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Review

Spatial expression of the Kallikrein-Kinin system during nephrogenesis

S.S. El-Dahr

Tulane University Health Sciences Center, Department of Pediatrics, Section of Pediatric Nephrology, New Orleans, Louisiana, USA

Summary. During nephrogenesis, new nephrons are induced in the periphery of the kidney, while maturing nephrons occupy a deeper position in the renal cortex. This centrifugal pattern of maturation is characterized by nephron patterning, establishment of proximal-distal segment identity, tubular and glomerular growth and differentiation, and acquisition of specialized functions. All of these processes are coordinated in time and space with renal vasculogenesis, glomerulogenesis and regional hemodynamic changes. The end-result ensures that tubular structure and function are tightly coordinated with glomerular filtration during normal kidney development. To achieve this delicate task of glomerulotubular balance, the developing kidney produces growth factors and vasoactive hormones that act in a paracrine manner to regulate nephrovascular growth, differentiation and physiological functions. One such paracrine system is the kallikrein-kinin system (KKS), which generates bradykinin (BK) from the cleavage of kininogen by kallikrein.BK activates a G-protein coupled receptor, B2R, to regulate renal blood flow and salt and water excretion. The developing kidney expresses an endogenous KKS. Expression of the KKS components and B2R is intimately coordinated with the terminal differentiation of the distal nephron. Kallikrein marks the onset of connecting tubule development, whereas kininogen and B2R map to the developing ureteric bud branches and maturing collecting ducts.Gene targeting studies indicate that the fetal KKS plays an important role in the maintenance of terminal epithelial cell differentiation.

Key words: Kidney development, Vasoactive hormones, Bradykinin B2 receptor, Terminal differentiation

Offprint requests to: Samir El-Dahr, M.D., Professor, Department of Pediatrics, Section of Pediatric Nephrology, SL-37, Tulane University Health Sciences Center, 1430 Tulane Avenue, New Orleans, LA 70112 USA. Fax: 504-984-1852. e-mail: seldahr@tulane.edu

Introduction

Kinins, including bradykinin (BK), are formed from partial hydrolysis of kininogen by a family of serine proteases called kallikreins (Fig. 1) (Pesquero and Bader 1998; Blais et al., 2000; Campbell, 2001). Kinins produce their effects by binding and activation of two types of receptors, B1R and B2R. The B1R is activated by Des-Arg^9-BK, a natural product of kinins produced by the carboxypeptidase, kininase I. B1R are induced by tissue injury and are believed to mediate inflammatory functions (Marceau et al., 1997; Marceau and Bachvarov, 1998; Marceau et al., 1998; Mahabeer and Bhoola, 2000; Pesquero et al., 2000). Activation of the B2R by BK stimulates nitric oxide and prostaglandin production and results in vasodilation and natriuresis (Bhoola et al., 1992). Hence, mice lacking the B2R gene have a higher blood pressure and salt-sensitive hypertension (Bao et al., 1992; Borkowski et al., 1995; Emanueli et al., 1997, 1998; Emanueli and Madeddu, 1997, 1999; Madeddu et al., 1998; Cervenka et al., 1999, 2001; El-Dahr et al., 2000; Katori and Majima, 2003). Accumulating evidence also indicates that the KKS plays important developmental functions in the kidney and elsewhere (El-Dahr and Dipp, 1993; El-Dahr 1994, 1997; El-Dahr et al., 2000; Harrison-Bernard et al., 2003). This review focuses on the developmental aspects of the KKS, particularly as related to the cellular expression of KKS components in the developing kidney.

Ontogeny of the renal KKS

Tissue Kallikrein

Tissue kallikreins are encoded by a large gene family (15 in the human and 20 in the rat) (Carbini et al., 1993; Carretero et al., 1993).True tissue kallikrein, the first member of the kallikrein gene family (KLK1), is the main kininogenase and therefore will be discussed in more detail. The KLK1 gene is expressed at relatively high levels in the submandibular gland, pancreas, and

kidney (Ashley and MacDonald, 1985; Clements et al., 1988, 1990a,b, 1996; Nolly et al., 1993; Clements, 1994; Jahnke et al., 1994; Jaffa et al., 1997). Other tissues expressing the KLK1 gene are the gastrointestinal tract, heart, blood vessels, and pituitary gland.The rat KLK1 gene is 4.5 kb in length, contains five exons and four introns and its transcription is regulated in a tissue-specific manner by a number of hormones, salt and protein intake, and mineralocorticoids. Diabetes mellitus down regulates and insulin treatment up regulates renal kallikrein gene expression (Harvey et al., 1992; Jaffa et al., 1992, 1995, 1996, 1997; Tschope et al., 1997; Zuccollet al., 1997; Koch et al.,2003). Expression of the renal kallikrein gene is suppressed in obstructive nephropathy (El-Dahr et al., 1993) and in the chronic phase of renovascular hypertension (el-Dahr et al., 1993).

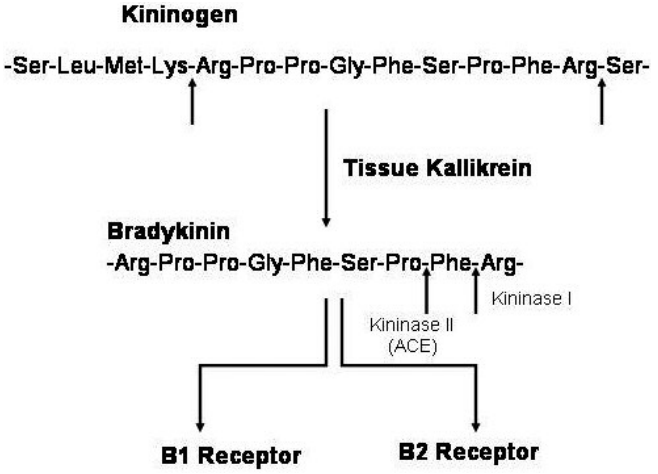

Fig. 1. The kallikrein-kinin system (KKS) cascade.

Intrarenal localization of tissue kallikrein

Mature kidney

It is generally agreed that the product of the KLK1 gene, true tissue kallikrein, is expressed in the cells of the connecting tubule (Omata et al., 1982; Orstavvik and Inagami, 1982; Barajas et al., 1986; Simson et al., 1987; Vio et al., 1988; Xiong et al., 1989; Vio et al., 1992; Cumming et al., 1994; Chen et al., 1995). We used a polyclonal antibody raised against rat urinary kallikrein in order to detect kallikrein distribution in the rat kidney (el-Dahr and Chao, 1992). As previously demonstrated, kallikrein-like immunoreactivity is found exclusively in the connecting tubules. However, at higher concentrations of the antibody, kallikrein-like immunoreactivity can be detected in the distal tubule from the macula densa to the outer cortical collecting duct (Fig. 2). These findings imply that, in addition to KLK1, other members of the kallikrein gene family are expressed in the distal tubule (El-Dahr and Chao, 1992). Vascular, glomerular, and other tubular segments did not contain kallikrein-like immunoreactivity. However, other investigators have localized kallikrein-like immunoreactivity in the glomeruli of rats with nephrotoxic acute renal failure (Orfila et al., 1993). It remains to be determined whether the redistribution of intrarenal kallikrein in pathological conditions represents de novo induction of a kallikrein-like gene or cellular uptake of kallikrein from the glomerular filtrate.

The intrarenal sites expressing the kallikrein genes were investigated by Xiong et al. (1989) using in situ hybridization techniques with a radiolabeled rat tissue kallikrein cDNA probe, which can recognize mRNAs of all the kallikrein-like genes. Accordingly, kallikrein mRNA is detected in both distal tubules and glomeruli.

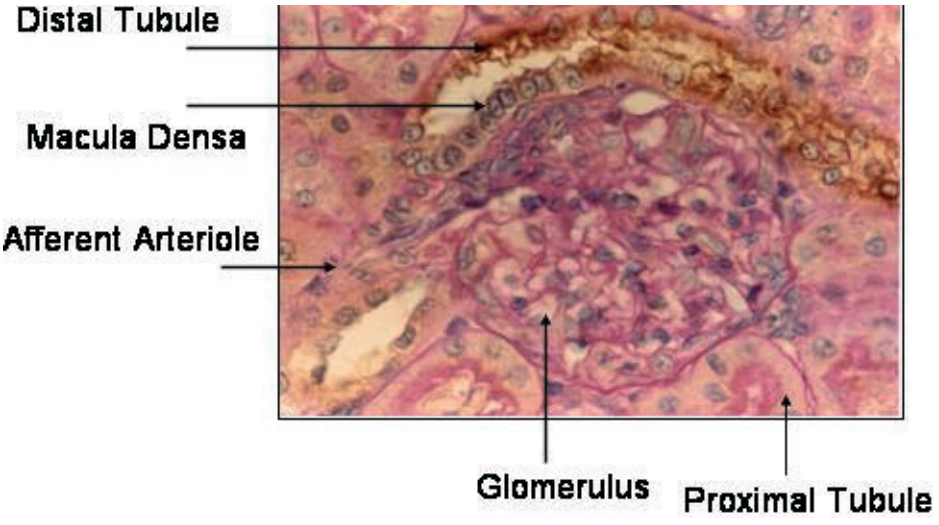

Fig. 2. Tissue kallikrein immunostaining utilizing a polyclonal kallikrein antibody, which cross-reacts with tissue kallikreins. Adult rat kidney. Periodic Acid-Schiff (PAS) counterstain. Kallikrein-like immunoreactivity extends along the distal tubule, excluding macula densa cells. Adapted with modifications from El-Dahr et al. 1992 (Am. J. Physiol. 262, F705-F711) with permission. x 400

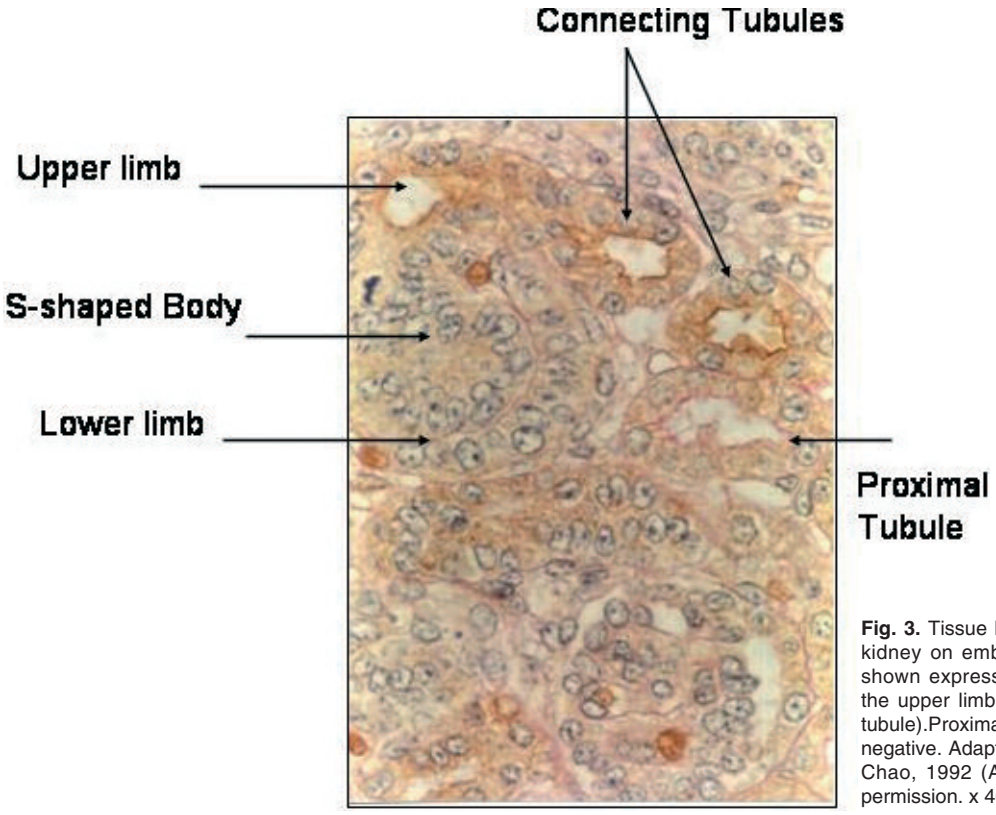

Fig. 3. Tissue kallikrein immunoreactivity in a fetal rat kidney on embryonic day 19. An S-shaped body is shown expression kallikrein-like immunoreactivity in the upper limb (precursor of distal tubule/connecting tubule).Proximal (PAS-positive) tubules are kallikrein-negative. Adapted with modifications from El-Dahr and Chao, 1992 (Am. J. Physiol. 262, F705-F711) with permission. x 400

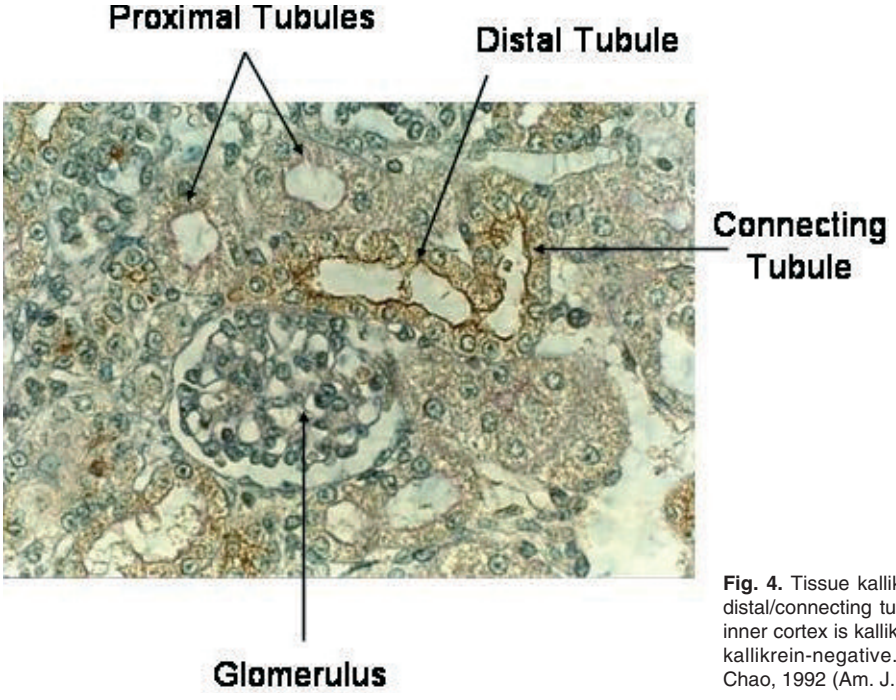

Fig. 4. Tissue kallikrein immunostaining in a newborn rat kidney. A distal/connecting tubule associated with a mature glomerulus in the inner cortex is kallikrein positive. Proximal (PAS-positive) tubules are kallikrein-negative. Adapted with modifications from El-Dahr and Chao, 1992 (Am. J. Physiol. 262, F705-F711) with permission. x 200

The glomerular kallikrein is possibly the product of the rKLK7 gene, which encodes for esterase B, whereas the mRNA detected in the distal tubule represents the rKLK1 and other renal kallikrein-like genes.

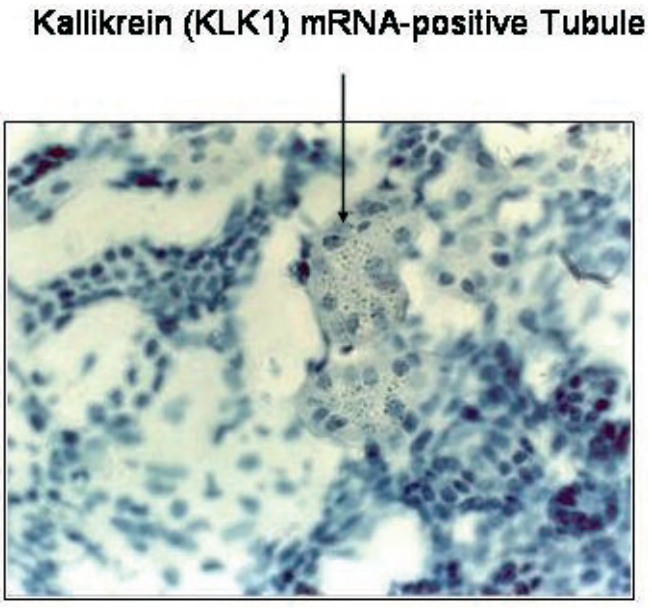

Fig. 5. Tissue kallikrein mRNA localization in a newborn rat kidney by in situ hybridization using an ^{35}S-labeled rKLK1-specific oligonucleotide probe. x 200

Developing Kidney

In the rat, specific kallikrein immunoreactivity is not detectable in the fetal kidney until day 19 of gestation (2 days before delivery) (El-Dahr and Chao 1992; Velarde et al., 1995). At this time, kallikrein is primarily localized in the upper limb of S-shaped bodies (precursor of distal tubule) (Fig. 3). Vesicles and comma-shaped bodies at the surface of the kidney do not contain kallikrein.In the newborn kidney, kallikrein is expressed in the distal tubules of deeper more mature nephrons (Fig. 4). In situ hybridization utilizing ^{35}S-labeled oligonucleotide probe complementary for rKLK1 mRNA revealed that kallikrein mRNA is expressed in the connecting tubules of maturing nephrons (Fig. 5) (El-Dahr and Chao 1992). Immature nephrons do not express detectable kallikrein mRNA.

Intrarenal kallikrein distribution is subject to developmental regulation. Once nephrogenesis is completed (around the second week of life in rodents), kallikrein distribution shifts from a limited distribution in the inner cortex to involve both inner and outer cortical distal tubules (El-Dahr and Chao 1992; Vio et al., 1992; Velarde et al., 1995) (Fig. 6). In the adult kidney, immunoreactive kallikrein is mainly distributed in the outer renal cortex on the luminal side of the connecting tubule.Apical localization of kallikrein is also noted in the developing kidney suggesting that the mechanisms responsible for kallikrein sorting and trafficking from the endoplasmic reticulum to the plasma membrane are conserved during ontogeny.

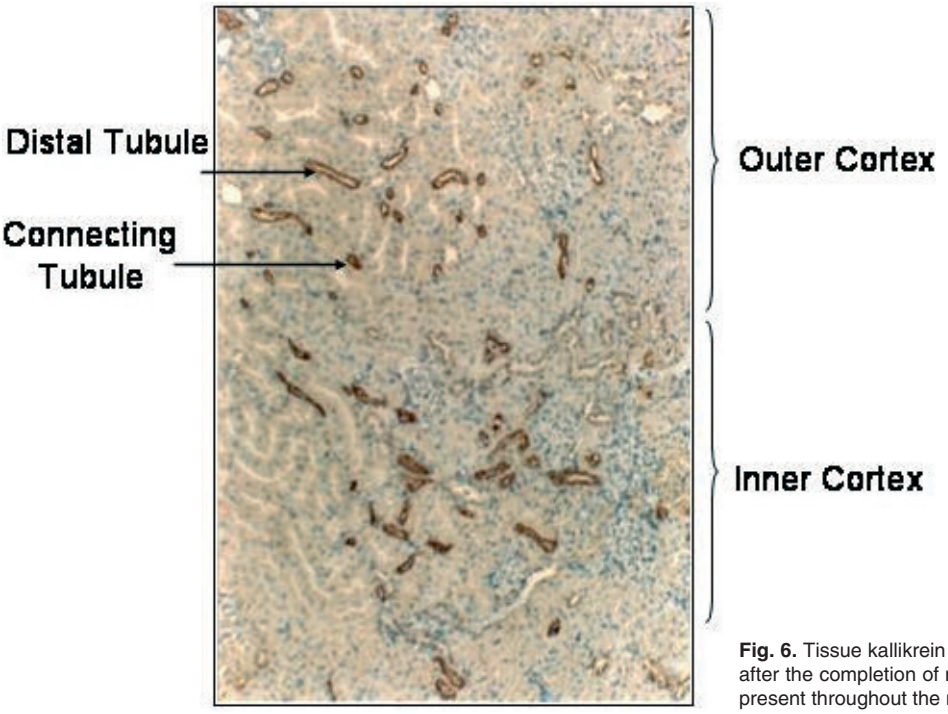

Fig. 6. Tissue kallikrein localization in rat kidney on postnatal day 12 after the completion of nephrogenesis. Kallikrein immunoreactivity is present throughout the renal cortex. x 200

Ultrastructural immunohistochemistry has shown that a portion of newly synthesized kallikrein is also sorted to the basolateral membrane of the connecting tubular cell (Vio and Figueroa, 1985). The distal tubular localization of tissue kallikrein is conserved among different species.

Functional implications related to sites of intrarenal kallikrein expression

The strategic localization of tissue kallikrein in the distal tubule permits the generation of BK from kininogen, a precursor protein synthesized and stored in the principal cells of the collecting ducts. Kinins generated intraluminally cause natriuresis. Kinins can also form in the interstitium where their levels can be modulated by variations in salt intake (Siragy, 1993; Siragy et al., 1993, 1994, 1997). Interstitial kinins, acting via nitric oxide generation, may participate in the regulation of medullary blood flow. In addition, the proximity of the distal tubule to the afferent arteriole may allow kallikrein to diffuse from the distal tubular cells to act in a paracrine manner on the preglomerular microvessels (Nishimura et al., 1980; Suzuki et al., 1981; Beierwaltes et al., 1985; Barajas et al., 1986;

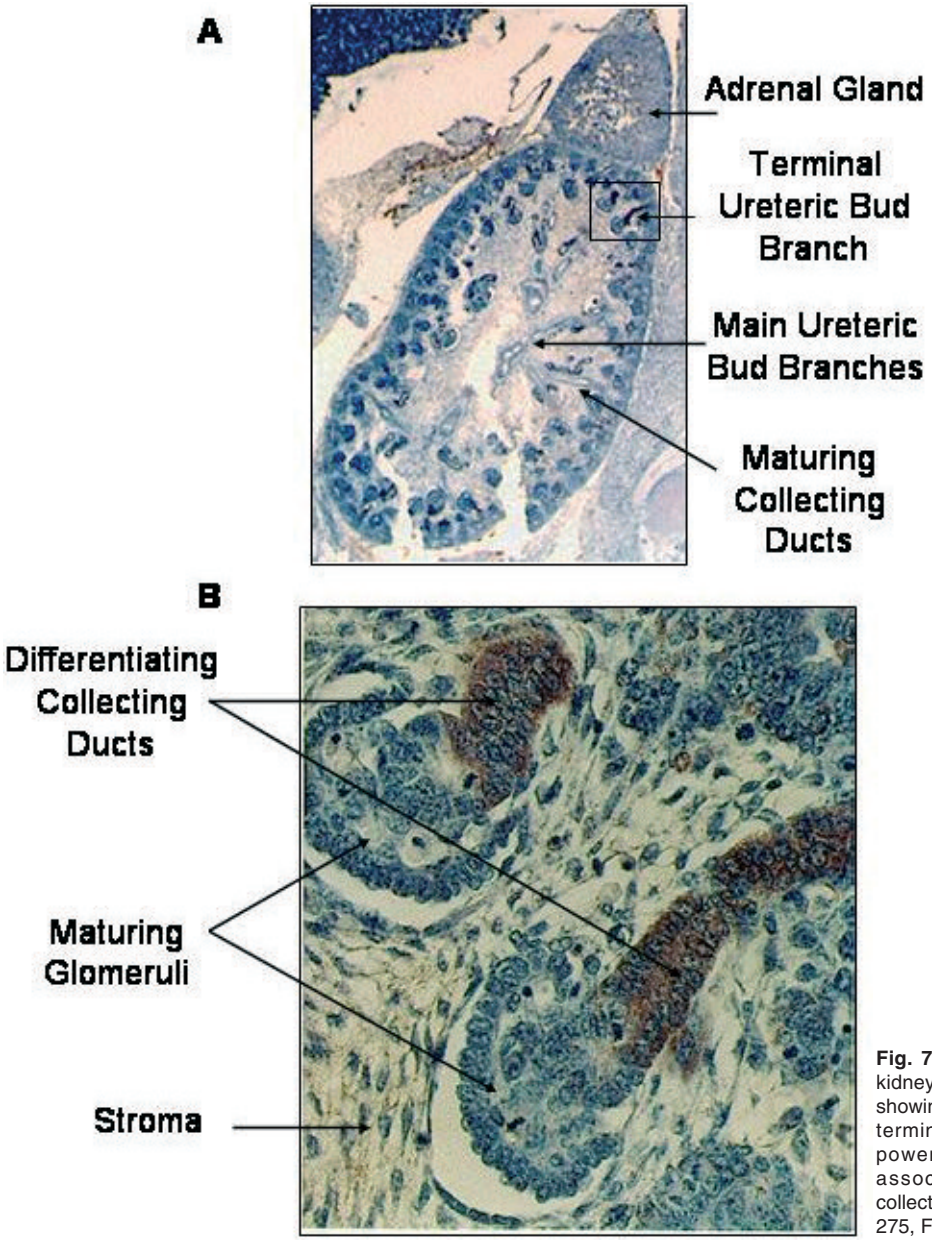

Fig. 7. LMW-kininogen immunostaining in fetal rat kidney on embryonic day 15. **A.** A low-power view showing the predominant localization of kininogen in terminal ureteric bud branches. x 40. **B.** A high power view (x400) showing two nephrons with associated kininogen-positive differentiating collecting ducts. El-Dahr et al. 1998 (Am. J. Physiol. 275, F343-F352) with permission. x 400

Velarde et al., 1995; Schmaier 2002, 2003). In this capacity, BK may stimulate renin secretion and synthesis from juxtaglomerular cells, which express B2R.

Kinnogen

The rat expresses a family of kininogen genes. The K-kininogen gene is the equivalent of the kininogen gene in humans and is transcribed into a primary transcript that is differentially spliced into a 2.3-kb high (HMW) and 1.8-kb low (LMW) mRNAs (Chen and Liao, 1993; Takano et al., 2000).The rat expresses the T-kininogen gene, which has extensive homology with the K-kininogen gene, particularly in the 5'-region. Interestingly, despite their homology, the two kininogen genes are differentially regulated during development (El-Dahr et al., 1992; El-Dahr, 1997). The near-term fetal liver expresses both HMW and LMW K-kininogen and T-kininogen mRNAs. Whereas the expression of K-kininogen transcripts does not change perinatally, the abundance of T-kininogen mRNA increases significantly perinatally only to decline after the first week of life.In addition to their role as precursors for kinins, kininogens possess potent inhibitory activity against lysosomal cysteine proteases, such as cathepsins B, H and L (Sueyoshi et al., 1985). This activity may be important for the survival of renal epithelial cells in the developing kidney.

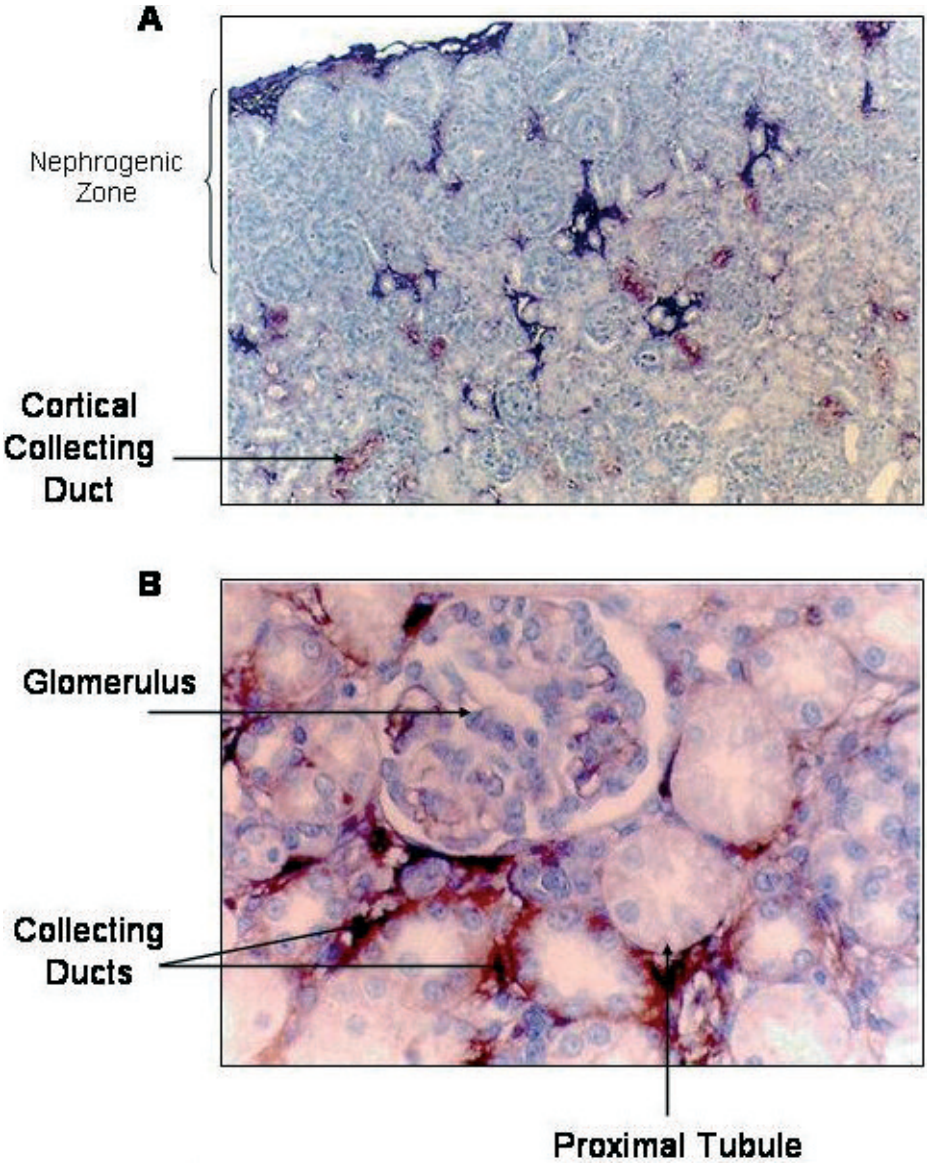

Fig. 8. Kininogen expression in a newborn rat kidney undergoing active nephrogenesis. **A.** Kininogen is expressed in cortical collecting ducts of maturing nephrons and in the peritubular interstitium. x 100. **B.** Kininogen expression in collecting ducts is seen on the basolateral aspects as well as in peritubular capillaries.The endothelium in glomeruli also expresses kininogen. x 400

Intrarenal localization of kininogen in the developing kidney

Kininogen immunoreactivity is detectable in the metanephros as early as E15 in the rat (El-Dahr et al., 1998). In the developing kidney, three temporal stage-specific patterns of kininogen expression are evident during nephrogenesis. During early-to-mid-fetal nephrogenesis (E15-E17), kininogen immunoreactivity is observed in the terminal ureteric bud branches (Fig. 7A,B). Only few kininogen-positive cells are observed within the main branches of the ureteric bud. Importantly, kininogen is not expressed in the nephrogenic mesenchyme but is expressed at low levels in stromal interstitial cells of the cortex and medulla (El-Dahr et al., 1998). During the later stages of nephrogenesis, kininogen immunostaining is seen mainly in the cortical collecting ducts (Fig. 8A). Following completion of nephrogenesis, kininogen assumes its classic adult-type distribution within the collecting ducts (Fig. 8B). In the adult kidney, higher concentrations of kininogen antibody are needed to reveal immunostaining due to declining abundance of kininogen with age. In addition to the collecting ducts, kininogen immunostaining is observed in the peritubular capillary network of the outer and inner medulla (Fig. 8B). Kininogen is expressed abundantly in other organs in the embryo such as in the hepatocytes of the liver and in the ducts and lobules of the salivary glands (Fig. 9). In summary, kallikrein and kininogen gene expression and BK production are activated in the ureteric bud branches and their epithelial derivatives during nephrogenesis, implicating an autocrine/paracrine role for the kallikrein-kinin system in distal nephron differentiation.

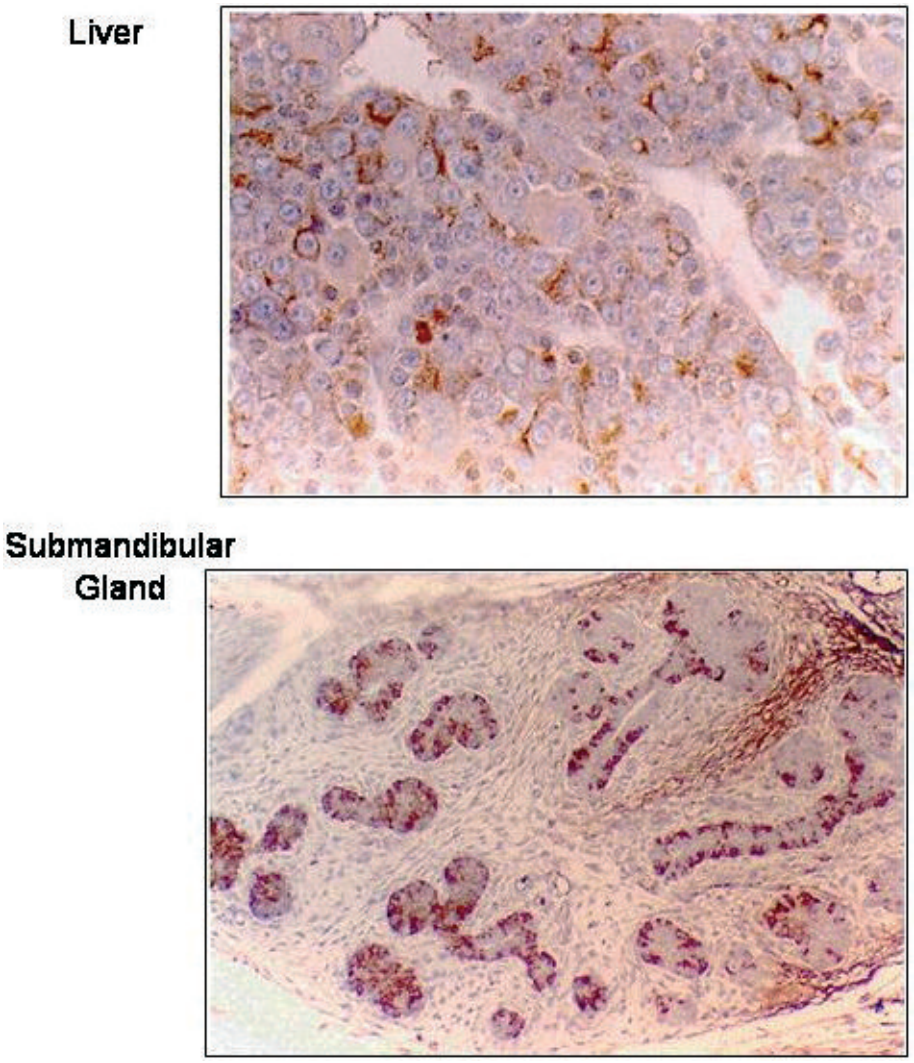

Fig. 9. Kininogen expression in the submandibular gland (glandular and ductal structures **(A)** and in the liver hepatocytes **(B)**. A, x 400; B, x 200

The bradykinin B2 receptor

The renal and cardiovascular actions of BK are mediated by the B2R. The rat B2R nucleic acid sequence predicts a protein of 366 amino acids having a MW of 41.6 kDa (McEachern et al., 1991). B2R is G-protein-coupled receptor.The developmental expression of B2R in the kidney was evaluated by immunohistochemical techniques using anti-peptide antibodies raised to various segments of the B2R protein (Figueroa et al., 1995, 1996; El-Dahr et al., 1997). Between day 1 and day 12, immunoreactive B2R is expressed in collecting ducts and connecting tubules (Fig. 10). Faint or no immunoreactivity is detected in mature glomeruli and proximal tubules. From day 22, in addition to the presence of immunoreactive B2R in distal segments and in cortical collecting ducts, B2R are concentrated in the outer stripe of the outer medulla including the medullary rays. At this site, the immunoreactivity is mainly localized in collecting ducts and to a less extent in the straight portion of proximal tubules. Furthermore, B2R immunoreactivity is observed in the inner stripe of the outer medulla and in the inner medulla (El-Dahr et al., 1997).

High power views of kidney sections from newborn rats revealed the presence of immunoreactive B2R in the upper limb of S-shaped nephrons and cortical collecting ducts of the developing cortex (Fig. 10) (El-Dahr et al., 1997).The immunolabeling of these structures is exclusively associated with their luminal membranes. In contrast, well differentiated nephron segments and cortical collecting ducts display immunoreactive B2R on both luminal and basolateral membranes.In marked contrast to the distinct immunolocalization of B2R in the differentiating tubular segments, no significant immunostaining is present in the subcapsular mesenchyme or pretubular aggregates (El-Dahr et al., 1997).

The results of the immunocytochemical localization of B2R provide important clues to the function of kinins during nephron maturation.The lack of B2R in the undifferentiated mesenchyme or pretubular aggregates indicates that kinins are unlikely neither to be involved in mesenchymal-epithelial conversion nor to modulate the number of induced nephrons.Rather, the distinct and restricted localization of B2R in the differentiating epithelium of maturing nephrons strongly suggests that activation of B2R is more important for tubular growth/differentiation and acquisition of function.

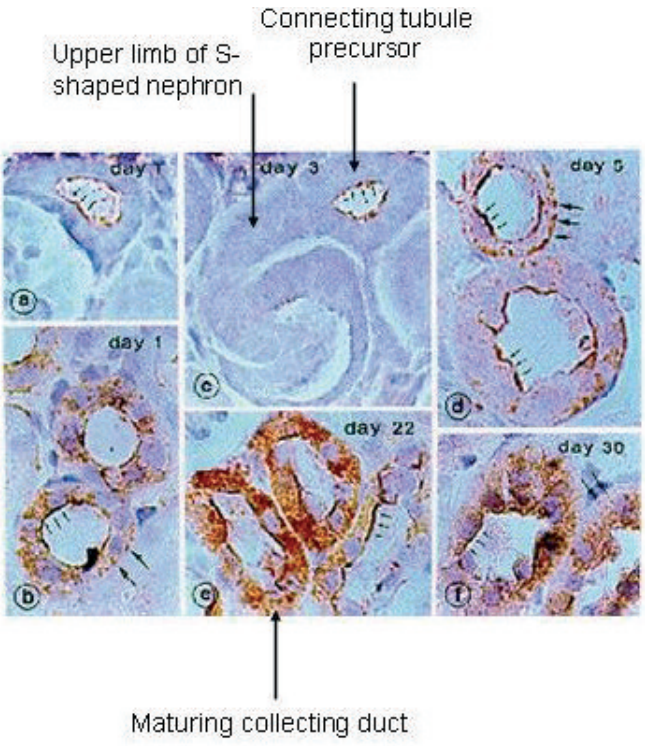

Fig. 10. Expression of bradykinin B2 receptors during successive stages of nephron maturation. Adapted with modifications from El-Dahr et al., 1997 (Kidney Int. 51, 739-749) with permission. x 1,300

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