Blood vessel bends and branches put the brakes on statins

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(PhysOrg.com) -- New British Heart Foundation (BHF) research revealed today suggests for the first time that the way blood flows through our arteries may boost an antioxidant effect of statin medicines. The discovery at Imperial College London is the first evidence of biomechanical forces affecting the action of a commonly- used drug, and could point the way towards new targets to improve artery health throughout the body.

Statins lower harmful LDL cholesterol - in 2008 nearly 50 million statin prescriptions were written for people at high risk of heart attack in England, where they are estimated to save nearly 10,000 lives each year. The drugs are also thought to have other heart-protective actions, which may include their ability to produce anti-oxidants in the cells of our arteries by boosting levels of the enzyme 'heme oxygenase-1' (HO-1).

Researchers in Cardiovascular Sciences at Imperial College London investigated the anti-oxidant potency of statins in different parts of the circulation by measuring the amount of HO-1 in 'endothelial' cells that line arteries.

Dr Justin Mason, Dr Faisal Ali and colleagues discovered that - in human tissue culture and in mice - the increase in HO-1 induced by the statin was significantly higher in cells exposed to fast and regular blood flow, compared to those cells exposed to sluggish or disrupted blood flow.

Dr Mason, who led the team from the National Heart and Lung Institute

at Imperial College London, said: “Arteries don’t clog up in a uniform way. Bends and branches of blood vessels - where blood flow is disrupted and can be sluggish - are much more prone to fatty plaques building-up and blocking the artery. What we’ve shown is that those regions of the arteries most likely to become diseased are the same regions that may not be benefiting maximally from statin treatment - a double whammy.”

“We now hope to use these findings to identify a way to get the most out of statins, or to find other ways to switch on protective mechanisms in vulnerable areas of arteries.”

Research suggests that the cells lining our arteries can sense ‘shear stress’ exerted by blood flowing past them, and that this affects their ability to keep the artery healthy. Straighter sections of arteries, with no branches, tend to have faster blood flow and are more protected from build-up of fatty plaques.

Professor Peter Weissberg, Medical Director of the BHF said “This research demonstrates how the physical forces inside blood vessels may influence the local action of drugs such as statins. The findings open avenues of investigation that could lead to greater health benefits of statins' being realised.

"Previous research has revealed that endothelial cells produce protective biological signals in parts of the artery where blood flow is fast and uniform and that this is lost in areas where blood flow is disrupted or non uniform, leading to build up of dangerous fatty deposits. This study shows that differing forces of blood flow may also cause the endothelial cells to be less responsive to a potentially protective antioxidant effect of statins.

"Research teams at Imperial - involving biologists and fluid engineers -

are now taking these findings forward to discover how best to restore disease-protection and drug-responsiveness in vulnerable parts of the circulation. Imperial College London is well placed to undertake such research having recently become a BHF Centre of Research Excellence - a scheme through which we support innovative multidisciplinary approaches to the fight against heart disease."

The research is published today in the *Journal of Biological Chemistry*.

More information: Induction of the cytoprotective enzyme heme oxygenase-1 by statins is enhanced in vascular endothelium exposed to laminar shear stress and impaired by disturbed flow. Ali F, Zakkar M, Karu K, Lidington EA, Hamdulay SS, Boyle JJ, Zloh M, Bauer A, Haskard DO, Evans PC, Mason JC. *J. Biol. Chem.*, Jul 2009; 284: 18882-18892; doi:10.1074/jbc.M109.009886

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