

# Stunning Finding: Compounds Protect Against Cerebral Palsy

February 25 2009

---

(PhysOrg.com) -- Two compounds developed by Northwestern University chemists have been shown to be effective in pre-clinical trials in protecting against cerebral palsy, a condition caused by neurodegeneration that affects body movement and muscle coordination.

"The results were just stunning, absolutely amazing," said Richard B. Silverman, John Evans Professor of Chemistry in the Weinberg College of Arts and Sciences at Northwestern, who led the drug development effort. "There was a remarkable difference between animals treated with a small dose of one of our compounds and those that were not."

The findings, which are published online by the journal *Annals of Neurology*, suggest that a preventive strategy for cerebral palsy may be feasible for humans in the future. (The paper also will appear in the journal's February issue, in print the week of March 2.)

None of the fetuses born to animals treated with the two compounds died; more than half of those born to untreated animals died. Eighty-three percent of animals treated with one of the compounds were born normal, with no cerebral palsy characteristics. Sixty-nine percent of animals treated with the other compound were born normal. There was no sign of toxicity in the treated animals, and their blood pressure was normal.

Cerebral palsy is caused by an injury to the brain before, during or shortly after birth, although it typically is not diagnosed until after the

age of one. Approximately 750,000 children and adults in the United States have a form of cerebral palsy, with the majority having been born with the condition.

The new compounds Silverman and his team developed inhibit an enzyme found in brain cells that produces nitric oxide, thus lowering nitric oxide levels. At normal levels, nitric oxide acts as a neurotransmitter and is important to neuronal functioning, but at high levels it has been shown to damage brain tissue. An overabundance of nitric oxide is believed to play a role in cerebral palsy.

After a lengthy drug development process, Silverman went to his collaborator Sidhartha Tan, M.D., a neonatologist from NorthShore University HealthSystem, to test the two best compounds on Tan's cerebral palsy animal model. A diminished supply of oxygen (hypoxia) from mother to fetus causes an increase in nitric oxide levels in the brain, which leads to brain damage and newborns with cerebral palsy characteristics.

Silverman and Tan wanted to see if they could prevent brain damage in the fetuses by administering one of the compounds to the mother before the hypoxic event. They expected some degree of success but were surprised by how effective the treatment was. The researchers attribute the protection from cerebral palsy to the decrease in the brain enzyme and the nitric oxide that is produced.

"We still have to bring the phenomenon to humans, which would be very exciting," said Tan, who has been investigating the impact of nitric oxide on neuronal damage. "There is such a dire need. If we could safely give the drug early to mothers in at-risk situations, we could prevent the fetal brain injury that results in cerebral palsy."

In developing the potential drugs, Silverman and his team were able to

produce something that pharmaceutical companies so far have not: highly selective compounds that inhibit the enzyme found in brain cells that produces nitric oxide but that do not affect similar nitric oxide-producing enzymes found in endothelial and macrophage cells.

Endothelial cells regulate blood pressure, and macrophage cells play an important role in the immune system. Reducing their production of nitric oxide would have deleterious effects on an animal, such as increasing blood pressure or compromising the immune system.

"The challenge was to lower only the nitric oxide in the brain and not in the other cells where the nitric oxide is very important," said Silverman, a member of Northwestern's Center for Drug Discovery and Chemical Biology.

"Early compounds developed by drug companies to target the brain enzyme actually bound to all three nitric oxide enzymes," he said. "This made me think that the three enzymes must be very similar in structure. We decided to look for differences away from the normal binding site to get selectivity for only the brain enzyme."

This approach paid off. Silverman and his team started with a molecule that showed good selectivity of the brain enzyme over the macrophage enzyme but with no selectivity over the endothelial enzyme. The researchers then made modifications to the molecule and built a library of 185 different compounds that could be tested for the selectivity they wanted. They found 10 good ones. More modifications were made until they had a few compounds that were very selective and very potent for the brain enzyme.

Silverman then started collaborating with Thomas Poulos, Chancellor's Professor of Molecular Biology and Biochemistry and a crystallographer from University of California, Irvine, who had been working on the

structure of the neuronal brain enzyme. Silverman sent him several potent and selective compounds, and Poulos produced crystal structures showing each compound bound to the brain enzyme.

"Thanks to the talents of Tom and his associate Huiying Li we could, for the first time, see visually why these compounds were selective and also see the difference between them," said Silverman.

Haitao Ji, a postdoctoral fellow who is an expert in structure-based design, joined Silverman's team. Ji took the crystal structures of their molecules bound to the enzyme and, using computer modeling, designed new structures with even better properties.

These compounds were more potent and much more selective than earlier ones. Poulos produced crystal structures of the new compounds. These are the compounds that Tan tested on his cerebral palsy animal model with such promising results, as reported by the research team in the *Annals of Neurology* paper.

"This is a great example of a multi-institutional collaboration that could not have been done without each of the parts -- we each contributed something different," said Silverman. "Science is going in that direction these days."

The researchers caution that taking the compounds to human clinical trials is a lengthy and complicated process. Silverman says they next plan to make the compounds even more potent, selective and bioavailable and then envision partnering with a company that would want to develop the drugs further.

More information:

[www3.interscience.wiley.com/journal/76507645/home](http://www3.interscience.wiley.com/journal/76507645/home)

Provided by Northwestern University

Citation: Stunning Finding: Compounds Protect Against Cerebral Palsy (2009, February 25)  
retrieved 26 April 2024 from  
<https://medicalxpress.com/news/2009-02-stunning-compounds-cerebral-palsy.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.