Neuron, Vol. 37, 889–893, March 27, 2003, Copyright ©2003 by Cell Press

Ironic Fate: Can a Banned Drug Control Metal Heavies in Neurodegenerative Diseases?

In this issue of *Neuron*, Kaur et al. demonstrate that iron chelation by ferritin transgene or the metal chelator clioquinol prevent oxidative damage and MPTP toxicity in mice. This raises the issue of specific iron chelators or clioquinol for control of oxidative damage in Parkinson's, Alzheimer's, and other neurodegenerative diseases, but not without safety concerns.

Free radical damage has long been implicated in the chronic diseases of aging, including devastating neurological disorders like amyotrophic lateral sclerosis, stroke, Alzheimer's (AD) and, perhaps most clearly, Parkinson's disease (PD). Control of free radical damage has been primarily attempted by manipulating oral antioxidant intake and levels of defense enzymes. Limited success has been obtained in clinical trials with vitamin E, but because trials have not gauged the control of oxidative damage, it remains unclear how significant a target oxidative damage really is. Because of toxicity concerns, less attention has been given to reducing radical production by control of the transition metal catalysts (notably Cu^{2+} and Fe^{2+}) that are responsible for converting less reactive superoxide and hydrogen peroxide into highly reactive species like hydroxyl radical. Whether a cause or consequence of the disease, iron levels are clearly elevated in the substantia nigra (SN) of PD patients where dopamine deamination by monoamine oxidase generates excess hydrogen peroxide. In this issue of *Neuron*, Julie Andersen at the Buck Institute and collaborators have addressed the possibility of a causal role for iron in the loss of dopaminergic cells in a Parkinson's model (Kaur et al., 2003). They suppressed the levels of reactive ferrous iron either by transgenic expression of the specific iron binding protein ferritin or by administration of a small bioavailable metal chelator (clioquinol, CQ). For the transgenic mice, the investigators used a tyrosine hydroxylase promoter to drive ferritin expression in dopaminergic cells that are damaged or lost after repeated injections of 1-methyl-4-phenyl-1,2,3,6-tetrapyridine (MPTP) in control wild-type mice. The results show that both the ferritin transgenics and CQ-treated wild-type mice had reduced SN-reactive iron levels and limited MPTP-induced losses in reduced glutathione, dopamine, and dopaminergic cell numbers. MPTP-induced behavioral deficits assessed by rotorod (transgenics) or motor activity (CQ treatment) were also ameliorated. The beneficial effects were attributed to control of oxidative damage demonstrated by a suppression of reactive oxygen species in ferritin transgenics and CQ-induced reductions in proteins with oxidative damage (carbonyls, 4-hydroxynonenal).

The Andersen group's promising in vivo results are supported by a report in press confirming an essential role for iron in MPTP toxicity (Kalivendi et al., 2003) and very recent evidence for increased oxidative stress in the brains of hemizygous H ferritin null mice (Thompson et al., 2003). Appropriate sequestration of iron is an increasingly compelling target for limiting oxidative damage, especially for prevention. In the case of PD, early detection and more effective intervention may be possible, combining very early clinical changes (olfactory dysfunction, depression, changes in handwriting or speech, or reduced ambulatory arm motion) with new techniques for imaging the nigral iron accumulation that precedes major clinical deficits (Becker et al., 2002).

Alzheimer's Disease (AD)

Chelation therapy with CQ has also shown evidence of significant protective effects in an amyloid precursor protein (APP) transgenic model for AD, dramatically reducing amyloid accumulation, an effect believed to be due to chelation of zinc ions destabilizing plaques (Cherny et al., 2001). In that study, no attempt was made to show a CQ effect on the limited neurodegeneration in the APP transgenics or the oxidative damage that is clearly present in AD and in the model (Pratico et al., 2001). However, an improvement in behavioral symptoms was observed. Because of the critical role of iron in oxidative damage, the present results of Kaur et al. suggest that, like the antioxidant curcumin (Lim et al., 2001), CQ has the potential to suppress both amyloid and oxidative damage, two very well-established factors in AD pathogenesis. Based on this and other evidence for the involvement of metals in amyloidosis and AD, a phase II double-blinded clinical trial on AD patients in Australia has been carried out by Masters and colleagues. While some indication of initial positive results in the trial have been presented at a meeting cited by Kaur et al., the website of the sponsoring company, Prana, cautiously states that the results "continue to be analyzed." The same website also notes an ongoing open label extension with CQ in AD patients, consistent with possible benefits and limited, if any, adverse events.

A Note of Caution

Kaur and colleagues conclude that "nontoxic iron chelation may be an effective therapy for prevention and treatment of the disease." For prevention this is very likely true, provided that the chelation therapy is truly nontoxic. First, because of the critical metabolic roles of essential minerals, specificity (achieved with ferritin) has been considered highly desirable to avoid depletion by chronic therapy in conditions with metal overload. As Kaur et al. point out, unlike deferrioxamine and other currently used iron chelators, CQ does not result in depletion of systemic iron levels. This should make it much less likely to produce depletion-related side effects. The second toxicity issue is the potential for problems from the free chelator itself or metal-chelate complexes that may have both anti- and pro-oxidant effects, depending on their dose and interactions with regenerating antioxidants. One needs to be especially cautious because three decades ago CQ was withdrawn from the market after its use was linked to some 10,000 cases

of a subacute myelo-neuropathy (SMON), primarily in Japan (Tabira, 2001; Tateishi, 2000). CQ iron chelates were initially implicated because they were found in urine of SMON patients and shown to increase lipid peroxidation. Further, SMON symptoms and distal axonopathy could be reproduced with high-dose CQ administration to dogs and cats with marked variation in the response due to dose and species (Matsuki et al., 1997). More recent findings have led to the hypothesis that CQ zinc chelates were the neurotoxin involved in SMON (Arbiser et al., 1998). As with most drugs, toxicity may occur at very high doses, but for useful agents, not within their effective therapeutic window. Because of the potential oxidative damage from metal chelates, their use may require appropriate dietary or supplementary antioxidants that were inadequate in postwar Japan. For example, for deferrioxamine to control oxidative damage in diabetic rats, an ascorbic acid supplement was required (Young et al., 1995). An alternative theory discussed by Kaur et al. is that indiscriminate high-dose CQ use aggravated B_{12} deficiency in postwar Japan and led to SMON in a subset of vulnerable patients. They have found no evidence for CQ toxicity with effective dosing in mice. More significantly, in a phase II clinical trial, therapeutic CQ has been coadministered with B_{12} to Alzheimer patients with no evidence of drug-dependent adverse events. Whether or not the toxicity issues with CQ can be ironed out, Andersen and colleagues' work with the ferritin transgenics provides strong evidence that control of oxidative damage by nontoxic iron chelation may be a viable approach for PD and perhaps other neurodegenerative diseases. Based on its success in animal models for both AD and PD and its apparent safety and possible efficacy in the clinic with AD patients, there is growing reason for the ironic hope that the drug CQ, once withdrawn from the market for causing neurodegeneration, may be used to prevent it.

Greg M. Cole
Greater Los Angeles VA Medical Center
UCLA Alzheimer's Disease Research Center
Sepulveda, California 91343

Selected Reading

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Interpolating between Cellular Biophysics and Computation in Single Neurons

What types of computations are performed on synaptic inputs within the dendritic trees of single neurons? In this issue of *Neuron*, Poirazi et al. (2003a, 2003b) present a systematic method to reduce complex, biophysically realistic neuron models to more tractable, simplified two-layered neural networks that could shed some light on this issue.

The complexity of synaptic integration mechanisms within single neurons has become mind-boggling following the explosive increase in databases on dendritic recordings in slice preparations during the past decade (Stuart et al., 1999; Reyes, 2001). Yet, to understand how ionic channels and their distribution are utilized by single cells to process information will require some abstraction from biophysical detail toward simpler models and a shift in focus from a faithful description to a more abstract representation of the relation between synaptic inputs and neuronal firing rate (Segev and London, 2000). Two papers in this issue of *Neuron* (Poirazi et al., 2003a, 2003b) address this question using the example of CA1 pyramidal cells. The results provide a general and explicit method to reduce biophysical complexity without losing the input/output relation of single neurons that could potentially lead to a better understanding of how neurons process synaptic inputs.

The authors start by constructing a detailed biophysical model of a CA1 hippocampal pyramidal cell based on anatomical and electrophysiological data from various laboratories. The model includes many of the conductances thought to play a role in synaptic integration, including I_h and I_A, as well as sodium conductances responsible for backpropagating action potentials, and several types of Ca^{2+} conductances. To calibrate the model, Poirazi et al. simulated current injection protocols from both somatic and dendritic locations and compared the results with experimental data under various conditions, including the use of pharmacological blockers (see the Supplemental Data for Poirazi et al., 2003a, available online at http://www.neuron.org/cgi/content/full/37/6/977/DC1).

The next step, described in Poirazi et al. (2003a), consisted in reproducing synaptic stimulation experiments in which pairs of inputs were activated simultaneously