Expression of a Hypertension-causing Mutation in Cullin 3 (CUL3Δ9) Specifically in Smooth Muscle Causes Vascular Dysfunction and Hypertension

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Pseudohypoaldosteronism type II (PHAII) patients with mutations in cullin 3 (CUL3) resulting in exon 9 deletion (CUL3Δ9), exhibit severe early onset hypertension correlated with impaired kidney function. However, the extra-renal mechanisms remain uninvestigated. We hypothesized that expression of CUL3Δ9 protein in smooth muscle in mice impairs endogenous wildtype CUL3 (CUL3-WT) function and causes vascular dysfunction and hypertension. We generated transgenic mice inducibly expressing CUL3Δ9 protein in smooth muscle (S-CUL3Δ9) and measured blood pressure (BP) by radiotelemetry. We assessed vascular responses in the cerebral basilar artery and aorta using a pressurized and a wire myograph, respectively. S-CUL3Δ9 mice exhibited reduced expression of endogenous CUL3WT protein compared to non-transgenic (NT) in aorta. Systolic BP was significantly increased in S-CUL3Δ9 mice (127±2 S-CUL3Δ9 vs 117±1 NT, p=0.02). Basilar artery from S-CUL3Δ9 mice exhibited significantly impaired vasorelaxation to acetylcholine (ACh) (at 100 μM: 15±4% S-CUL3Δ9 vs 65±5% NT, p<0.0001), and to the nitric oxide donor sodium nitroprusside (SNP) (at 100 μM: 59±2% S-CUL3Δ9 vs 90±5% NT, p<0.05). Vasocontraction to angiotensin II (Ang II), phenylephrine (PE) and to endothelin 1 (ET-1) were significantly elevated in S-CUL3Δ9 transgenic mice. Consistent with data from basilar artery, aorta from S-CUL3Δ9 transgenic mice exhibited impaired ACh-mediated relaxation (at 100 μM: 55±2% S-CUL3Δ9 vs 71±7% NT, p<0.0001). Total RhoA protein was significantly elevated in aorta of S-CUL3Δ9 transgenic mice (1.6±0.2 S-CUL3Δ9 vs 1.0±0.1 NT, P<0.05). Serotonin stimulation caused a significant increase in active RhoA in S-CUL3Δ9 aorta (1.83±0.04 S-CUL3Δ9 versus 1.52±0.06 NT, p=0.005). Preincubation with the Rho-kinase inhibitor (Y27632) restored endothelium-dependent relaxation in basilar artery and aorta of S-CUL3Δ9 mice. Ang II infusion via osmotic minipump (200 ng/kg/min) resulted in elevated BP response (Systolic BP: 147 ± 2 S-CUL3Δ9 versus 130 ± 5 NT, p=0.04) and increased aortic stiffening in S-CUL3Δ9 mice. We conclude that CUL3Δ9 acts in a dominant negative manner by interfering with CUL3-WT and contributes at least in part to hypertension via its effects on the vasculature.

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