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Thioredoxin reverses age-related hypertension by chronically improving vascular redox and restoring eNOS function

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Hypertension is a major risk factor for cardiovascular diseases, and especially poses health problems for aging people. However, the pathogenesis of hypertension and the basic mechanism of blood pressure responses to aging are incompletely understood. Cytosolic thioredoxin (Trx-1) is a small (12kDa) antioxidant protein that protects against oxidative stress. As a reducing agent, it regenerates proteins and enzymes inactivated by oxidation. Considering that inactivated oxidized vessel protein accumulation is a major factor in age-related hypertension, we hypothesized a potential role of Trx-1 in amelioration of age-related hypertension by regenerating oxidized vessel proteins. To investigate this possibility, we recently developed a transgenic mouse line that is deficient in functional Trx-1 (dnTrx-Tg), and a complementary line that overexpresses functional Trx-1 (Trx-Tg). We observed that young dnTrx-Tg mice had significantly higher blood pressures than Trx-Tg mice. However, aged (>2 years) dnTrx-Tg and wild-type (WT) mice showed markedly decreased arterial relaxation, while aged Trx-Tg mice continued to function normally. Functional NO release, phosphorylation of eNOS, and decreased levels of superoxide generation were observed in aged Trx-Tg mice in contrast to aged WT or dnTrx-Tg mice. Further, injection of recombinant human Trx-1 for three consecutive days reversed hypertension in aged WT mice, and this effect lasted for at least 20 days. Our study established that the preservation of vessel redox state in aged mice is critical in protection against endothelial dysfunction and maintenance of normal blood pressure. Further, our study shows that reversal of hypertension in aging could be achieved by pharmacological intervention with redox-active drugs, which is a novel conceptual advance over the current treatment strategies in hypertension.

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