B (NF-κB) nuclear translocation and reveals an anti-inflammatory effect in peritoneal macrophages by reducing LPS-induced secretion of tumor necrosis factor (TNF)-α and IL-1β [30]. Similar findings are observed using *in vitro* model of gastric epithelial cells [37].

Lutein blocks the degradation of inhibitory kB-a from the cytosolic fraction and prevents NF-kB translocation in rat model of endotoxin-induced uveitis [38].

Lutein significantly reduces several skin inflammatory responses, including increased expression of IL-6 from LPS-treated macrophages, up-regulation of cyclooxygenase (COX)-2 and the enhancement of matrix-metallopeptidase (MMP)-9 level in ultra violet-irradiated keratinocytes [39].

Lutein and the newborn

Several reports correlated ROP to OS on ocular tissues [40-43]. ROP is an ocular disease characterized by vascular abnormalities induced by two phases of pathological changes. The first phase starts when premature infants are exposed to high oxygen inside the incubator soon after birth: the relative hyperoxic environment leads to the downregulation of vascular endothelial growth factor with the cessation of retinal vessel growth. After the cessation of oxygen therapy, infants are returned to normal oxygen tension and a condition of relative hypoxia occurs. Therefore, the relatively hypoxic condition of the retina triggers the abnormal proliferation of vessels and leads to neovascularization, the second phase of ROP progression [44]. As consequence, a great deal of interest has been focused on the protective role of lutein as antioxidant compound [45].

At now few data are available about the effects of lutein supplementation in newborns. It has been suggested but not experimentally verified that dietary lutein enhances visual development in infants [46-49]. Few studies evaluated the effectiveness of lutein in reducing preterm and term infant morbidity with no definitive results [50-52]. Manzoni et al. found that lutein supplementation in very low birth weight infants, even if well tolerated, did not decrease the incidence of ROP [50]. Dani et al. also demonstrated the inefficacy of lutein supplementation in preventing ROP in preterm infants [51]. Romagnoli et al. showed that lutein was not able to reduce the occurrence and severity of ROP in a cohort of preterm infants [52]. Among papers encompassing the effects of lutein supplementation on OS, Costa et al. found that total antioxidant status did not result statistically different between lutein-supplemented group and placebo group, even if a significant linear correlation was evidenced between plasma lutein concentration and total antioxidant status [53]. A pilot randomized control trial in healthy newborns reported that lutein administration was effective in increasing the levels of biological antioxidant potential by decreasing the total hydroperoxides (TH) as markers of OS [14]. The ability to enhance biological antioxidant potential and reduce lipid peroxidation in term newborns were also demonstrated in a randomized double-blind prospective clinical study [15].

Conclusions

The newborn, especially if preterm, is highly prone to OS and to the toxic effects of FR. At birth, the neonate is exposed to a relatively hyperoxic environment caused by an increased oxygen bioavailability with enhanced generation of FR. Additional sources (inflammation, hypoxia, ischemia and free iron release) occur as well as higher OS. The propensity of oxidative cellular injury in newborn babies relates not only to several pro-oxidant characteristics but also to deficient antioxidant defenses. Considering the growing role of OS in preterm newborn morbidity with respect to the higher risk of FR damage, antioxidant treatment to protect human cell against the adverse effects of FR on cell and tissue appears to be beneficial. Due to its antioxidant and anti-inflammatory properties, lutein is a well-ascertained safety molecule with a promising role in protecting newborns [54, 55]. There still remains much work to be done to identify the proper timing as well as the precise dosing and duration of lutein supplementation in the neonatal period.

Declaration of interest

The Authors declare that there is no conflict of interest.

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