Nuclear (receptor) power: retinoids in rat mesangioproliferative disease

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Abstract

Cytokine-driven proliferation and inflammation play important roles in the response of the kidney to injury and precede the development of glomerulosclerosis. There is great interest in agents which may interfere with such proliferation and inflammation. Therefore, a rat model of mesangioproliferative glomerulonephritis was studied and the effects of all-trans retinoid acid (RA) and isotretinoin, powerful anti-proliferative and anti-inflammatory substances, on glomerular damage and cell proliferation were examined. The use of retinoids was also warranted because of their known (suppressive) effects on genes involved in the pathogenesis of renal damage. RA prevented the blood pressure increase evoked by anti-Thy1.1 nephritis. Treatment with either RA or isotretinoin reduced the albumin excretion rate by 70%. Periodic acid–Schiff (PAS) stains revealed significantly fewer glomerular cells in nephritic rats treated with retinoids. Similarly, the number of mitoses and of cells which stained positively for proliferating cell nuclear antigen was significantly less in nephritic glomeruli treated with retinoids compared with the vehicle-treated group. Glomerular expression of platelet-derived growth factor B-chain was significantly reduced in the presence of retinoids. It was concluded that retinoids limit glomerular proliferation, glomerular lesions and albuminuria in an established model of renal damage. These findings point to retinoids as potential novel modulators of glomerular injury.

Keywords: all-trans retinoic acid; glomerulonephritis; renal disease; retinoid

The retinoid system

Retinoids are derived from retinol (vitamin A). Retinoids, however, are not involved in the visual process [1] but are responsible for development and embryology [2]. These effects are mediated through retinoid receptors, which are expressed in a tightly controlled tissue- and time-dependent fashion [2,3]. These receptors, which are not membrane bound, act as transcription factors and enter the nucleus after binding to ligand. They directly influence gene expression of target genes or modulate the action of other transcription factors [4]. This mode of receptor action implicates that retinoids act through steroid-like mechanisms. These compounds, unlike retinol or carotenoids, do not act as vitamins but as hormones [5].

The retinoid receptors belong to the steroid receptor superfamily which also comprises the vitamin D receptor, the PPAR receptor or the thyroid hormone receptor, and others. This is suggested by the modular composition of retinoid receptors which contain a ligand-binding and a DNA-binding domain similar to steroid receptors [4]. Although retinoid receptors share common features with the steroid family, they differ in their spectrum of actions.

In the last few years, the importance of retinoids in renal development became more and more evident, and is addressed further by the contribution of other groups in this issue.

What is the objective of using retinoids in the treatment of renal disease?

Retinoids act on renal and cardiovascular cells and the kidney

Mesangial cells, vascular smooth muscle and endothelial cells express different types of retinoid receptors [6,7]. In these cells, retinoids inhibit serum- or angiotensin II-induced proliferation or the expression of factors involved in renal disease, e.g. transforming growth factor-β1 (TGF-β1), endothelin-1, platelet-derived growth factor (PDGF) or nitric oxide synthase (NOS) [8–10]. They inhibit the action of these factors, i.e. angiotensin II through blockade of activator protein-1 [7]. The kidney expresses the different types of retinoid receptors [11].
Retinoids have anti-proliferative and anti-inflammatory actions

The anti-proliferative actions of retinoids have long been known. There is more than one pathway by which retinoids slow cellular growth; one is inhibition of activator-protein-1 [12], but it also involves the inhibition of cyclin 1 [6] and the stimulation of p21 and p27, inhibitors of the cell cycle. Beyond control of cell growth, retinoids may also induce apoptosis [13,14]. The anti-inflammatory action of retinoids is known from treatment of skin disease, and may depend at least in part on inhibition of NF-κB or modulation of expression of interleukins [15].

Retinoids as therapeutic agents in oncology and dermatology

The above-described effects of retinoids were exploited therapeutically in the treatment of promyelocytic leukaemia [16], certain lymphomas or bladder tumours. In dermatology, retinoids are being used in the treatment of nodular acne or psoriasis [17].

Retinoids in rat acute mesangioproliferative glomerulonephritis (anti-Thy1.1 nephritis)

Anti-Thy1.1 nephritis comprises both a proliferative component with a marked increase in the number of mesangial cells in the early repair phase of this disease and an inflammatory component which is indicated by the immigration of monocytes and macrophages into nephritic glomeruli. Mesangial cell proliferation is maximal ∼8 days after initiation of the disease in the rat [18]. In nephritic glomeruli, the number of mesangial cells per cross-section rose to 97 ± 3.2, compared with 69 ± 1.3 in non-nephritic control glomeruli. In contrast, in the presence of all-trans retinoic acid (RA), a prototypic retinoid, this increase was significantly blunted (80 ± 4.4) [8]. The reduction in mesangial cell number by retinoids was due to less proliferation, which was also indicated by immunohistochemical markers of cell proliferation such as proliferating cell nuclear antigen or Ki-67, or by counting the number of glomerular mitoses per glomerular cross-section. Furthermore, glomerular expression of PDGF-B, a strong pro-proliferative factor for mesangial cells, was reduced by retinoids [8].

Retinoids also reduced glomerular inflammation, as indicated by markers of monocytes/macrophage, i.e. ED-1 and Ki-M2R. In anti-Thy1.1 nephritic rats, 5.5 ± 0.9 ED-1-positive cells were found per glomerular cross-section (0.9 ± 0.2 in non-nephritic controls) whereas in the presence of 13-cis retinoic acid, only 1.9 ± 0.2 cells were found [8].

These changes on glomerular cell proliferation and inflammation induced by retinoids were accompanied by a significant reduction in the extent of glomerular capillary occlusion and by an ∼70% reduction in albuminuria (Figure 1). This supports the notion that retinoids reduce glomerular damage instead of just slowing glomerular repair by, for example, a reduced mesangial cell proliferation rate. Systolic blood pressure levels rose significantly in nephritic rats compared with non-nephritic controls. In the presence of RA, this blood pressure increase was abolished, probably due to the lesser degree of renal damage in the presence of retinoids [8]. Glomerular TGF-β1 gene and protein expression as well as urinary excretion of TGF-β1 protein increased in nephritic kidneys but was markedly less in the presence of retinoids [10]. TGF-β1 has been shown to be a factor which contributes to renal damage in this model. This suggests that the beneficial effects of retinoids may—at least in part—be mediated by a reduction in TGF-β1 expression.

The kidneys express both retinoid A receptor (RAR) and retinoid X receptor (RXR) [11]. These receptors are addressed by different retinoids, i.e. RARs by RA, and RXRs by 9-cis-RA. To answer the question of whether the renal retinoid effects are mediated through RAR- or RXR-dependent pathways, anti-Thy1.1 nephritic rats were treated by receptor-specific retinoids. With respect to anti-proliferation and anti-inflammation, no significant difference was evident between RAR- and RXR-specific compounds, indicating that retinoids act through both receptor subtypes on the kidney [19]. This, however, allows the selection of retinoids which are effective on the kidney, but limited in their side effects.

These results strongly encourage further testing of retinoids on immune- and non-immune-mediated models of retinoids and suggest that their important role in renal development and embryology may be extrapolated to treatment of adult renal disease. However, further studies are required to characterize their effects in the kidney and to clarify their mode of action, before these compounds might be considered as a novel therapeutic approach for renal therapy.

Fig. 1. Reduction of the 24 h albumin excretion rate by all-trans retinoic acid in rats with anti-Thy1.1-induced glomerulonephritis. Pre-treatment with all-trans retinoic acid attenuated the increase in albumin excretion rates. No change in albuminuria was observed in control rats treated with all-trans retinoic acid. Veh = vehicle, RA = all-trans retinoic acid, adapted from reference [8].
References