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Ironing out neurodegeneration: iron chelation for neuroprotection

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Iron is one of the substances for which the adage “Too much of a good thing is not better” holds true. Iron's ability to readily shift its redox state facilitates cellular respiration but can also catalyze the production of harmful hydroxyl radical when iron's level or location is inappropriate. In this issue of *Free Radical Biology & Medicine*, the paper by Obolensky et al. highlights the neuroprotective potential of iron chelation, even when iron dysregulation is not the primary cause of the degeneration.

Their carefully executed study shows that retinal degeneration in rd10 mice can be ameliorated by treatment with the iron chelator zinc–deferioxamine (Zn-DFO). Rd10 mice have a mutation in the rod photoreceptor phosphodiesterase, required for phototransduction, resulting in a nearly complete loss of both rod and cone photoreceptors by about 6 weeks of age. Mice given Zn-DFO by ip injection beginning at postnatal day 4 have relatively preserved retinal structure and function at several ages, as well as diminished oxidative stress. The number of rods and cones is higher in the treated mice. Electroretinography reveals improved rod and cone function with the Zn-DFO treatment. Both immunostaining and biochemical assays reveal diminished oxidative stress in the Zn-DFO-treated mice.

This study builds upon several previous publications showing neuroprotection by iron chelation. DFO protects the rat retina from photo-oxidative stress [1] and from ischemia–reperfusion injury [2]. The oral iron chelator deferiprone protects iron-overloaded retinas of ceruloplasmin/hephaestin knockout mice against oxidative stress and retinal degeneration. It also ameliorates a movement disorder and early mortality associated with brain iron accumulation in these mice [3]. Intraperitoneal injection of the endogenous iron-chelating protein transferrin also markedly protects the rd10 retina from degeneration [4]. Iron chelation can also protect the brain. The chelator salicylaldehyde isonicotinoyl hydrazine protects the rodent spinal cord against trauma [5]. Both elevated levels of the endogenous iron-storage protein ferritin and administration of the metal chelator clioquinol protect the mouse brain against the neurotoxin MPTP, which induces a Parkinson-like neurodegeneration [6].

The mechanism of neuroprotection by these iron chelators is probably prevention of iron-catalyzed oxidative stress, as several of the above studies correlate diminished oxidative stress with chelator administration. Iron excess, or mislocalization, has been associated with

age-related neurodegeneration such as age-related macular degeneration [7], Alzheimer disease [8], and Parkinson disease [9], so it is primed to exacerbate ongoing degeneration in these conditions. It can also be released from red blood cells after hemorrhage, or from dying neighbors in ongoing neurodegeneration.

Iron dysregulation caused by ongoing neurodegeneration could also accelerate disease. For example, retinas of rd10 mice have altered levels of iron, ferritin, and transferrin [10]. Iron may be mishandled during neurodegeneration because its regulation is also influenced by inflammation and hypoxia, potentially leading to toxic iron stores. Inappropriate iron handling can clearly lead to brain and retina degeneration, as in the hereditary diseases aceruloplasminemia [11], Friedreich ataxia [12], and pantothenate kinase-associated neurodegeneration [13]. Mice with iron-regulatory protein knockout or low ferritin levels also experience neurodegeneration [14]. The above studies support the use of iron chelators in clinical trials for neurodegeneration such as in Alzheimer disease [15] and Friedreich ataxia [16]. Route of administration and toxicity are important considerations. Some chelators can readily cross the blood–brain and blood–retinal barriers. Iron deficiency must be avoided, but it is likely that this could be achieved by careful monitoring and by choosing chelators that can bind or redistribute loosely bound, potentially toxic iron in the central nervous system without stripping iron from iron requiring proteins.

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