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**Pathophysiological concentrations of ADMA alter human coronary artery endothelial cell gene expression: an insight into the pathophysiological significance of raised plasma ADMA levels.**

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**Pathophysiological concentrations of ADMA alter human coronary artery endothelial cell gene expression: an insight into the pathophysiological significance of raised plasma ADMA levels.**

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**Introduction:** Asymmetric dimethylarginine (ADMA) is a naturally occurring inhibitor of nitric oxide synthases. ADMA accumulates in a wide range of diseases associated with endothelial dysfunction and enhanced atherosclerosis. Clinical studies implicate plasma ADMA as a major novel cardiovascular risk factor, but the mechanisms by which low concentrations of ADMA produce adverse effects on the cardiovascular system are unclear.

**Methods & Results:** Human coronary artery endothelial cells were treated with pathophysiological concentrations of ADMA and the effects on gene expression were assessed using U133A GeneChips (Affymetrix). More than 50 genes were significantly altered in endothelial cells after treatment with pathophysiological concentrations of ADMA (2  $\mu$ M). Changes in several genes (including bone morphogenetic 2 inducible kinase (BMP2K), Smad5, BMP receptor 1A (BMPR1A) and protein arginine methyltransferase 3 (PRMT3)) were confirmed by northern blotting, Q-PCR and in some instances western blotting analysis to detect changes in protein expression. To determine whether these changes also occurred in vivo, tissue from gene deletion mice with raised ADMA levels was examined. Changes in BMP2K and PRMT3 were confirmed at mRNA in vivo.

**Conclusions:** We detected specific patterns of changes that identify pathways involved in processes relevant to cardiovascular risk and pulmonary hypertension. Pathophysiological concentrations of ADMA are therefore sufficient to elicit significant changes in coronary artery endothelial cell gene expression. Changes in BMP signalling, and in enzymes involved in arginine methylation may be particularly relevant to understanding the pathophysiological significance of raised ADMA levels. This study identifies the mechanisms by which increased ADMA may contribute to common cardiovascular diseases and thereby indicates possible targets for therapies.