

Novel catalytic antioxidant for CKD and hypertension

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Hypertensive chronic kidney disease (CKD) progresses relentlessly to end-stage renal disease independent of a low blood pressure goal or angiotensin-converting enzyme inhibition. Although CKD enhanced renal and vascular generation of reactive oxygen species (ROS), and the catalytic redox-cycling anti-oxide nitroxide tempol prevented ROS accumulation and moderated hypertension and renal damage in animal models, it is short lived and lacks potency. Therefore, a novel nitroxide was designed and synthesized (YK-4-250) with a prolonged duration of action (plasma disappearance half-time 5.4 hours) and compared to tempol in preventing cellular ROS (from lucigenin enhanced chemiluminescence in preglomerular vascular smooth-muscle cells cultured with 10^{-6} M angiotensin II) and in reducing mean arterial pressure (MAP) in conscious spontaneously hypertensive rats (SHR fitted with telemeters). YK-4-250 was more than 1000-fold more sensitive than tempol in preventing cellular ROS generation ($P < 0.01$), blocked $> 50\%$ of the pressor response to bolus IV doses of angiotensin II ($P < 0.01$) and displaced [^3H] angiotensin II competitively from cell membranes. Gavage with 30 micromol/kg YK-4-250 in conscious SHR produced an 80% greater reduction in MAP as equimolar tempol ($P < 0.05$) and MAP remained below baseline for 48 hours with tempol and for > 96 hours with YK-4-250 ($P < 0.005$). Conscious SHR receiving 4 daily gavages of 10 micromol/kg of each drug had only a modest reduction in MAP with tempol of -6 ± 2 mmHg but a progressive daily reduction with YK-4-250 to -26 ± 2 mmHg by day 4 ($P < 0.001$). We conclude that YK-4-250 is a novel catalytic antioxidant with angiotensin blocking and potent antihypertensive actions and a sufficiently prolonged duration to confer a cumulative action that greatly enhanced its efficacy, compared to tempol.

Biography

Wilcox C S is the Chief of the Division of Nephrology and Hypertension, Director of the Hypertension, Kidney and Vascular Research Center and Associate Director of the Angiogenesis Program in the Lombardi Cancer Institute. His special interests include secondary forms of hypertension (including renovascular hypertension, adrenal hypertension, and Hypertension complicating kidney disease), management of complicated and drug-resistant hypertension, and renal disease.

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