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## L-4F REVERSES THE EXPERIMENTAL METABOLIC SYNDROME VIA THE HO-1, ADIPONECTIN AND LKB1 SIGNALLING PATHWAY

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**Objectives** The hallmarks of metabolic syndrome such as obesity, insulin resistance, hyperglycemia and associated increase in reactive oxygen species (ROS) are known to decrease hame oxygenase (HO) levels. There are two forms of HO, the inducible HO-1 and the constitutively expressed HO-2. HO-1 and HO-2 catabolise hame into equimolar concentrations of carbon monoxide, bilirubin, and free iron, generating an antioxidant effect and increasing nitric oxide (NO) bioavailability and providing cardiovascular protection. Recently developed HO-2 knock out (−/−) mice have displayed characteristics of a metabolic syndrome-like phenotype with enhanced systemic inflammatory and oxidative stress response. These mice also demonstrate a failure to induce stress-dependent HO-1 upregulation along with suppression of adiponectin levels. That attenuated HO-1 upregulation in an HO-2(−/−) mouse is accompanied by metabolic imbalance led us to examine the effects of an HO-1 inducer in such a setting.

**Methods** The apo-A1 mimetic peptide (L-4F), which have been shown to induce HO-1 expression and decrease oxidative stress and adiposity, was administered to HO-2(−/−) mice so as to rescue HO-1 expression. This apo-A1-mimetic peptide was synthesised from amino acids that improved the ability of HDL to protect LDL against oxidation in animals with atherosclerosis. In this regard, HO-2(−/−) mice were injected with 2 mg/kg/day L-4F, or vehicle, i.p., for 6 weeks. Superoxide production, glucose levels and insulin tolerance tests were performed. And the expression of HO-1/2, adiponectin, LKB1 and pAMPK were measured by western blot Analysis and Real-Time Quantitative PCR.

**Results** As before, compared to WT animals, the HO-2(−/−) mice were obese, displayed insulin resistance, and had elevated blood pressure. These changes were accompanied by enhanced tissue oxidative stress along with attenuation of HO-1 expression and activity and reduced adiponectin, pAMPK (which regulates genes involved in fatty acid and cholesterol synthesis), and LKB1 (the major kinase of AMPK) expression. Treatment with L-4F restored HO-1 expression and activity and increased adiponectin, LKB1, and pAMPK in the HO-2(−/−) mice. These alterations resulted in a decrease in blood pressure, insulin resistance, blood glucose, and adiposity.

**Conclusions** Taken together, our results show that a deficient HO-1 response, in a state with reduced HO-2 basal levels, is accompanied by disruption of metabolic homeostasis which is successfully restored by an HO-1 inducer, i.e., L-4F, via HO-1, adiponectin and LKB1 signalling pathway.