Separating the brain's 'bad' from 'good' iron

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Duke University chemists are developing ways to bind up iron in the brain to combat the neurological devastation of Parkinson's and Alzheimer's diseases. The key is to weed out potentially destructive forms of iron that generate harmful free radicals while leaving benign forms of iron alone to carry out vital functions in the body.

"Using existing chelating (metal-binding) molecules to target iron in the brain can be tricky," said Katherine Franz, an assistant chemistry professor at Duke, because iron is essential to the body. "We want to go after only the iron that is causing the damage. We don't want to pull the iron out of healthy sites."

On Aug. 23, during the American Chemical Society's August 2007 national meeting in Boston, Franz will describe her work with graduate student Louise Charkoudian to formulate sensitive chemical sentinels they call "pro-chelators." Those are metal-binding agents wrapped in chemical "cages" so they can enter the brain and wait in reserve until they encounter a site of potential damage.

Such a site contains both iron and the molecule hydrogen peroxide. The reaction between these two players -- known as a "Fenton reaction" -- can lead to the production of a highly reactive oxygen-containing chemical group called a hydroxyl radical, Franz said.

These toxic chemical radicals can cause oxidative stress in brain cells that has been associated with Parkinson's and Alzheimer's as well as other age-related maladies such as macular degeneration in the eyes, she

said.

The pro-chelators that Franz will describe at the ACS meeting contain phenols that wear chemical "masks" around themselves to keep them from binding with benign forms of iron or other metals, such as those found in some essential enzymes. But the presence of excessive amounts of hydrogen peroxide will trigger an unmasking, allowing the phenols to sop up and inactivate the bad iron, she said.

Franz and Charkoudian described their first formula for a pro-chelator in a report printed in the Sept. 27, 2006, issue of the Journal of the American Chemical Society. The work is being supported by the Parkinson's Disease Foundation and Duke University.

Franz's Aug. 23 talk at the society's latest national meeting will concentrate on a second generation of pro-chelator compounds that are better tailored in both sensitivity and response time to the brain's chemical environment, she said.

A report on those newer compounds is also pending in the journal Dalton Transactions and includes contributions by post-doctoral associate David Pham and Duke undergraduate students Ashley Kwon and Abbey Vangeloff.

While their previous experiments have been in laboratory glassware, the Duke pair has now begun working with living cells.

"That work looks promising," Franz said. "It looks like we're seeing iron binding only when we increase the levels of hydrogen peroxide. This level of peroxide normally kills cells, but we are seeing cell survival with the pro-chelators, so we're very excited."

Source: Duke University