Expression of receptors for advanced glycation end-products in occlusive vascular and renal disease

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Abstract. Formation and deposition of advanced glycation end-products (AGEs) has been linked to late diabetic complications. Interactions of AGEs are at least partly mediated by binding of AGEs to their cellular surface receptor RAGE. This review summarizes the immunohistological data obtained for RAGE distribution in vessel segments of diabetic and non-diabetic patients with peripheral occlusive vascular disease and in kidneys of patients with diabetic nephropathy, and inflammatory and non-inflammatory renal disease. It is demonstrated that increased RAGE expression is not restricted to diabetes mellitus but contributes to a range of vascular and renal disorders.

Key words: AGE; diabetes; endothelium; occlusive vascular disease; RAGE; renal disease

Introduction

Nonenzymatic glycation of proteins and lipids, leading to the formation of advanced glycation end-products (AGEs), has been demonstrated to occur during ageing and at accelerated rate in diabetes mellitus [1-6]. The accumulation of AGEs in tissues has been correlated with the development of diabetic complications [4,6-14]. In vitro studies demonstrated that one mechanism through which AGEs exert their cellular effects is by specific interactions with cell surface associated receptors initially identified on endothelial cells and mononuclear phagocytes [13,15-23] In vitro studies demonstrated, that binding of AGEs to endothelial cells induces pleiotropic responses such as activation of the transcription factor NFκB [22], release of cytokines and growth factors [24-27], induction of procoagulant activity [28], increased adhesiveness for mononuclear phagocytes [21,25], increased membrane permeability [28], alterations of the basement membrane and quenching of NO [5]. These AGE-dependent modulations of endothelial function might be part of the pathomechanism that underlies long-term complications in diabetes mellitus, atherosclerosis and vascular disease.

The most completely characterized receptor for AGEs, RAGE, has been isolated [16] and cloned from bovine lung [15] and has been classified as a member of the immunoglobulin superfamily of cell surface molecules [15]. In vivo studies have demonstrated that RAGE mediates the clearance of AGEs from the intravascular space as well as AGE-dependent gene expression [20,21]. A survey for bovine tissues of normal animals showed that RAGE is constitutively expressed in various cells such as smooth muscle cells, mesangial cells and neurons [23], while under normal circumstances the vascular endothelium is mainly RAGE-negative [23]. Human atherosclerotic plaques [11,23] or experimental AGE-induced inflammatory lesions [17], however, have demonstrated increased expression of RAGE in the proximal vasculature [11,17,23]. These observations imply that RAGE is under regulatory control in vivo and demand the determination of pathophysiological relevant situations in which RAGE expression is modulated. In this context we studied the expression of RAGE in peripheral occlusive vascular [29] and renal disease [30]. This review summarizes the immunohistological results obtained for RAGE distribution in vessel segments of diabetic and non-diabetic patients with peripheral occlusive vascular disease and in kidneys of patients with diabetic nephropathy, and inflammatory and non-inflammatory renal disease.

Routinely excised vessel segments and kidney biopsies were immunostained with detailed characterized antisera to RAGE [16,20,23]. The immunohistochemical results were evaluated according to the staining intensity and scored as negative (−), faintly positive (+) and positive (++), whereas the score applied refers to the staining intensity and not to the frequency of positive cells [29,30].
RAGE expression in vascular and renal disease

Fig. 3. RAGE expression in VSMC of normal kidneys (column 1), kidneys from patients with non-inflammatory renal disease (column 3) and kidneys from patients with inflammatory and/or immune complex disease (column 4). The intensity of immunohistological staining for RAGE was graded from negative (−) to faintly positive (+) and positive (++), and is expressed as percentage of patients investigated.

Fig. 4. RAGE expression in podocytes of normal kidneys (column 1), kidneys from patients with diabetes (column 2), kidneys from patients with non-inflammatory renal disease (column 3) and kidneys from patients with inflammatory and/or immune complex disease (column 4). The intensity of immunohistological staining for RAGE was graded from negative (−) to faintly positive (+) and positive (++), and is expressed as percentage of patients investigated.

Expression of RAGE in capsular and tubular epithelial cells in renal disease

While most of the capsular (Figure 5a) and tubular (Figure 5b) epithelial cells were negative for RAGE expression in controls, they stained positive in renal disease (Figure 5a and b). Prominent staining for RAGE was observed in inflammatory and/or immune complex disease (Figure 5a and b). RAGE positivity was less pronounced in biopsies of non-inflammatory renal disease and only moderate in diabetes (Figure 5a and b).

Conclusion

Examination of RAGE immunostaining in vasa vasorum and kidney biopsies of patients with various occlusive vascular and renal diseases demonstrated that, compared with healthy controls, increased RAGE expression was not restricted to diabetes but was also observed in other types of vascular and renal disease. Particularly in kidney biopsies, staining for RAGE was only modest in diabetes, but prominent in inflammatory and/or immune complex disease. Although AGEs are known to accumulate in renal failure [31], RAGE positivity was also found in inflammatory and/or immune complex disease with only a slight decrease in renal function. This implies that AGEs are not the only determinant of RAGE expression and that non-AGE ligands present in inflammatory and/or immune complex disease might interact with RAGE to modulate cell–cell interactions, growth and cytokine release. This hypothesis is supported by the observation that the macrophage-derived receptor for AGEs is up-regulated by TNFα [32]. In accordance with this, preliminary in vitro studies have demonstrated TNFα inducible endothelial RAGE expression (unpublished results).
Since RAGE expression in vessels and kidneys is not specific for diabetic complications but is also observed in different pathophysiological reactions, these findings lend themselves to elucidating the role of cytokines, growth factors, lipoproteins and other factors as pathophysiologically relevant modulators of RAGE expression.

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References