X-Rays May Show The Way To Better Alzheimer's Drugs

Weizmann Institute scientists explain how a plant substance blocks a key brain enzyme involved in Alzheimer's disease.
Galanthine (Galanthus nivalis)

Huperzine A already works to restore acetylcholine levels by inhibiting the enzyme, Acetylcholinesterase

REHOVOT, Israel -- December 27, 1999 -- Weizmann Institute researchers have revealed the exact nature of the 3-D interaction between galanthamine, a natural substance extracted from the common snowdrop (Galanthus nivalis) and the brain enzyme acetylcholinesterase (AChE). Their findings, appearing in the December 17 issue of the Federation of European Biochemical Societies (FEBS Letters), may provide crucial information in designing a new family of Alzheimer¹s drugs.

Alzheimer's disease is a severe degenerative disorder causing memory loss and other cognitive deficits in roughly 10 percent of the elderly. One of its pathological hallmarks is the deterioration of nerve cells releasing acetylcholine a neurotransmitter that helps ferry "messages" in the form of nerve impulses between brain cells. The acetylcholine shortage that ensues is compounded by the action of acetylcholinesterase (AChE), the enzyme which breaks down acetylcholine in the body at an astonishing rate of 20,000 molecules per second.

Blocking acetylcholine breakdown

While scientists have yet to understand the cause of the disease, several Alzheimer¹s drugs already exist, including Aricept, HupA (huperzine A), and Cognex (tacrine). Their underlying approach is to attempt to restore acetylcholine levels by inhibiting AChE activity.

Using X-ray crystallography, Dr. Harry Greenblatt of the Weizmann Institute¹s Department of Structural Biology, has revealed that galanthamine acts in a similar manner, replenishing acetylcholine levels by binding to AChE¹s active site and shutting off its "cutting machinery."

Greenblatt conducted the research together with Dr. Gitay Kryger, and Professors Joel Sussman, and Israel Silman, all of the Weizmann Institute, as well as Dr. Terry Lewis of Zeneca Agrochemicals, in England.

However, according to Greenblatt, parallel to boosting acetylcholine levels, galanthamine may go an extra lap.

Dual-action power

"In addition to its effect on AChE, galanthamine also binds to acetylcholine receptors (proteins on the surface of the nerve cell which are activated by acetylcholine) thus directly stimulating neuronal function," says Greenblatt. "This dual mode of action, coupled with the evidence that galanthamine has reduced side-effects in comparison to tacrine make it a particularly exciting candidate for designing improved potency drugs."

And this is where the "blueprint" generated by the Weizmann team may prove highly beneficial. One of the most important steps toward understanding how a molecule works is to map it out, explains Prof. Sussman. For instance, after Watson and Crick demonstrated DNA's structure through their tinker-toy model, the secret of genetic replication became suddenly, almost intuitively, clear. In a similar fashion, X-ray crystallography can be used to capture highly accurate 'snapshots' of natural complexes, such as that of galanthamine with AChE. ³By studying these interactions, we can see how modifying certain chemical properties can potentially enhance their binding, leading to greater drug efficacy," says Sussman.

The scientists worked with high quality crystals of AChE derived from electric organ tissue of the Torpedo fish, one of the richest sources of this enzyme. The Torpedo AChE crystals were soaked with galanthamine, and then exposed to a narrow X-ray beam, producing a diffraction pattern from which a 3-D computer image of the AChE-galanthamine complex could be obtained.

Ancient defense mechanisms--new applications

The current Weizmann study builds upon previous Alzheimer¹s disease research completed by Sussman, Silman and Dr. Michal Harel, of the Structural Biology Department. Several years ago, they were the first to completely solve the three-dimensional structure of AChE, showing that it has a deep, canyon-like chasm known as the "aromatic gorge", where acetylcholine is broken down. Later, the team solved the structures of complexes formed between AChE and diverse synthetic and natural compounds, including the synthetically produced Aricept, fasciculin - a snake venom toxin, and huperzine A an extract from a Chinese herb used for centuries to treat memory disorders. All of these substances, as well as the newly examined galanthamine, are joined by a common denominator. Although they differ in their mode of association, they inhibit AChE by blocking its active site located at the bottom of the aromatic gorge. AChE inhibition is also the principle mode of action of many pesticides.

While fasciculin clearly has a predatory function in the case of snake venom, might the plant products act in defense against insects or parasites? "This question has not been explored, says Sussman. However, the fact that unrelated plants from different parts of the world produce AChE inhibitors is striking."

The Weizmann Institute team is currently collaborating with France[1]s Institut de Chimie des Substances Naturelles and Zeneca Agrochemicals, with the aim of applying the knowledge gleaned from these natural compounds toward improved Alzheimer's drugs and "environment-friendly" insecticides.

This study of the galanthamine-AChE binding was funded by the European Union 4th Framework Program in Biotechnology, the U.S. Army Medical and Material Command, the Weizmann Institute's Kimmelman Center for Biomolecular Structure and Assembly, and the Dana Foundation. The generous support of Mrs. Tania Friedman is gratefully acknowledged. The coordinates of the complex between AChE and galanthamine have been deposited with the Protein Data Bank (at EBI, code 1dx6). Prof. Israel Silman, a member of the Weizmann Institute's Neurobiology Department, holds the Bernstein-Mason Chair of Neurochemistry. Prof. Joel Sussman is the former head of the Protein Data Bank of the Brookhaven National Laboratory in Upton, New York.