Bile acids may hold clue to treat heart disease

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Heart disease is a major cause of death in industrialised countries, and is strongly associated with obesity and diabetes. Many scientists believe that what links these conditions is a chronic, low-grade inflammation. The current study, published in the scientific journal *Cell Metabolism* (December 6, 2011), supports that theory by demonstrating that a modified bile acid called INT-777 prevents atherosclerosis, the build-up of fatty plaques in the walls of arteries, and a leading cause of heart disease—and that it does so by exerting an anti-inflammatory effect.

INT-777 activates a receptor in the membrane of gut cells called TGR5, and in so doing enhances the secretion of a hormone called Glucagon-Like Peptide-1 (GLP-1). GLP-1 is normally induced by feeding, and it stimulates insulin secretion in response to glucose. In earlier work, Profs Kristina Schoonjans and Johan Auwerx of the EPFL's Laboratory of Integrative Systems Physiology (LISP), in collaboration with Prof Roberto Pellicciari of the University of Perugia (Italy) and Intercept Pharmaceuticals (New York, USA), found that they could protect mice fed a high-fat diet from obesity and diabetes by supplementing their food with INT-777.

Anti-diabetic drugs already exist that prolong the activity of GLP-1 in the body. The EPFL group's discovery that INT-777 enhances GLP-1 secretion raised the exciting prospect of combining the two therapeutic approaches for a more effective treatment of diabetes. But how would INT-777 affect any underlying inflammation, and in particular, atherosclerosis?

To find out, LISP members Dr Thijs Pols and Mitsunori Nomura treated mice prone to atherosclerosis with INT-777, and found a significant reduction in plaque formation. Atherosclerotic plaques contain inflammatory cells called macrophages that are generated in the bone marrow. When the bone marrow of the atherosclerosis-prone mice was replaced by bone marrow from either healthy, wild-type mice, or from mice genetically engineered to lack TGR5, the researchers found that only those that received the wild-type marrow showed significantly reduced plaque formation following INT777 treatment. "That was the evidence we needed that it was the anti-inflammatory effect of the compound, acting via TGR5 in bone marrow-derived cells, that accounted for the protective effect," says Dr Schoonjans.

INT777 therefore looks like a promising candidate for the treatment of metabolic syndrome, she says. Unlike some existing anti-diabetes drugs, it is unlikely to have the side-effect of hypoglycaemia, or very low blood glucose, because it only triggers GLP-1 secretion when glucose is in sufficient supply. And though its anti-inflammatory effects are significant, they are moderate, meaning that it would be unlikely to interfere with the normal immune response. The next step will be to devise clinical trials, to test its safety and efficacy in humans.

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