Potential role of retinoids in the therapy of renal disease

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**Introduction**

It is by now common knowledge that the processes of tissue injury and repair in renal disease do not depend on the action of single genes but involve a complex network of growth factors, cytokines, and vasoactive peptides that are further modulated by haemodynamic and metabolic factors. In this context retinoids, which are derivatives of vitamin A, have recently attracted attention as potential therapeutic agents. Their effects are pleiotropic, since retinoids modulate the function of several key transcription factors which are involved, among others, in damage and repair mechanisms that are operative in renal diseases. These considerations have raised hopes that the therapeutic potential of retinoids goes beyond dermatology and oncology to include also renal disease.

**Retinoid system**

It has long been known that retinol (vitamin A) is an essential component of the diet [1]. Both clinical and experimental studies documented that retinoids, i.e. biologically active derivatives of vitamin A, are necessary for normal growth, maintenance of tissues, reproduction, immune response and survival [2]. Retinol is stored in the liver and is further oxidized to retinoic acid in many target cells. Retinoic acid can substitute for vitamin A in vitamin A deficiency with the exception of reversing impaired vision and possibly also spermatogenesis [3]. In the embryologic state retinoic acid influences tubulogenesis and co-determines the number of glomeruli per kidney [4]. There is not only one single retinoid but rather a group of active retinoic acids with somewhat differing biological activities, i.e. all-trans RA, 9-cis RA, 4-oxo-RA, and others (Figure 1) [5,6]. Further complexity is introduced by the fact that there exist different cytoplasmic retinoic acid-binding proteins, CRABP I and CRABP II, which exhibit tissue-specific patterns of expression [7]. On the one hand these intracellular proteins protect retinoids from oxidation and degradation, but on the other they provide fine tuning of the intracellular concentrations

![Chemical structure of retinol (vitamin A) and its derivatives](image)

**Fig. 1.** Chemical structure of retinol (vitamin A) and of biologically active retinoids such as all-trans RA, the RXR-agonist 9-cis RA, and 13-cis RA (Isotretinoin).
of free, i.e. active retinoids. Still further complexity results from the fact that there are several types of retinoid receptors.

**Retinoid receptors**

The link between retinoids and steroids had not been appreciated until the retinoid receptors were discovered. Retinoic acid receptors belong to the supergene family of ligand-inducible transcriptional regulatory factors that includes steroid hormone, thyroid hormone, and vitamin D3 receptors as well as the peroxisome proliferator activated receptors (PPAR) and others. In this superfamily some functional principles are shared and this has facilitated the understanding of the receptor-mediated action of retinoids [8]. Since 1987, when the first retinoic acid receptor was detected, two families of retinoid receptors have been described, i.e. the retinoic acid receptors (RAR) and the retinoid X receptors (RXR), which are further subdivided into isotypes -α, -β, and -γ respectively [5,9,10]. The retinoid A receptors are activated by the prototypic retinoids all-trans retinoic acid (RA) and 9-cis RA. In contrast, the retinoid X receptors are activated exclusively by 9-cis RA. The analogy to the function of steroid receptors became obvious when the modular structure of the retinoid receptors and its 6 domains (A–F) had been clarified. The retinoid receptors comprise a DNA-binding domain (region C) and a ligand-binding domain (region E), but also numerous regulatory sequences [11]. The ligand binding domain of the retinoid receptors, unlike that of the steroid receptors, does not bind heat shock proteins [12]. The retinoid receptor subtypes are expressed in a tissue- and developmental-stage-specific pattern. RARα is the most widely expressed retinoid receptor isotype. In the kidney both RARs and RXRs are cell-specifically expressed. This organ is, therefore, potentially responsive to activation of both receptors by their respective agonists [13–15]. Double knock-out models, i.e. mice in which both RA and RX receptor subtypes have been deleted, have several malformations, including kidney agenesis, hypoplasia, or aplasia of the ureteral bud [16].

Retinoid receptors act as heterodimers. These are composed of one RAR and one RXR subunit, but RXRs may also heterodimerize with the other members of the nuclear hormone receptor family, such as the vitamin D, thyroid, PPAR receptors or others. As a result cross-talk between the different regulatory systems is possible [8].

**Retinoid receptor action**

Retinoid receptors are not membrane-bound. They are nuclear receptors, which enter the cell nucleus only after a ligand has been bound. They bind to specific sequence elements on the promoters of responsive genes, so-called RA- and RX-responsive elements, which allow the retinoid receptors to directly modulate gene transcription (such elements are contained in the promoters of genes coding for collagenase, laminins, collagens etc.) [17]. Retinoid receptors may also influence gene expression indirectly, however, by interfering with the expression or action of other transcription factors. The inhibition of activator protein-1 (AP-1) by retinoids is a well-studied example of retinoid action. AP-1, the composite of c-fos and c-jun proteins, is an important regulator of cell proliferation [18,19]. Retinoids inhibit AP-1-dependent gene activation by different mechanisms, i.e. down-regulation of c-fos in mesangial cells, or direct formation of an inactive complex with c-jun or inhibition of AP-1-DNA binding [20]. Retinoids, moreover, inhibit Nuclear factor-κB, which is involved in the regulation of inflammatory processes [21]. Retinoids also interact with CREB-binding protein complex, which integrates the signalling cascade of a number of regulatory pathways [22]. The above-mentioned transcription factors regulate many pro-proliferative and inflammatory pathways and integrate several signalling pathways.

**Actions of retinoids with potential relevance to kidney disease**

The above genetic experiments indicated a role of retinoids in renal development. Surprisingly, however, the action of retinoids in the adult kidney has not been studied, and the kidney is usually not considered a relevant primary target for retinoids. As mentioned above, these compounds interfere with cell proliferation, inflammation and the extracellular matrix. All these processes are relevant in the genesis of renal disease.

How do retinoids affect the kidney? This issue can first be addressed by considering the effects of retinoids in non-renal tissues or cell culture on genes which are known to play a role in renal disease. Retinoids lower the expression of PDGF, IGF-I, and their receptors [23,24]. All-trans RA blocks the interleukin-1-induced stimulation of inducible NO synthase activity [25]. Retinoids lower endothelin-1 expression and inhibit its proliferative action in cardiac myocytes [26]. Retinoids lower the expression of the AT1 receptor in vascular smooth-muscle cells. They modulate the expression of transforming growth factor-β1 (TGF-β1) in a cell- and context-specific manner in fibroblasts and myocytes [27]. Tissue-specific TGF-β1 expression depends on the retinoid status in the rat [28].

Recently, information on the action of retinoids in renal damage models, i.e. anti-Thy.1.1 nephritis, ureteral ligation, and subtotal nephrectomy has become available. In anti-Thy.1.1 nephritis (Figure 2), treatment of nephritic rats with all-trans RA or isotretinoin (13-cis RA, a retinoid pan-agonist) effectively limited renal damage and mesangial cell proliferation [29]. This was indicated by the reduction of the capillary
occlusion score as a measure of glomerular damage. The retinoids attenuated the increase in mesangial-cell proliferation in the repair phase, as demonstrated by the reduction of PCNA- and αSMA-positive cells in the glomerulus and by the reduction in total glomerular cell counts. In parallel, the glomerular expression of PDGF B chain was significantly less in retinoid-treated nephritic glomeruli. Retinoids lower endothelin-1 expression and down-regulate the endothelin A and B receptors in the kidney [Lehrke et al., in preparation]. Glomerular inflammation was partially abrogated and fewer infiltrating cells were found in the glomeruli after treatment with retinoids. Less glomerular expression of TGFβ1 on the gene and protein expression level was found in glomeruli of retinoid-treated rats compared to vehicle-treated ones. This was paralleled by less extracellular matrix deposition [30]. Renal function was better preserved in retinoid-treated rats and albuminuria was reduced by 70%. Beneficial effects were also observed in non-immune-mediated models of renal damage, i.e. unilateral ureteral obstruction and subtotal nephrectomy [Jocks et al., in preparation].

**Outlook**

These results illustrate that the interaction of retinoids with retinoid receptors represent a sophisticated molecular system which not only affects one specific pathway, but rather interferes with the activation of ‘gene programmes’ which are crucial in the response to injury. If the results of the animals experiments can be confirmed in human studies, the properties of retinoids to down-regulate inflammatory/proliferative programmes makes them attractive potential candidates for future therapeutic use in human renal disease.

In the past, the then available pan-agonistic retinoids were less attractive candidates because of their toxicity (vitamin A-like toxicity) and teratogenic effects, which mirror their role in embryogenesis [31]. This field has been revolutionized with the development of new synthetic retinoids, which are retinoid receptor-specific, do not isomerize into other retinoids in vivo, and are less toxic [32]. These pharmacological tools also allow us to specifically interfere with the different retinoid-receptor-specific pathways in the kidney. Retinoids are not complete newcomers in the arena of human therapy. Classically, in dermatology, retinoids

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Fig. 2. Representative PAS stains of anti-Thy1.1 nephritic rat glomeruli. Animals were treated either with vehicle (A) or with daily subcutaneous injections of all-trans retinoic acid (B) until 7 days after induction of anti-Thy1.1 nephritis by injection of the Thy1.1 antibody. Note fewer glomerular cells and less glomerular capillary collapse in glomeruli of retinoid-treated rats (B) compared to vehicle-treated animals (A) (adapted from [29]).
have been used for the treatment of hyperplastic skin disease to reconstitute skin integrity; in oncology, they are also used to inhibit the recurrence of skin tumours in chronic renal transplant patients. [33,34]. We feel the new available data support the assessment of the effects of retinoids in human renal disease. But we need more information on their efficacy and safety before their therapeutic potential can be fully assessed.

References