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Major review

Iron, zinc, and copper in retinal physiology and disease

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ABSTRACT

The essential trace metals iron, zinc, and copper play important roles both in retinal physiology and disease. They are involved in various retinal functions such as phototransduction, the visual cycle, and the process of neurotransmission, being tightly bound to proteins and other molecules to regulate their structure and/or function or as unbound free metal ions. Elevated levels of "free" or loosely bound metal ions can exert toxic effects, and in order to maintain homeostatic levels to protect retinal cells from their toxicity, appropriate mechanisms exist such as metal transporters, chaperones, and the presence of certain storage molecules that tightly bind metals to form nontoxic products. The pathways to maintain homeostatic levels of metals are closely interlinked, with various metabolic pathways directly and/or indirectly affecting their concentrations, compartmentalization, and oxidation/reduction states. Retinal deficiency or excess of these metals can result from systemic depletion and/or overload or from mutations in genes involved in maintaining retinal metal homeostasis, and this is associated with retinal dysfunction and pathology. Iron accumulation in the retina, a characteristic of aging, may be involved in the pathogenesis of retinal diseases such as age-related macular degeneration (AMD). Zinc deficiency is associated with poor dark adaptation. Zinc levels in the human retina and RPE decrease with age in AMD. Copper deficiency is associated with optic neuropathy, but retinal function is maintained. The changes in iron and zinc homeostasis in AMD have led to the speculation that iron chelation and/or zinc supplements may help in its treatment.

1. Introduction

Iron, zinc, and copper are essential trace elements playing key roles in retinal structure and physiology.[117,144,145,151,230,232,244,322,331,347,352,362] Inherited disorders of their metabolism are associated with retinal dysfunction and significant visual loss. Iron accumulation in the retina of patients with aceruloplasminaemia,[88,383,391] hemochromatosis,[137] and Friedrich's ataxia[26,33] results in yellow deposits. Poor dark adaptation is a common manifestation of systemic zinc depletion (i.e., acrodermatitis enteropathica).[46,312] The peripheral retinal appears hypopigmented in patients with inherited

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Table 1 – Previously reported measurements of iron, zinc, and copper in mammalian RPE/choroid and neuroretina

A. Iron

Sample	Age	Sex	Method	Iron	Authors
RPE/choroid					
Rat Long-Evans	2–8 weeks	N/A	PIXE	178.4[a]	Yefimova et al[395]
Rat					
Brown-	4 months	Male	ICP-OES	65.0 + 8[a]	Chen et al[49]
Norway	30 months	Male		195.4 + 33[a]	
Mouse					
c57BL/6	3–6 months	Male + Female	GF AAS	103 + 9[b]	Hahn et al[127]
	16–19 months	Male + Female		147 + 8[b]	Hadziahmetovic et al[123]
Neuroretina					
Human	N/A	N/A	GF AAS	117.63 + 14.58[a]	Eckhert[91]
Human					
white	17.8 years (4–32)	Female	AAS	96.1 + 14.8[b]	Hahn et al[128]
	73.1 years (65–88)	Female		137 + 13.8[b]	
Human					
white	24.8 years (17–35)	Male		57.2 + 8.06[b]	
	74.1 (65–83)	Male		95.4 + 13.6[b]	
Mouse					
c57BL/6	3 weeks	N/A	N/A	41.1 + 6.5[b]	Deleon et al[79]
	3–6 months	Male + Female	GF AAS	47 + 4[b]	Hahn et al[127]
	12–19 months	Male + Female		29 + 2[b]	Hadziahmetovic et al[123]

B. Zinc

Sample	Age	Sex	Method	Zinc (μg/g dry weight)	Authors
RPE/choroid					
Human					
No AMD	73 ± 12 years	Men + Women	ICPMS	292.1 + 98.5	Erie et al[92]
AMD-MGS 2–4	78 ± 10 years	Men + Women		223.7 + 94.0	
Human					
Caucasian	15–87 years	N/A	ICPMS		Wills et al[378,377]
Rat					
Sprague-Dawley	N/A	N/A	ICPMS	75.8 + 7.4	Fabe et al[94]
Neuroretina					
Human	N/A	N/A	AAS	3.8 + 0.9	Eckhert[91]
Human					
No AMD	73 ± 12 years	Men + Women	ICPMS	123.1 + 62.2	Erie et al[92]
AMD-MGS 2–4	78 ± 10 years	Men + Women		98.6 + 27.9	
Human					
Caucasian No AMD	15–87 years	Men + Women	ICPMS	9.8	Wills et al[378]
Rat					
Sprague-Dawley	N/A	N/A	ICPMS	~72	Fabe et al[94]

C. Copper

Sample	Age	Sex	Method	Copper (μg/g dry weight)	Authors
RPE/choroid					
Human					
No AMD	73 ± 12 years	Men + Wom	ICPMS	6.6 + 1.4	Erie et al[92]
AMD-MGS 2–4	78 ± 10 years	Men + Wom		5.1 + 1.1	
Human					
white	15 ± 87 years	N/A	ICPMS	estimated ~2	Wills et al[378]
Neuroretina					
Human	N/A	N/A	AAS	6 ± 1	Eckhert[91]
Human					
No AMD	73 ± 12 years	Men + Wom	ICPMS	9.0 + 5.0	Erie et al[92]
AMD-MGS 2–4	78 ± 10 years	Men + Wom		8.3 + 3.0	
Human					
white	15–87 years	Men + Wom	ICPMS	estimated ~2	Wills et al[378]

AAS = atomic absorption spectrometry; GF = graphite furnace; ICPMS = inductively coupled plasma mass spectrometry; ICPOES = inductively coupled plasma–optical emission spectrometer; MGS = Minnesota grading system; N/A = not available.

[a] μg/g dry weight.

[b] ng/retina.