Our Agenda

**Part I: THE IMPORTANCE OF CAROTENOIDS**
- Background of carotenoids
- Functions of carotenoids
- Hypothesis

**Part II: EVIDENCE-BASED RESEARCH AND FINDINGS**
- NRCI and our research standards
- Key peer-reviewed studies
- Implication of findings

**PART I**
The Importance of Carotenoids

**Carotenoids Found**

- ~700 in nature
- ~50 in diet
- ~20 in serum

**FUNNEL EFFECT**
Carotenoids in the Eye

PART I: BACKGROUND OF CAROTENOIDS

Distribution of Carotenoids in the Macula

Recent findings illuminate the importance of zeaxanthin and meso-zeaxanthin over lutein.

Molecular Structure of Carotenoids C_{40}H_{56}O_{2}

BROTHERS AND SISTERS
Lutein, Zeaxanthin, AND Meso-Zeaxanthin are very close in structure

Functions of Carotenoids

Problem: Oxidative Stress and the Retina

Cell damage caused by unstable molecules
Problem: Oxidative Stress and the Retina

The trigger that leads to AMD

imbalanced oxidative status

Pro-oxidant System

Antioxidant System

Cell Damage

Solution: Antioxidant

PART I: FUNCTIONS OF CAROTENOIDS

Studies on the Singlet Oxygen Scavenging Mechanism of Human Macular Pigment

Binxing Li, Faisal Ahmed, and Paul S. Bernstein*

Department of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT 84132

Abstract

It is thought that direct quenching of singlet oxygen and scavenging free radicals by macular pigment carotenoids is a major mechanism for their beneficial effects against light-induced oxidative stress. Corresponding data from human tissue remains unavailable, however. In the studies reported here, electron paramagnetic resonance (EPR) spectroscopy was used to measure light-induced singlet oxygen generation in postmortem human macula and retinal pigment epithelium/choroid (RPE/choroid). Under white-light illumination, production of singlet oxygen was detected in RPE/choroid but not in macular tissue, and we show that exogenously added macular carotenoids can quench RPE/choroid singlet oxygen. When the singlet oxygen quenching ability of the macular carotenoids was investigated in solution, it was shown that a mixture of meso-zeaxanthin, zeaxanthin, and lutein in a ratio of 1:1:1 can quench more singlet oxygen than the individual carotenoids at the same total concentration.

Keywords

Human macula; singlet oxygen; electron paramagnetic resonance (EPR)

1. Introduction

Macular pigment (MP) was first described as a "yellow spot" centered on the fovea of the human eye in the eighteenth century, and it was classified spectroscopically as a xanthophyll carotenoid by Wald in 1945 [1], but it was not until 1985 that Bone and Landrum chemically identified that the macular pigment is a mixture of the carotenoids lutein and zeaxanthin [2]. Macular pigment is diffusely found in the peripheral retina, but it is highly concentrated (~100-fold) in the foveal region of the macula, often exceeding a peak value of 1 mM in many humans [3–7]. In addition to spatial specificity, there is also remarkable chemical specificity of uptake into the human macula. Despite over a dozen readily detectable carotenoids found in human serum, only lutein, zeaxanthin, and their metabolites are found in the retina. In the fovea, the ratio of (3R,3'R,6'R)-lutein to (3R,3'R)-zeaxanthin to (3R,3'S-meso)-zeaxanthin is 1:1:1, while in the peripheral retina, lutein predominates over the zeaxanthins by a 3:1:0 ratio [1,6,8].

PART I: FUNCTIONS OF CAROTENOIDS

Problem: Blue Light

Electro-magnetic radiation spectrum

Reducing intensity or time = reduces the probability of damage

Solution: Optical Filtration

PART I: FUNCTIONS OF CAROTENOIDS

Problem: Inflammation

Ongoing or persistent insult or aggression = Chronic Inflammation

More tissue damage

Solution: Optical Filtration

Reducing intensity or time = reduces the probability of damage

PART I: FUNCTIONS OF CAROTENOIDS
Solution: Anti-inflammatory

Chronic Inflammation

Lutein, zeaxanthin, and meso-zeaxanthin break the cycle of chronic inflammation and help in the resolution.

Sources of Carotenoids

In the Western World, the typical dietary intake is only 1.5mg per day of lutein and zeaxanthin combined.

Problem: Devolution

We live in an era of nutrient-deficient foods.

2000

38 Beets of Spinach has the same nutritional content as...

Solution: Supplementation

Hypothesis

Carotenoid nutrition score is directly correlated to visual function.

If patients supplement their diet with carotenoids, then their visual function will improve.

Diet vs Supplements
PART II
Evidence-based Research and Findings

NRIC: State-Of-The-Art Research Facility

Macular Pigment

Dual-wavelength fundus autofluorescence (AF) Technique

In the fovea, excitation light within the absorbance range of MP is partially absorbed by the carotenoids, resulting in an area of reduced fluorescence.

The Contrast Sensitivity Function

Measuring for 20/20 vision is only 9% of the spatial world.

Peak of the CSF is roughly 4 cpd (20 / 100 letter)
Contrast Sensitivity vs. Visual Acuity

One may read 20/20, but may exhibit a wide range of CS

Key Peer-Reviewed Studies

Carotenoids Stability and Efficacy

Capsule Types

Atypical Central Dips in MP

MPOD Spatial Profile Results from Supplementation
Atypical Central Dips in MP

The mountain and volcano analogy

Supplementation with Triple-Carotenoid Formula

Supplementation in atypical dips in macular pigment (MP)

2010 2011 2012 2014

Significant response to Meso-zeaxanthin

Pathology analysis suggested no adverse clinical implications of consuming these carotenoids.

The formulation containing all three macular carotenoids (in a MZ:L:Z [mg] ratio of 10:10:2) was the most efficacious.

Serum MZ response is positively related to MP improvement.

RESPONSE SAFETY EFFICACY MP SPATIAL PROFILE

MZ Ocular Supplementation Trial (M.O.S.T.) Summaries

2012 2014

VISUAL PERFORMANCE: Supplementation with all three macular carotenoids offered advantages over preparations lacking MZ to improve visual performance.

SAFETY AND VISUAL PERFORMANCE IN AMD: Enhancements in contrast sensitivity were best achieved after supplementation with a formulation containing high doses of MZ in combination with L and Z (in a MZ:L:Z [mg] ratio of 10:10:2).

The safety of consumption of this formulation was confirmed following extensive clinical pathology analysis.

M.Z Ocular Supplementation Trial (M.O.S.T.) Continued

This final report from M.O.S.T found that the inclusion of MZ in a supplement formulation confers benefits in terms of MP augmentation and in terms of enhanced contrast sensitivity in subjects with early AMD.

CREST Studies: Setting the Gold Standard

Funded by the European Research Council (ERC). The main goal of the ERC is to encourage the highest quality research in Europe on the basis of scientific excellence through competitive funding. €1,493,342 over five years, Grant No. 281096.

CREST Normal: Trial 1 Design

Sample size: N=105

Study Design: Double blind placebo controlled RCT

Population: Healthy participants with low MP

Intervention:
- L10mg:MZ10mg:Z2mg
- Placebo

Outcomes:
- Contrast Sensitivity
PART II: KEY PEER-REVIEWED STUDIES

Making the invisible visible

Owsley & Sloane (1987): Contrast sensitivity at middle and low spatial frequencies (e.g. 6 cpd) was a significant predictor of real-world object detection and identification. 

• CS determined to be a better predictor of performance than age!
• VA was not a significant contributor to real-world visual performance.

PART II: IMPLICATION OF FINDINGS

Implication of Findings: Healthy Subjects

Implication of Findings: Visually-Demanding Occupations

Implication of Findings: Sports Performance

Age-Related Macular Degeneration

11 MILLION in the United States have some form AMD. 

BY 2050, this number is expected to double to nearly 22 million.
CREST AMD: Trial 2 Design

- Sample size: N=121
- Study Design: Double-blind RCT
- Population: Early AMD
- Intervention:
  - L (10mg): MZ (10mg): Z (2mg) + Vit C + Vit E + Zn + Cu
  - AREDS
- Time: 24 months
- Outcomes:
  - Visual Performance
  - Macular Pigment

CREST AMD: Trial 2 Results

75% (24 of 32) of vision-related measures (e.g., contrast sensitivity, glare disability, photo stress recovery) exhibited significant improvements.

Implication of CREST Findings

Recommend a Triple-Carotenoid Formulation

- 10:10:2 mg/day (MZ:L:Z)

The benefits for your patients:

- Optimize their vision
- Decrease the risk of progression of AMD

If the doctor prefers an AREDS-like formula:

- Lower zinc (safer)
- Fortified with Meso-Zeaxanthin (better)

Please note the AREDS study demonstrated a benefit of the active ingredient for reducing risk of AMD progression for patients with intermediate AMD only.

COAST

Carotenoid Omega BioAvailability STudy

Diacetate Solubilzate and Crystallized Carotenoids

Aim:

To investigate the bioavailability of the hydroxy-carotenoids (HC) in different formulations by measuring serum and tissue response.
Study Design

- 6-month randomized, double-blind, placebo-controlled study
- Block randomization stratified by sex

**ELIGIBILITY CRITERIA:**

**Inclusion criteria:**
- Adults aged 18 to 60 years
- Informed consent
- Pregnancy and lactation
- Consumption of supplements
- Malabsorption
- Retinal disease

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- Adults aged 18 to 60 years
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**Study Sample**
10 Healthy adults assessed for eligibility

**Study Design**
- 6-month randomized, double-blind, placebo-controlled study
- Block randomization stratified by sex

**Results**

Response: Serum L
- Serum L change over time
- L serum response was significantly higher in all active groups compared to placebo (p=0.001 to p=0.002)

Response: Serum Z
- Z serum response was significantly higher in all active groups compared to placebo (p=0.001 to p=0.002) except for Group 2 (p=0.004)

Response: Serum MZ
- MZ serum response was significantly higher in all active groups compared to placebo (p=0.001 to p=0.002).
PART II: COAST

RESULTS

Response: Serum MZ

Effect of different formulations on change in MZ serum concentrations

*MZ serum response in Group 4 was significantly higher compared to Group 1 (p<0.001), Group 2 (p<0.001), and Group 3 (p<0.001).*

Tissue Response

MPOV change over time

*MPOV response was significantly higher in all active groups compared to placebo (p<0.001 to p<0.029).*

Skin Response

Change in Skin Condition Score

*Skin response in Group 4 was significantly higher compared to Group 2 (p<0.014).*

SUMMARY
CONCLUSIONS

Z and MZ diacetates presented an increased bioavailability most likely due to improved bioaccessibility. Micellarization and absorption efficiency is a plausible rationale for their enhanced bioavailability.

Advanced supplement technology with solubilized L, Z, and MZ diacetates instead of crystals enhances the bioavailability when compared to traditional carotenoid supplements.

COAST: Boosting Bioavailability

The latest research

In addition

Take-home Message

If patients supplement their diet with carotenoids,

then their visual functions will improve.

Research Collaborators

ON TOP OF INNOVATION!

www.profjohnnolan.com
THANK YOU
Questions?

Find my work at profjohnnolan.com