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BU SCHOOL OF MEDICINE RESEARCHERS IDENTIFY PROMISING THERAPY FOR DIABETES

Boston, MA—Researchers at Boston University School of Medicine (BUSM) believe they have identified a promising therapy for controlling the effect of diabetes on blood vessels by blocking the effects of thromboxane. The results of this study currently appear on-line in the publication *Circulation*.

Diabetes mellitus is a chronic disease afflicting more than 18 million Americans (6.3 percent of the U.S. population). It can lead to serious complications such as blindness, kidney damage, and lower-limb amputations. Apart from diabetes mellitus' own serious effects, it exerts a powerful influence upon cardiovascular disease. In fact, diabetes is one of the biggest accelerators of the development of atherosclerotic plaques.

It is known that strict control of blood glucose levels, a classic diabetes control mechanism, lowers the risk of disease of the small vessels in the eye and kidney. Whether or not atherosclerosis is prevented by careful blood glucose control is uncertain, however. Using a mouse model of apolipoprotein E deficiency (mice that develop hyperlipidemia and atherosclerotic plaques spontaneously), researchers from two laboratories in the United States and France had previously shown that a thromboxane A₂ receptor antagonist, S18886, significantly inhibited atherosclerosis.

The investigators also knew, from previous work, that treatment with aspirin, a known anti-inflammatory agent, did not prevent the development of atherosclerotic lesions. Because aspirin blocks thromboxane production, it decreases complications due to thrombosis of advanced atherosclerotic plaques but does not prevent their formation. Thus they wanted to explore the thromboxane antagonist further to see whether it is involved in limiting atherosclerosis and how the process exerted its beneficial effects on atherosclerosis. They also hypothesized that completely blocking the receptors for the arachidonic acid pathway is very important.

Diabetes mellitus was induced in the Apo E-deficient mice that were treated with S18886 and their aortic lesions were compared with mice that hadn't been treated with this agent after six weeks. The aortic lesion area was more than four-fold larger in the Apo E-deficient mice. The thromboxane A₂ receptor antagonist prevented the diabetes-related increase in lesion area without affecting the diabetes-related hyperglycemia or hypercholesterolemia. It prevented deterioration of endothelial function and of the expression of endothelial nitric

oxide synthase. It also prevented increases in markers of vascular inflammation, which are thought to exacerbate atherosclerosis. Testing the antagonist further, the BUSM researchers found that in human aortic endothelial cells in culture, it prevented the inflammatory cell adhesion molecule, VCAM-1, from being induced and also prevented nitric oxide synthase from being decreased. The researchers obtained such compelling results that they concluded that blocking thromboxane receptors inhibits inflammation of arteries, which in turn prevents the formation of the atherosclerotic plaques that are so accelerated by diabetes. They surmised that the most likely reason is by counteracting the effects of high-circulating levels of glucose in the blood that increases the formation of thromboxane as well as other products of arachidonic acid.

“Aspirin has long been used for its beneficial blood-thinning effects, but it does not prevent formation of atherosclerotic lesions,” said senior author Richard Cohen, MD, a professor of medicine and research professor of physiology at BUSM. “These findings identify a very promising therapeutic avenue to be explored for treatment of the accelerated atherosclerotic plaques of diabetes. It potentially offers a new therapeutic intervention that blocks thromboxane receptors which mediate the effects not only of thromboxane, but of all other arachidonic acid derivatives harmful for arteries.”

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