

## Effects of Endogenous Cardiotonic Steroids on Renal Vascular Smooth Muscle.

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Hypertension is the most prevalent disease in the U.S., and it is dependent upon a myriad of regulatory systems. The inherent relationship between blood pressure and renal sodium excretion establishes the central role of the kidney in the pathogenesis of hypertension. In addition to many well-described mechanisms that regulate renal sodium excretion, there is recent data suggesting that endogenous digitalis-like compounds, which act to inhibit the Na,K-ATPase, may play a central role in regulation of the kidney. These so-called cardiotonic steroids (CTS) potentially act through a variety of pathways, including by directly affecting Na,K-ATPase isoforms on renal vascular smooth muscle. In this study, therefore, we sought to examine the effects of endogenous CTS on renal vascular resistance in response to salt loading. Vascular smooth muscle expresses two different Na,K-ATPase isoforms, designated  $\alpha 1$  and  $\alpha 2$ . Thus, to evaluate the relative contribution of these isoforms to CTS-mediated responses, renal vascular reactivity was compared in three groups of mutant mice: 1) mice with CTS-sensitive  $\alpha 1$  and CTS-resistant  $\alpha 2$  (SR mice); 2) mice with CTS-resistant  $\alpha 1$  and CTS-sensitive  $\alpha 2$  (RS); and 3) mice with CTS-resistant  $\alpha 1$  and  $\alpha 2$  (RR). Anesthetized mice were instrumented to measure blood pressure and renal blood flow, and renal vascular resistance was calculated (Ohm's Law) before, during and after a 30-minute infusion of saline (3.3 $\mu$ l/min/gBW). Results are shown in the figure. Compared to RR, mice with a sensitive Na,K-ATPase isoform (either SR or RS) responded to saline infusion with a vasodilation. During the recovery period, RVR returned to baseline levels in both RR and RS mice, but in SR mice there was a dramatic vasoconstriction. These data indicate that endogenous CTS interact with both  $\alpha 1$  and  $\alpha 2$  Na,K-ATPase isoforms to regulate renal

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