

Inflammation and advanced glycation end products in uremia: Simple coexistence, potentiation or causal relationship?

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Inflammation and advanced glycation end products in uremia: Simple coexistence, potentiation or causal relationship? The causes for the high frequency of cardiovascular disease in dialysis patients are multifactorial in origin. Disturbances in the carbohydrate and lipid metabolism, the balance between oxidants and antioxidants and the immuno-inflammatory system are thought to play a role. Chronic uremia is characterized by the accumulation of advanced glycation end products (AGEs) and advanced oxidation products (AOPP) as well as activation of the acute phase response. High serum levels of these products and acute phase reactants such as C-reactive protein (CRP), fibrinogen and serum amyloid A can be found. CRP has been shown to predict cardiovascular and overall mortality in hemodialysis patients. Whether CRP is involved causally in atherosclerosis or merely represents a marker of disease is as yet unknown. Since CRP has been detected in colocalization with modified apolipoproteins or complement components in atherosclerotic lesions, a pathophysiological role seems very likely. AGEs as well have been detected in aortas of hemodialysis patients. Incubation of endothelial cells with AGEs induced expression of adhesion molecules with consecutive attraction of monocytes to the vessel wall. Thus far, clinical studies investigating the predictive effects of AGEs on cardiovascular mortality in hemodialysis patients are lacking. There is considerable debate about what factors turn on the acute phase response in this population. Proinflammatory effects of AGEs mediated through one receptor for AGEs, RAGE, have been described. We hypothesize that there may be a link between increased hepatic CRP production and the accumulation of AGEs in uremia. AGEs may stimulate CRP production in hepatocytes either directly or indirectly via interaction with monocytes.

Aldehyde or ketone groups of carbohydrates react nonenzymatically with primary amino groups of free amino acids or proteins to form a Schiff base. After rearrangement to the Amadori products (1-aminodesoxyketoses), a variety of complex compounds, the advanced glycation end products (AGEs), are formed by dehydration, condensation and elimination reactions [1]. In the presence of transition metal ions protein-bound

Amadori products are oxidized and the formation of AGEs is accelerated. Reactive dicarbonyls such as methylglyoxal, 3-deoxyglucosone and glyoxal are formed by glycooxidation of Amadori products and have been identified as important intermediates of AGE formation [2]. Reactive dicarbonyls, especially glyoxal and methylglyoxal, are also formed in the course of other reactions, where autooxidation of glucose is the most important one [3, 4]. Only few of the AGEs are well characterized, including carboxymethyllysine (CML), pentosidine, imidazolone and pyrraline.

AGEs accumulate in the course of ageing and at accelerated rates in diabetes and uremia. Their deposition in several tissues (skin, kidney, vessels) has been linked to activation of inflammatory cytokines, initiation of oxidative stress via generation of oxygen free radicals with subsequent development of atherosclerosis and glomerulosclerosis.

The reasons for AGE accumulation in uremia are only partly understood. Diminished renal clearance of AGEs may play a part [5]. Animal studies demonstrated that the kidneys remove circulating AGEs by clearing AGE peptides and metabolizing AGE proteins via the endolysosomal apparatus of the proximal tubules [6]. A significant relationship between AGE peptides and serum creatinine was observed and AGE concentration decreased rapidly after transplantation [7]. On the other hand, AGE accumulation may also rely on increased concentration of reactive dicarbonyls during uremia [8–10].

UREMIA: A VASCULOPATHIC STATE

Chronic renal failure has been described as a vasculopathic state [11]. Cardiovascular disease is the major cause of morbidity and mortality in patients on renal replacement therapy, accounting for approximately half of all deaths [12]. The accelerated aging of the vasculature in uremia has been attributed to the coexistence of several traditional and nontraditional risk factors. These factors are altered by uremia such as dyslipidemia, hyper-

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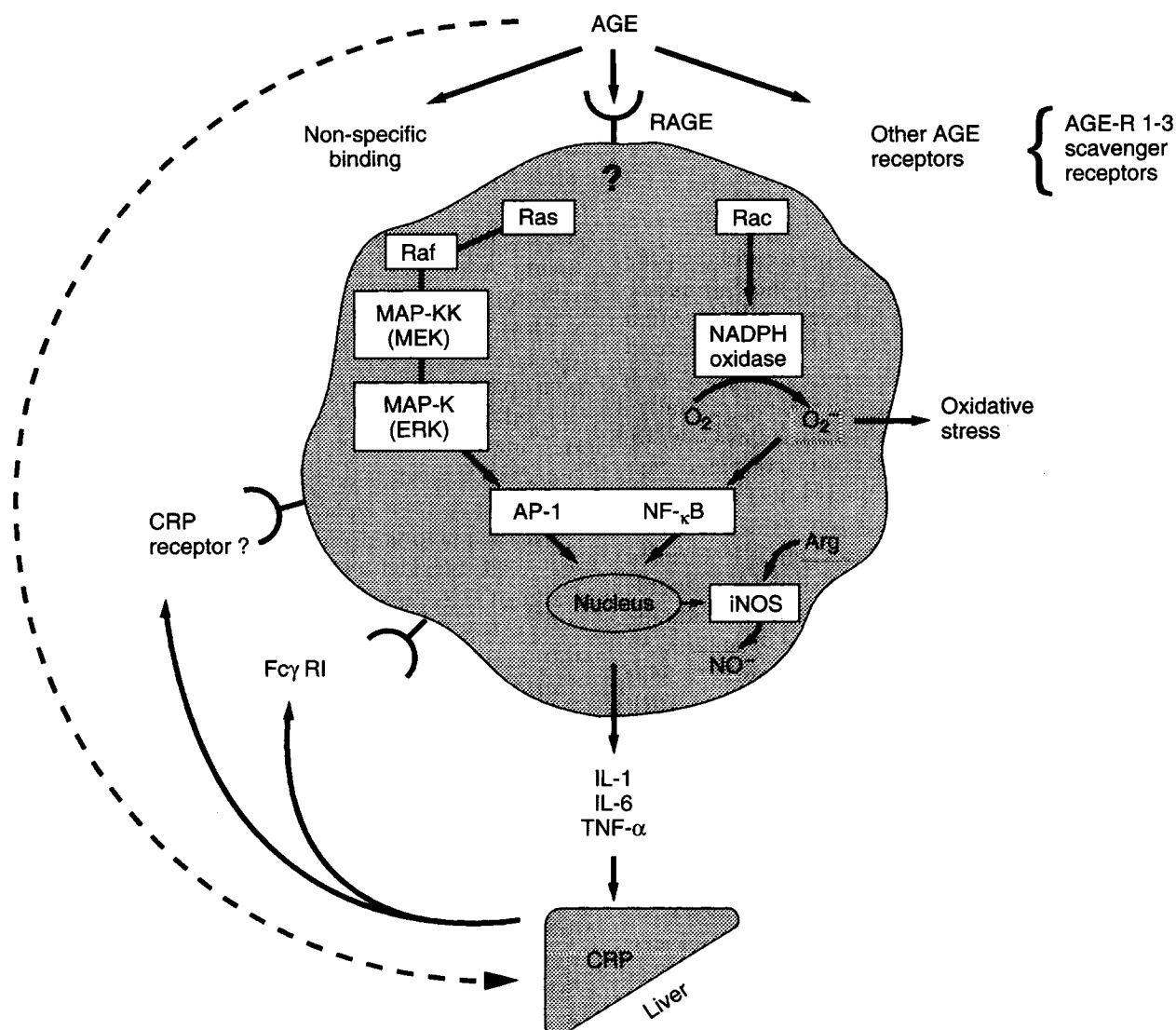


Fig. 1. Schematic drawing of the inflammatory cascade starting with the interaction of advanced glycation end products (AGEs) with monocytes leading to the production of proinflammatory cytokines, with a subsequent induction of the acute-phase-response in the liver. Besides the classical receptor for AGEs (RAGE) [49] several other receptor systems such as AGE receptors R1-3 or the scavenger receptors [50, 51] could also be implicated. AGE ligation of RAGE activates the Ras-MAP kinase and Rac pathway with subsequent activation of the nuclear transcription factors nuclear factor-κB (NF-κB) and activated protein-1 (AP-1) [19, 46, 52–54]. AGEs may lead to generation of superoxide anions (O₂⁻) through activation of the NADPH oxidase system [55]. A feedback mechanism may be present since C-reactive protein (CRP) produced by the liver again may interact with IgG receptors or the CRP receptor, which seems to be a distinct receptor [56, 57]. Whether AGEs can directly stimulate CRP production in hepatocytes needs further investigation.

lipoprotein(a)emia, prothrombotic factors (such as fibrinogen and PAI-1), hyperhomocyst(e)inemia or are uremia-related such as hemodynamic overload, anemia, increased oxidative stress, hypoalbuminemia, inadequate dialysis dose, divalent ion abnormalities (for example, hyperphosphatemia), metabolic acidosis and hypo/hyperkalemia [13]. There is good evidence that AGEs represent another stimulus for vascular disease in this population as they have been shown to accumulate in plasma and vasculature of nondiabetic uremic patients [14–16]. AGEs may promote atherosclerosis through in-

teraction with one RAGE on endothelial cells with consecutive expression of adhesion molecules such as vascular cellular adhesion molecule (VCAM-1) and further attraction of circulating monocytes to the vessel wall [17]. In nondiabetic uremic patients RAGE expression in endothelial cells was markedly increased compared to non-uremic controls [18]. AGEs also interacted with binding sites on monocytes/macrophages with resultant increased generation of oxygen species [19]. When activated monocytes release a cascade of reactive oxygen species, AGE formation is further promoted, thus per-

petuating the vicious cycle of atherogenesis. AGE peptides may also contribute to atherogenesis by enhancing apolipoprotein B modification, thus leading to enhanced uptake of low density lipoprotein (LDL) via the macrophage scavenger receptor pathway [20].

INFLAMMATION IN UREMIA

Chronic renal failure is not only characterized by the accumulation of AGEs, but also by an increase in the acute phase proteins C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen [21–25]. In several clinical studies CRP, SAA and fibrinogen were predictive of myocardial events, cardiovascular mortality, ischemic stroke and peripheral vascular disease [26–30]. Stenvinkel et al showed that CRP was associated with an increase in the intima-media thickness of carotid arteries in chronic renal failure patients [31]. Bergström et al first reported that elevated levels of CRP were the most powerful predictors of death in dialysis patients (abstract; *J Am Soc Nephrol* 6:573, 1995). This finding was confirmed in a prospective study by Zimmermann et al in which CRP predicted overall and cardiovascular death over a period of two years [25]. Whether CRP is causally involved in atherosclerosis (direct effect) or merely represents a marker of ongoing vascular damage (indirect effect) is a matter of current debate. Colocalization of CRP and oxidized or nonoxidatively but enzymatically modified LDL within the arterial wall of patients suggests a pathophysiological role in the atherosclerotic process [32–34]. Binding of enzymatically modified LDL to CRP was found to be Ca^{2+} -dependent, inhibitable by phosphorylcholine and accompanied by complement activation, important features in the course of early atherogenesis.

INFLAMMATION AND AGEs: WHAT DO WE KNOW?

Interleukin-6 (IL-6) is one of the principal mediators of the acute inflammatory response reflected by the production of fibrinogen and CRP in the liver [35–39]. IL-6 is produced by activated monocytes and macrophages, but also by activated T and B cells as well as endothelial cells. Renal insufficiency is associated with increased IL-6 levels [40, 41]. Among a number of other stimuli macrophages release IL-6, tumor necrosis factor- α (TNF- α) and IL-1 β upon stimulation with AGE proteins [42, 43]. Purified AGE- β_2 -microglobulin ($\beta_2\text{m}$) from long-term hemodialysis patients also stimulates synthesis and secretion of IL-6, TNF- α and IL-1 β [44]. In human astrocytes exogenous AGEs regulate the transcription and protein synthesis of granulocyte macrophage-colony stimulating factor (GM-CSF), another inflammatory cytokine [45]. These in vitro studies show that AGEs can

trigger inflammatory responses. Recently, RAGE could be identified as a signal transduction receptor for EN-RAGE, a member of S100/calgranulin polypeptides that accumulate at sites of inflammation [46]. While EN-RAGE interaction with RAGE promoted cell migration, proliferation and generation of proinflammatory cytokines, these responses could be prevented by blocking access of the ligand to RAGE or inhibiting RAGE signaling. A recent clinical study in patients with diabetic nephropathy revealed that elevated serum levels of free pentosidine and the monocyte activation marker neopterin were both correlated with the rate of progression of diabetic nephropathy [47]. Since a strong correlation existed between free pentosidine and neopterin levels, the authors concluded that there may be a link between monocyte activation and the release of free pentosidine from protein-bound pentosidine by these cells.

The stimulation of the monocyte by AGEs could be an initial signal of an important inflammatory cascade leading to CRP production in the liver (Fig. 1). Whether AGEs may also directly induce CRP production in hepatocytes and what type of AGEs could be involved needs further investigation. Miyata et al found that plasma pentosidine levels were highest in patients with rheumatoid arthritis as compared to patients with osteoarthritis, diabetes mellitus and normal subjects [48]. A strong correlation was found between pentosidine and CRP. Whether glycooxidation is upstream or downstream of inflammatory processes and whether CRP may modulate AGE action on endothelial cells or monocytes/macrophages remains to be investigated. In conclusion, much more work needs to be done to dissect the interactions between inflammation, glycation and oxidative stress and to find strategies for improving long-term outcome of patients with chronic renal insufficiency.

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