Abstract

**Background:** Statins suppress the progression of atherosclerosis by reducing low-density lipoprotein (LDL) cholesterol levels. Pemafibrate (K-877), a novel selective peroxisome proliferator-activated receptor α modulator, is expected to reduce residual risk factors including high triglycerides (TGs) and low high-density lipoprotein (HDL) cholesterol during statin treatment. However, it is not known if statin therapy with add-on pemafibrate improves the progression of atherosclerosis. The aim of this study was to assess the effect of combination therapy with pitavastatin and pemafibrate on lipid profiles and endothelial dysfunction in hypertension and insulin resistance model rats.

**Methods:** Seven-week-old male Dahl salt-sensitive (DS) rats were divided into the following five treatment groups (normal diet (ND) plus vehicle, high-salt and high-fat diet (HD) plus vehicle, HD plus pitavastatin (0.3 mg/kg/day), HD plus pemafibrate (K-877) (0.5 mg/kg/day), and HD plus combination of pitavastatin and pemafibrate) and treated for 12 weeks. At 19 weeks, endothelium-dependent relaxation of the thoracic aorta in response to acetylcholine was evaluated.

**Results:** After feeding for 12 weeks, systolic blood pressure and plasma levels of total cholesterol were significantly higher in the HD-vehicle group compared with the ND-vehicle group. Combination therapy with pitavastatin and pemafibrate significantly reduced systolic blood pressure, TG levels, including total, chylomicron (CM), very LDL (VLDL), HDL-TG, and cholesterol levels, including total, CM, VLDL, and LDL-cholesterol, compared with vehicle treatment. Acetylcholine caused concentration-dependent relaxation of thoracic aorta rings that were pre-contracted with phenylephrine in all rats. Relaxation rates in the HD-vehicle group were significantly lower compared with the ND-vehicle group. Relaxation rates in the HD-combination of pitavastatin and pemafibrate group significantly increased compared with the HD-vehicle group, although neither medication alone ameliorated relaxation rates significantly. Western blotting experiments showed increased phosphorylated endothelial nitric oxide synthase protein expression in aortas from rats in the HD-pemafibrate group and the HD-combination group compared with the HD-vehicle group. However, the expression levels did not respond significantly to pitavastatin alone.

**Conclusions:** Combination therapy with pitavastatin and pemafibrate improved lipid profiles and endothelial dysfunction in hypertension and insulin resistance model rats. Pemafibrate as an add-on strategy to statins may be useful for preventing atherosclerosis progression.

**Key Words:** pemafibrate, statin, endothelial function