Uric Acid Induces C-Reactive Protein (CRP) Expression Via Regulation of Angiotensin II Receptors in Vascular Smooth Muscle Cells

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Background : The systemic inflammatory reaction (SIR) plays a critical role in the development of cardiovascular disease (CVD) but the mechanisms responsible for inducing this response remain unknown. Recently we reported that noncrystalline uric acid (UA) could induce an inflammatory response in rat vascular smooth muscle cells. Since UA is elevated in subjects known to have SIR, we hypothesized that UA might induce production of C-reactive protein (CRP), which is a classic inflammatory marker as well as probable mediator of endothelial dysfunction and atherosclerosis.

Methods and Results : The effect of UA on CRP expression of human vascular smooth muscle cells (HVSMC) was studied. UA (6-9 mg/dL) stimulated HVSMC proliferation assessed by MTS assay and 3H-thymidine uptake. Interestingly, HVSMC expressed CRP constitutively, revealing that vascular cells are another source of CRP production. UA up-regulated CRP mRNA expression in HVSMC with a concomitant increase in CRP protein release into cell culture media. Compared to the effect of lipopolysaccharide (LPS, 100 ng) on CRP expression of HVSMC, UA showed an earlier and higher expression from 1 hour of stimulation. UA-induced up-regulation of CRP production in HVSMC was blocked by the organic anion transport inhibitor, probenecid (0.1 mmol/L), suggesting entry of UA into cells is responsible for CRP expression. UA-induced up-regulation of CRP was also attenuated by an angiotensin converting enzyme (ACE) inhibitor (Enalaprilat, 1 μM) or AT1 receptor (AT1-R) blocker (Losartan, 2 μM) whereas there was no effect on constitutional CRP expression. To understand the mechanism of the attenuation of UA-induced CRP expression by blocking of renin-angiotensin system, we investigated the expression of AT1-R and AT2-R in vascular cells. UA induced the mRNA expressions of AT1-R and AT2-R in HVSMC.

Conclusion : UA induced CRP expression in cultured human vascular cells, thus identifying a novel mechanism for the development of the systemic inflammatory response. The ability of UA to induce endothelial dysfunction, cause local activation of the renin-angiotensin system, and stimulate the expression of inflammatory mediators in human vascular cells provides direct and important evidence that UA has a key role in the pathogenesis of cardiovascular disease