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UCSD Researchers Identify New Role For Drugs In Prevention, Treatment Of Atherosclerosis

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Drugs that work in the liver to reduce fatty triglyceride levels and improve insulin resistance, are also effective at inhibiting the formation of cholesterol-laden plaques that cause atherosclerosis in artery walls, according to researchers at the University of California, San Diego (UCSD) School of Medicine.

In studies with mice published in the Dec. 1, 2004 issue of the *Journal of Clinical Investigation*, the researchers found that drugs that activate two types of proteins called peroxisome proliferators-activated receptors (PPARs), specifically PPAR-gamma and PPAR-alpha, have a direct effect in the artery wall that prevents the accumulation of cholesterol in atherosclerotic lesions by up to 70 percent, as compared to untreated mice fed a high cholesterol diet. The scientists also determined the molecular pathways taken by the two versions of the PPAR drugs, a finding that could potentially be used to develop new anti-atherosclerotic medications.

"While current preventative therapy for cardiovascular disease is primarily based on reducing global risk factors such as hypertension, cholesterol levels and smoking, these findings provide a potential new strategy for the prevention and treatment of atherosclerosis," said the study's co-senior author, Christopher Glass, M.D., Ph.D., UCSD professor of Cellular and Molecular Medicine. "We've shown that drugs that activate PPAR-gamma and PPAR-alpha will not only reduce triglyceride levels and improve insulin levels, as previously known, but will also inhibit key processes in the artery wall that are directly responsible for the development of atherosclerosis."

Nearly 5 million Americans have atherosclerosis, which is the deposit of fatty substances, cholesterol and waste materials on the innermost layer of the walls of large and medium-sized arteries. These plaques, as they are called, can grow significantly large enough to restrict blood flow and cause a heart attack.

The UCSD team focused their study on the three subtypes of PPAR - alpha, gamma and beta/delta - in mice fed a high cholesterol diet. Although the UCSD scientists and others demonstrated in the past that PPAR- *gamma* drugs such as Rosiglitazone inhibit the development of atherosclerosis in mice, they did not know, until now, the cascade of molecular events that accomplished this in the living body.

The new study in mice also demonstrated that PPAR- *alpha* drugs that are similar to Gemfibrizol (used to lower triglyceride levels), but much more potent, were effective as an anti-atherosclerotic medication. Reductions in atherosclerosis ranged from 50 to 70 percent, depending upon the location within the arteries. This effect was similar to the 40 to 70 percent reductions previously observed for PPAR-gamma drugs under similar experimental conditions.

On the other hand, PPAR- *beta/delta* agents failed to inhibit atherosclerosis with the results not significantly different from those of control animals receiving non-active drugs.

While the three PPARs are very similar proteins and are expressed in all major cell types that make up atherosclerotic lesions, including immune system macrophages, smooth muscle cells, lymphocytes and endothelial cells, the researchers unexpectedly found that PPAR-alpha and PPAR-gamma drugs worked to inhibit

atherosclerosis through different molecular pathways. PPAR-alpha worked in the artery wall by regulating the genes involved in the transport and metabolic breakdown of cholesterol, called LXRs. In contrast, the ability of PPAR-gamma to inhibit atherosclerosis was independent of LXR and, instead, induced expression of another protein called ATP-binding cassette G1 (ABCG1) in macrophages and artery walls. ABCG1 has recently been shown by other investigators to transfer cholesterol from cells to high density lipoproteins (HDL), the carrier of so-called "good cholesterol" in the blood. The discovery that this transport process is stimulated by Rosiglitazone provides an important clue as to how PPAR-gamma might prevent the accumulation of cholesterol in the artery wall.

"These findings define distinct biological roles for the PPAR subunits," said the paper's co-senior author Wulf Palinski, M.D., UCSD professor of medicine, Department of Medicine. "This raises the possibility that these different roles taken by PPAR-alpha and PPAR-gamma might be exploited therapeutically through the use of combined drugs to synergistically inhibit the development of atherosclerosis."

The study's observations also have potentially important clinical implications for the millions of patients who have Type 2 diabetes mellitus, Glass said, adding that "diabetes is a strong risk factor for the development of atherosclerosis and its clinical complications. The findings presented in this study raise the possibility that the use of anti-diabetic drugs that activate PPAR-gamma, such as Rosiglitazone and Piaglitazone, will not only reduce the risk of developing atherosclerosis by improving blood glucose levels, but also by acting directly within the artery wall. Clinical studies now in progress should determine whether the use of these drugs reduce cardiovascular events in diabetic patients over the next few years."

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