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Poster presentation

The uremic retention solute *p*-cresyl sulfate alters NO signal transduction by alteration of the soluble guanylate *cyclase* redox state

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Introduction

Chronic kidney disease (CKD) is associated with excessive cardiovascular disease and mortality. Nitric oxide (NO) – soluble guanylate cyclase (sGC) signaling is impaired in CKD patients, contributing to a near ubiquitous endothelial dysfunction. Loss of kidney function induces major alterations in the blood concentration of numerous molecules. Several of these so-called uremic retention solutes are known to interfere with NO-sGC signaling. *p*-Cresol/*p*-cresyl sulfate (PCS), a prototypic representative of the protein-bound uremic retention solutes, is independently associated with overall mortality and incident cardiovascular disease in hemodialysis patients. The mechanisms underlying this association remain elusive. We hypothesized that PCS interferes with NO-sGC signaling, thereby contributing to CKD-associated endothelial dysfunction and cardiovascular mortality.

Materials and methods

We investigated the effects of PCS on NO and cGMP generation and on eNOS, sGC and caveolin-1 expression by human umbilical vein endothelial cells (HUVEC). The effects of PCS on sGC activity were studied using purified rat sGC and sGC overexpressing CHO cells. Rabbit saphenous arteries were used for functional studies on the effect of PCS on vascular relaxation. The reduced (NO sensitive) sGC was activated by the sGC stimulator BAY 41-2272. Activity of the oxidized (NO-insensitive) sGC was probed using the sGC activator BAY 58-2667. *p*-Cresyl sulfate was synthesized according to Feigenbaum. Purity was > 99%.

Results

PCS reduced the calcium-ionophore stimulated cGMP generation by HUVEC in a time and dose-dependent fashion. While we observed a small significant reduction in eNOS expression (-15%, $P = 0.01$), NOx concentrations were not changed. Moreover, PCS reduced the NO-donor NOC-9 stimulated cGMP generation. As PCS did not affect sGC expression, we speculated that PCS changed the sGC redox state, thereby affecting sGC activity. BAY 58-2667 stimulated cGMP generation was increased in the presence of PCS, both at purified rat sGC and in sGC overexpressing CHO cells. In a model of phenylephedrine precontracted rabbit saphenous arteries, presence of PCS increased vasodilator activity of BAY 58-2667, while reducing the effects of sodium nitroprusside.

Conclusion

The uremic retention solute *p*-cresyl sulfate reduces NO-sGC signaling, through a shift of the sGC redox status towards the NO-insensitive oxidized/heme-free state. We believe PCS is the first known endogenous molecule to

change the sGC redox equilibrium. As altered sGC redox status contributes to impaired NO-sGC-cGMP signaling in patients with chronic kidney disease, this pathway may prove a novel therapeutic target in patients with chronic kidney disease and beyond.