

A Sweet Solution to a Sticky Problem

ALZHEIMER'S DISEASE MAY ONE DAY BE TREATABLE BY DRUGS BASED ON A SUGAR ALREADY PRESENT IN THE HUMAN BODY.

Sugar might be bad for your teeth and waistline, but some sugars just might be good for your brain. A research team led by HHMI international research scholar Peter St George-Hyslop of the University of Toronto has discovered that certain forms of the sugar alcohol inositol may rid the brain of amyloid beta plaques implicated in Alzheimer's disease.

Alzheimer's is literally a sticky problem, in which small proteins, called amyloid beta, adhere to each other to form plaques in the brain. These masses cause the choking and death of neurons, resulting in behavioral changes and—Alzheimer's most notable symptom—memory loss.

The group screened various compounds for their potential to unclog these clumps and ultimately chose inositol, which is present at the tips of certain cell-membrane molecules. Like many sugars, inositol has a ring-like structure. It also contains groups of paired hydrogen and oxygen molecules, typical of alcohols, which contort the structure into several distinct conformations called isomers.

St George-Hyslop and colleagues combined different inositol isomers with amyloid beta. Those that kept the sticky protein from clumping they fed to mice engineered to have Alzheimer's-like disease; the mice were given the isomers either before or after the onset of symptoms. Regardless of when it was administered, one isomer—*scyllo*-inositol—produced substantial improvements:

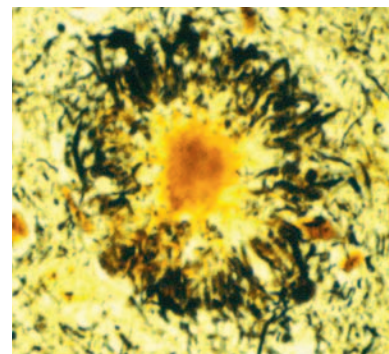
reduction and prevention of plaque formation and increased cognitive function and longevity. Two other isomers were less effective: *epi*-inositol worked transiently only when it was used before the disease's progression; *myo*-inositol, found in supplements in nutritional stores, had no effect.

The team's research appeared in the July 2006

issue of *Nature Medicine*. The results, according to St George-Hyslop, are the final missing element in the evidence that amyloid beta plaques play a key role in causing Alzheimer's disease.

Because *scyllo*-inositol is already present in humans and can cross the blood-brain barrier to reach the brain, it holds therapeutic promise. Transition Therapeutics, Inc. (Toronto, Ontario) in which St George-Hyslop has a small financial interest, is already performing human clinical trials with the compound. ■

—JACQUELINE RUTTIMANN



Amyloid-beta peptide plaques (orange) in brain tissue are cleared by the sugar alcohol inositol.

IN BRIEF

HUMAN DNA ON THE FAST TRACK

Since completing the sequencing of the chimpanzee genome last year, geneticists have spent hours comparing human DNA sequences to those of our closest evolutionary relative, looking for the differences that distinguish the two species. Now a team of researchers led by HHMI investigator David Haussler of the University of California, Santa Cruz, has found the human DNA sequence with the most dramatically increased rate of change. Published in an August 16, 2006, advance online publication of *Nature*, the work looks in depth at a region called HAR1 (for human accelerated region 1).

Incredibly, since the human lineage separated from that of the chimp, 18 of the 118 nucleotides within this region have changed. The researchers determined that HAR1 is part of a larger DNA that is transcribed into RNA in the brain and that this first occurs in human embryos between the 7th and 9th weeks of gestation. Furthermore, the RNA is produced by a Cajal-Retzius neuron, a particular type of cell that plays a critical role in creating the six layers of neurons in the human cortex by producing a protein called reelin.

According to Haussler, the possibility that the HAR1 regions may play a role in the

function of reelin is especially interesting since defects in reelin expression have been associated with schizophrenia and other mental disorders.

"STICKY" MICE PROVIDE CLUES TO TOXIC SLUDGE

Researchers have long known that neurodegenerative disorders can be caused by the accumulation of misfolded proteins in neurons, which eventually triggers cell death. Yet new studies by HHMI investigator Susan L. Ackerman and colleagues at The Jackson Laboratory point to a novel mechanism behind the toxic protein buildup in neurons: rather than resulting from a faulty gene, the diseases could be caused by errors in genetic instruction.

The researchers studied a strain of mutant mice called sticky (*sti*). Named for their fur's unkempt appearance, these mice also exhibit poor muscle control due to death of Purkinje cells in the cerebellum. To learn why these cells were dying, they searched for the gene disrupted by the *sti* mutation. Instead, they found a subtle defect in a gene that codes for part of the cell's protein synthesis machinery—an enzyme called alanyl tRNA synthetase, which loads or "charges" the amino acid alanine onto protein-building

molecules called transfer RNAs (tRNAs). The mutant enzyme charges an incorrect amino acid—serine—to tRNAs, leading to the incorrect amino acid being incorporated into proteins. Proteins resulting from this substitution folded improperly, clogging and eventually killing the Purkinje cells in sticky mouse mutants.

In their August 13, 2006, advance online article in *Nature*, the researchers showed that the problem could be corrected by inserting a normal version of the tRNA synthetase gene.

MOVIE SPIES ON MALARIA PARASITE'S SNEAKY BEHAVIOR

Malaria has been outsmarting the human immune system for centuries. Now, researchers have discovered one of the parasite's sneakiest tricks—using dead liver cells to cloak and transport itself back into the bloodstream after leaving the liver. Robert Ménard, an HHMI international research scholar, and his postdoctoral fellow, Rogerio Amino, at the Pasteur Institute in Paris, caught the behavior on film. Their images—published online in *Science Express* on August 3, 2006—clear up a perennial puzzle about the malaria parasite's life cycle.