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A Blueprint for Better Cholesterol-Lowering Drugs

A better strategy for developing more effective cholesterol-lowering drugs may come from the first studies of the structural mechanism by which the widely prescribed statin drugs, such as Lipitor and Zocor, lower cholesterol.

In an article published in the May 11, 2001, issue of the journal *Science*, Howard Hughes Medical Institute (HHMI) investigator Johann Deisenhofer at the University of Texas Southwestern Medical Center, and colleague Eva S. Istvan, reported x-ray crystallography data that show how six different statin compounds fit into the active site of the enzyme HMG-CoA reductase (HMGR). HMGR catalyzes a key step in cholesterol production.

After making crystals of the HMGR protein bound to each of the statins, Deisenhofer and Istvan then passed a beam of x-rays through the crystals. By analyzing the pattern of diffraction created as the X-rays bounced off atoms in the crystals, the scientists deduced the three-dimensional structures of the drugs bound to HMGR.

Deisenhofer and Istvan found that statins bind to HMGR's active site — the catalytic region of enzymes that binds biological substances — and prevent the enzyme from producing a molecule that is crucial to cholesterol synthesis. The studies also showed that statins do not block an additional region of HMGR's active site, suggesting that the drugs might be improved. Statins that target HMGR more effectively might prove better at reducing the enzyme's activity.

Deisenhofer and Istvan studied compactin (also known as mevastatin), simvastatin (Zocor), fluvastatin (Lescol), cerivastatin (Baycor), atorvastatin (Lipitor), and rosuvastatin (Crestor). Simvastatin and two others not studied — lovastatin (Mevacor) and pravastatin (Pravachol) — closely resemble compactin, which is not in clinical use.

"Although there is room for improvement in these drugs," said Deisenhofer, "there is no desperate need because the known inhibitors work quite well."

Deisenhofer emphasized that he and his colleagues undertook these studies to learn more about how the cholesterol-synthesis pathway works at the molecular level. "It was clear that statins compete with one of the substrates for binding to the enzyme," said Deisenhofer. "But it was not known whether

all the compounds bind the same way and what they do to the structure of the enzyme."

The scientists divided the statins into two groups based on their structure. Type 1 statins included lovastatin, pravastatin and simvastatin; and type 2 statins included fluvastatin, cerivastatin, atorvastatin, and rosuvastatin.

"They are structurally quite different," said Istvan, who was formerly a graduate student in Deisenhofer's laboratory and is now postdoctoral fellow in the laboratory of HHMI investigator Daniel Goldberg at Washington University School of Medicine in St. Louis. "Type 1 statins are generally smaller and have a smaller surface area and fewer interactions with HMGR," she said. "The type 2 inhibitors are larger and form more interactions with the enzyme's active site. While all the compounds inhibit the enzyme well, the type 2 statins have more interactions with the active site and appear to be better inhibitors."

One of the most significant findings, said Istvan, was that the statins do more than just compete with the normal substrate in the enzyme's active site. They also alter the conformation of the enzyme when they bind to its active site. This prevents HMGR from attaining a functional structure. "The change in conformation at the active site, which we didn't understand before, makes these drugs very effective and specific," said Istvan.

Istvan and Deisenhofer found that none of the statins affected a second important region of the HMGR enzyme. "From the structures we determined, there is an indication that new statins might be developed that occupy a second pocket close to the active site that is now unoccupied by the existing drugs," Istvan said. The unoccupied pocket is the portion of the enzyme that binds a second substrate — an energy-containing molecule called NADPH that drives the enzyme's catalytic reaction.

"It might be possible to produce a more specific drug that fits into both of these pockets and interacts even more tightly with the enzyme," said Istvan.

Deisenhofer emphasized, however, that tight binding of statins to the enzyme might not be the whole story. "The suspicion is that the effects of the statins stem not just from their inhibition of HMGR, but from interactions with other completely different proteins," he said. "There is very little known about these possible interactions, and there may be some surprises out there in the bush waiting for us that might make a big difference in the clinical effects of different statins." Reports in the scientific literature indicate that statins can also affect blood vessel growth, bone formation and the immune system, said Deisenhofer.

Now that Deisenhofer and his colleagues understand how statins interfere with HMGR, they are beginning to concentrate on how HMGR senses the concentration of cholesterol in the bloodstream. "There is currently no good idea how this sensing occurs," he said. "It is a critical element in the regulation of HMGR and also in the regulation of expression of a number of genes that react to changes in cholesterol concentration."