HEALTH RESEARCH ABSTRACT SUBMISSIONS #35

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College *	College of Medicine
Department *	Molecular Physiology & Biophysics, Internal Medicine
Title of Research *	Interference with Peroxisome Proliferator Activated Receptor Gamma in smooth muscle causes aortic dysfunction via a Rho-kinase-dependent mechanism
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Introduction & Purpose *

The nuclear hormone receptor PPARγ is the molecular target of the thiazolidinedione (TZD) class of anti-diabetes drugs. TZDs function as PPARγ agonists and improve insulin sensitivity and reduce blood pressure in type II diabetes patients. Dominant negative (DN) missense mutations in the ligand-binding domain of PPARγ (i.e. P467L, V290M) in humans are associated with insulin resistance and hypertension. We reported that transgenic mice expressing DN PPARγ under the control of smooth muscle myosin heavy chain promoter (S-P467L mice) develop hypertension and aortic dysfunction, supporting a protective role for PPARγ in the vasculature. However, the mechanism remains unclear.

Experimental Design *	We previously showed that aortic rings from S-P467L mice displayed impaired vasodilation to acetylcholine (Ach) and sodium nitroprusside (SNP); and augmented contraction to endothelin-1 (ET-1) that was blocked by pre-incubation with a Rho-kinase inhibitor. In the current study, we tested the role of basal nitric oxide (NO) as an endogenous inhibitor of RhoA/Rho-kinase signaling using a wire myograph preparation of aortic rings.
Results *	The level of total and phospho-Ser1177 eNOS protein did not differ between S-P467L and non-transgenic (NT) aorta. NOS inhibition (L-NAME 100μM) augmented contraction of S-P467L aorta to a greater extent than NT in response to ET-1, 5-HT, PGF2α and KCl. Rho-kinase-dependent phosphorylation of MYPT1, the myosin binding subunit of myosin light chain phosphatase, was enhanced in S-P467L aorta. Pre-incubation with Rho-kinase inhibitor (1μM Y-27632) significantly improved relaxation responses to Ach and SNP in S-P467L aorta, but did not affect NT.
Conclusions *	We conclude that interference with PPARγ-dependent pathways in aortic smooth muscle of S-P467L mice causes increased sensitivity of the contractile apparatus and decreased NO-mediated dilator responses via a mechanism involving elevated Rho-kinase activation.

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