Review Articles

Cyclooxygenase enzymes expression in the kidney

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Abstract

Chronic kidney disease (CKD) is one of a common cause of death in both human and animals. Persistent proteinuria of renal origin and systemic hypertension are clinical and biological findings that are usually associated with more progressive kidney disease. In human medicine, renal cyclooxygenase (COX) enzymes (especially COX-2) have been involved in the progression of CKD as one of the biological mechanism that modulates hypertension and/or proteinuria via their products, prostanoids. Furthermore, COX-2 has been proposed to play a pathophysiological role in experimental models of progressive renal injury. However, inhibition of COX enzyme activity by non-steroidal anti-inflammatory drugs (NSAIDs), when used in clinical practice to provide pain relief and anti-inflammatory effects, can lead to renal adverse effects. This is because the prostanoids generated by renal COX enzymes have important physiological roles in the kidney.

Keywords: cyclooxygenase; prostanoids; kidney; chronic kidney disease

การแสดงออกของเอนไซม์ Cyclooxygenase ในไต

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บทคัดย่อ

โรคไตเรื้อรังเป็นหนึ่งในสาเหตุหลักของการเสียชีวิตทั้งในมนุษย์และสัตว์ การพบภาวะโปรตีนในปัสสาวะเรื้อรังที่มีต้นกำเนิดมาจากไต และภาวะความดันโลหิตสูงถือเป็นสองปัจจัยที่มีความเกี่ยวข้องกับการพัฒนาของโรค การศึกษาในมนุษย์พบว่าเอนไซม์ cyclooxygenase (COX) โดยเฉพาะ COX-2 ที่แสดงออกในไตมีส่วนร่วมในการพัฒนาของโรคไตเรื้อรัง โดยเป็นหนึ่งในกลไกทางชีวภาพในการปรับเปลี่ยนระดับความดันโลหิตและโปรตีนในปัสสาวะ ผ่านทางสารที่เกิดจากปฏิกิริยาทางเคมี คือ prostanoids นอกจากนี้จากการทดลองโดยเหนี่ยวนำให้ไตเกิดความเสียหายพบว่า COX-2 มีบทบาทในการก่อให้เกิดพยาธิสรีระวิทยา อย่างไรก็ตามการศึกษาทางคลินิกพบว่าเมื่อยับยั้งการทำงานของเอ็นไซม์ COX ด้วยยา non-steroidal anti-inflammatory (NSAIDs) เมื่อยับยั้งการทำงานของเอ็นไซม์ COX ด้วยยา non-steroidal anti-inflammatory (NSAIDs) ก่อให้เกิดผลเสียต่อไต ทั้งนี้เนื่องจาก prostanoids ที่ได้จากเอ็นไซม์ COX ของไต มีบทบาทสำคัญทางสรีระวิทยาของไต

คำสำคัญ : cyclooxygenase; prostanoids; ไต; โรคไตเรื้อรัง

Introduction

After the discovery of COX in 1971 by Sir John Vane (Vane 1971), alternative forms of this enzyme were speculated to exist. In early 1990s many studies identified 2 isoforms of COX, designated COX-1 and COX-2 (Rosen, Birkenmeier et al. 1989; Simmons, Levy et al. 1989; Fu, Masferrer et al. 1990; Kujubu, Fletcher et al. 1991; Smith 1992). COX-1 was believed to be a constitutive form or housekeeping enzyme involved in physiological processes that are protective, while COX-2 was an inducible enzyme involved in inflammation. However, it soon became clear that this was a simplistic classification. In the kidney for example, COX-2 and COX-1 both appear to play important homeostatic and protective roles. In the absence of inflammation, COX-2 is also detectable in both normal and diseased human kidney and there are indications that COX-2 plays an important role in normal kidney function (Harris and Breyer 2001; Simmons, Botting et al. 2004).

COX-1 expression

Studies localising COX-1 mRNA or protein to different sites within the kidney show variability between a species and with age within a given species making the situation somewhat confusing. COX-1 protein has been localized by immunohistochemistry to the endothelial cells of the renal afferent arterioles in humans (Komhoff, Grone et al. 1997; Khan, Venturini et al. 1998; Zidar, Odar et al. 2008), monkeys, dogs and rodents (Khan, Venturini et al. 1998). COX-1 immunoreactivity was seen in the human (Komhoff, Grone et al. 1997; Zidar, Odar et al. 2008), rabbit (Schumacher, Castrop et al. 2002), rat (Campean, Theilig et al. 2003) and mice (Campean, Theilig et al. 2003; Radi and Ostroski 2007; Meskell and Ettarh 2009) glomeruli, while COX-1 protein was reported thin loop of Henle of human but not animal tissue (Komhoff, Grone et al. 1997; Nantel, Meadows et al. 1999). COX-1 protein was discovered in the proximal tubule (Meskell and Ettarh 2009), the macula densa in mice (Radi and Ostroski 2007; Meskell and Ettarh 2009) and the distal tubule of rats and mice (Campean, Theilig et al. 2003; Meskell and Ettarh 2009). However, a previous study failed to detect COX-1 in the macula densa of the rat (Campean, Theilig et al. 2003). There is a report of COX-1 expression in the thick ascending limb of the loop of Henle in mice (Radi and Ostroski 2007).

COX-1 antigenicity was widely detected in the collecting duct of humans (Komhoff, Grone et al. 1997; Khan, Venturini et al. 1998; Nantel, Meadows et al. 1999; Zidar, Odar et al. 2008), monkeys (Khan, Venturini et al. 1998), dogs (Khan, Venturini et al. 1998), rabbits (Schumacher, Castrop et al. 2002), rats (Harris, McKanna et al. 1994; Khan, Venturini et al. 1998; Campean, Theilig et al. 2003) and mice (Campean, Theilig et al. 2003; Radi and Ostroski 2007). COX-1 mRNA and COX-1 protein were detected in the collecting duct ampula of neonatal rabbit kidney suggesting a role of this isoform in tubulogenesis (Schumacher, Castrop et al. 2002). The consistent finding of constitutive collecting duct COX-1 indicated that COX-1 may play a role in water homeostasis. COX-1 expression in the medullary interstitial cells was reported in humans (Komhoff, Grone et al. 1997; Khan, Venturini et al. 1998; Nantel, Meadows et al. 1999), monkeys (Khan, Venturini et al. 1998), rabbits (Schumacher, Castrop et al. 2002), and rats (Harris, McKanna et al. 1994; Khan, Venturini et al. 1998; Campean, Theilig et al. 2003) but this isoform was not detected in dog interstitial cells (Khan, Venturini et al. 1998). Only the human vasa recta were found to express COX-1 protein (Komhoff, Grone et al. 1997). In rats, renal medullary infusion of a COX-1 selective inhibitor induced salt-sensitive hypertension (Ye, Zhang et al. 2006). This suggested roles of COX-1 in natriuresis and blood pressure regulation. The renal localization and proposed functions of COX-1 are summarized in Tables 1-3.

COX-2 expression

Similarly, species and age-dependent differences in the expression of COX-2 occur and complicate the interpretation of these studies. COX-2 expression appears, in general, to be more affected by physiological state (diet, sodium loading, and water deprivation) than COX-1. COX-2 expression has been localized to the afferent arteriole of adult humans (Khan, Venturini et al. 1998; Nantel, Meadows et al. 1999; Therland, Stubbe et al. 2004), monkeys (Khan, Venturini et al. 1998) and dogs (Khan, Venturini et al. 1998) but was not found in rabbits (Schumacher, Castrop et al. 2002), rats (Harris, McKanna et al. 1994; Vio, Cespedes et al. 1997; Khan, Venturini et al. 1998; Campean, Theilig et al. 2003) and mice (Campean, Theilig et al. 2003; Radi and Ostroski 2007). Controversially, from the other studies, in adult human subjects, COX-2 expression could not be detected in the afferent arteriole (Komhoff, Grone et al. 1997; Zidar, Odar et al. 2008). Expression of COX-2 protein in glomeruli was reported in human (Komhoff, Grone et al. 1997; Khan, Venturini et al. 1998; Nantel, Meadows et al. 1999; Therland, Stubbe et al. 2004; Zidar, Odar et al. 2008), monkey (Khan, Venturini et al. 1998) and rabbit kidneys (Schumacher, Castrop et al. 2002) but not in dogs (Khan, Venturini et al. 1998) or rats and mice (Harris, McKanna et al. 1994; Vio, Cespedes et al. 1997; Khan, Venturini et al. 1998; Campean, Theilig et al. 2003; Radi and Ostroski 2007). Only two studies have found COX-2 to be expressed in the proximal tubule of normal humans (Zidar, Odar et al. 2008) and mice (Radi and Ostroski 2007) whereas in other species COX-2 does not appear to be found in this location. The thick ascending limb of the loop of Henle showed dense expression of COX-2 in older humans (Nantel, Meadows et al. 1999), human foetal tissue (Therland, Stubbe et al. 2004), dogs (Khan, Venturini et al. 1998), rats (Harris, McKanna et al. 1994; Vio, Cespedes et al. 1997; Khan, Venturini et al. 1998; Campean, Theilig et al. 2003) and mice (Radi and Ostroski 2007). However, one study reported that COX-2 expression was absent from the thick ascending limb of the loop of Henle in mice (Campean, Theilig et al. 2003). In humans, by contrast, studies involving younger human subjects (<50 years old) did not identify COX-2 in the thick ascending limb of the loop of Henle (Komhoff, Grone et al. 1997; Khan, Venturini et al. 1998; Zidar, Odar et al. 2008). It is not clear whether this difference between reports is because of a true age-related change in COX-2 expression in the human kidney or whether the findings are related to methodological differences.

The macula densa is a site in the kidney where constitutive expression of COX-2 has been reported in most species examined, with the possible exception of humans and non-human primates. Thus, COX-2 immunopositive cells were found in the macula densa of kidney tissues from dogs (Khan, Venturini et al. 1998), rabbits (Schumacher, Castrop et al. 2002; Fuson, Komlosi et al. 2003), rats (Harris, McKanna et al. 1994; Khan, Venturini et al. 1998; Campean, Theilig et al. 2003) and mice (Campean, Theilig et al. 2003; Radi and Ostroski 2007). In rabbits, macula densa COX-2 co-locatized with PGE_2 synthase, and expression was elevated in response to salt depletion (Fuson, Komlosi et al. 2003). The first report of presence of COX-2 in the human macula densa was in 1999. COX-2 immunoreactivity has been seen in this structure from all subjects over 50 years old (Nantel, Meadows et al. 1999) and foetal human kidney (Therland, Stubbe et al. 2004), whereas other studies have failed to detect COX-2 in the normal adult human macula densa (Komhoff, Grone et al. 1997; Khan, Venturini et al. 1998). Again, the reasons as to why some studies did not detect COX-2 protein in the macula densa might be either because of a true age effect or related to methodological differences between the studies. However, human patients with a clinical history of compromised renal function associated with diabetic nephropathy, hypertension, and congestive heart failure, COX-2 protein and mRNA was also observed in the macula densa whereas no

expression could be detected using the same techniques in normal kidneys (Khan, Stanfield et al. 2001).

COX-2 expression has been reported in distal tubules of mice only (Radi and Ostroski 2007). There was no evidence of COX-2 immunostaning in the distal tubule in humans (Komhoff, Grone et al. 1997; Khan, Venturini et al. 1998; Nantel, Meadows et al. 1999; Zidar, Odar et al. 2008) and other animals (Vio, Cespedes et al. 1997; Khan, Venturini et al. 1998; Campean, Theilig et al. 2003). COX-2 expression has been found in the collecting duct of rabbits (weak) (Schumacher, Castrop et al. 2002) and mice (Radi and Ostroski 2007) but not in human (Komhoff, Grone et al. 1997; Nantel, Meadows et al. 1999) and rats (Harris, McKanna et al. 1994; Vio, Cespedes et al. 1997; Ye, Zhang et al. 2006). COX-2 immunoreactivity in the medullary interstitial cells was observed in human (Nantel, Meadows et al. 1999), dog (Khan, Venturini et al. 1998) and rat tissue (Harris, McKanna et al. 1994; Khan, Venturini et al. 1998; Campean, Theilig et al. 2003; Ye, Zhang et al. 2006; Radi and Ostroski 2007) but not in the monkey (Khan, Venturini et al. 1998). A study in rat found remarkable COX-2 expression in the medullary interstitial following chronic salt loading supporting a role of this enzyme in blood pressure homeostasis during high-salt intake (Ye, Zhang et al. 2006). Once again, not all studies agree and two studies involving human tissue were unable to find COX-2 expression in the interstitial cells (Komhoff, Grone et al. 1997; Khan, Venturini et al. 1998). Similar patterns of COX-2 distribution were found in vasa recta of human subjects (Komhoff, Grone et al. 1997). The renal localization and function of COX-2 are summarized in Table 4-6.

The importance of COX-2 in renal physiology has been confirmed by studies which show upregulation of this enzyme in response to physiological stimuli. It is possible that changes in expression according to the physiological state of the animal or subject could in part explain the differences between studies in terms of COX-2 protein expression. For example, COX-2 derived prostanoids (in this case PGE_2) are important in dealing with an increase in sodium chloride intake in rats. A high salt diet enhances COX-2 expression in the renal medulla whereas selective infusion of a COX-2 inhibitor into the renal medulla leads to a rise in systolic blood pressure (SBP) in response to the increased sodium chloride intake (Chen, Zhao et al. 2008). Evidence that COX-2-derived prostanoids are involved in regulation of renin secretion includes the observations that COX-2 is expressed in the macula densa and that reducing sodium intake, which leads to an increase in plasma renin activity, also leads to up-regulation of COX-2 protein expression in the macula densa (Harris 2003). Rats treated with selective inhibitors of COX-2 or genetically modified mice deficient in the COX-2 gene have a blunted response to reduction in salt intake in terms of renin secretion (Vaneckova, Cahova et al. 2004). Finally, COX-2 expression is increased in the renal medulla in rats deprived of water. If COX-2 is inhibited in animals deprived of water, medullary interstitial cells undergo apoptosis demonstrating the protective properties of COX-2-derived prostanoids in this hypertonic area of the kidney (Neuhofer, Holzapfel et al. 2004).

Renal cyclooxygenase system and chronic kidney disease

In the kidney, COX system has received particular interest as one of the biological systems that modulates renal blood flow and glomerular filtration rate (GFR) due to the regulation of vascular tone and regulates renal tubular functions (particularly sodium and water handling) as a result of the actions of prostanoids produced. COX-2 is constitutively expressed and plays important roles in normal kidney function (Vio, Cespedes et al. 1997; Harris and Breyer 2001; Khan, Stanfield et al. 2001; Luo, He et al. 2005). However, the contribution of each COX isoform in regulating the kidney is not entirely clear, there appear to be species variations, perhaps related to physiological variability.

Although COX-2 selective inhibitors have been introduced into human and veterinary medicine as drugs with potentially fewer side effects than the non-selective COX inhibitors, it is clear that COX-2 selective drugs are likely to have significant effects on kidney function. For example, a selective COX-2 inhibitor, celecoxib, at high dose markedly reduced renal blood flow and GFR during salt depletion in human subjects (Rossat, Maillard et al. 1999).

Given the importance of COX-derived products in regulating vascular and tubular functions in the kidney and adapting these according to different physiological conditions, it would be surprising if COX enzymes were not involved in the adaptations occurring in the kidney in response to the loss of renal mass. The remnant kidney model has been used to investigate this. In a mouse model, COX-2 was upregulated in the remnant tissue and treatment of mice with a selective COX-2 inhibitor reduced the expression of mediators of tubulointerstitial injury. The rat remnant kidney model is characterised by abnormal COX-2 expression in glomeruli, vessels and interstitium. Treatment of this model with a non-selective COX inhibitor (nitroflurbiprofen) alone or in combination with losartan (angiotensin AT) 1 receptor blocker) greatly reduced the structural injury apparent in this model (Goncalves, Fujihara et al. 2004). Similar effects have been demonstrated in the same rat remnant kidney model with a selective COX-2 inhibitor, celecoxib (Fujihara, Antunes et al. 2003).

COX-2 and lipoxygenase inhibitors could reduce proteinuria in nephrotic syndrome without alter renal function (Lee, Kwak et al. 2009). In diabetic rats, oral administration of prostagladin E receptor 1 (EP1) antagonist significantly ameliorated progression of nephropathy by attenuating the glomerular hypertrophy, mesangial matrix expansion and transforming growth factor beta (TGF-β) expression. Moreover, this intervention reduced the proteinuria and increased the expression of COX-2 (Makino, Tanaka et al. 2002). These findings implicate COX-2/prostaglandin E2 (PGE_2)/EP1 system in progression of diabetic kidney disease. By contrast, in a model of nephrotoxic serum nephritis, proteinuria did not differ between wild-type and EP1 knock out nephritis groups (Rahal, McVeigh et al. 2006) suggesting that mechanisms of renal injury are highly model dependent. In rats, a high dietary intake of protein stimulates glomerular hyperfiltration as seen in the remnant kidney model. Rats that were fed either a high or low protein diet for 2 weeks were shown to have an increase or decrease in COX-2 expression in the thick limb of the loop of Henle and the macula densa, respectively, while COX-1 expression was not affected by dietary protein (Yao, Xu et al. 2006). These experimental findings support the hypothesis that COX enzymes, particularly COX-2, might be involved in the maladaptive responses to loss of functioning nephrons which ultimately drive intrinsic progression of renal injury.

From its vasoconstrictor and pro-mitotic effects, activation of thromboxane receptor (TP) could contribute to elevated blood pressure and the end-organ damage in hypertension associated with angiotensin II (ANG II). Urinary excretion of (thromboxane B2) TxB2 was elevated in N (G) nitro-L-arginine methyl ester (L-NAME)-induced hypertension model via COX-1 dependent pathway (Francois, Makhanova et al. 2008). The same study also reported that glomerulosclerosis and tubulointerstitial inflammation were more pronounced in 58 hypertensive TP knockout mice than hypertensive wild type mice. In 2-kidney-1-clip hypertensive rats, a COX-1 antagonist reduced blood pressure and urinary TxB2 excretion, while a COX-2 antagonist did not reduce blood pressure and increased renal TxB2 production (Welch, Patel et al. 2007). This finding supports the role of COX-1 dependent TxA2 in hypertension.

In summary, there is much evidence from experimental models to support a role for renal COX enzymes (particularly COX-2) in the adaptive responses to nephron loss. Whether these findings will translate to clincial patients is still to be investigated. The proposed function of COX system in renal homeostasis is summarized in Figure 1.

Table 1 Renal localization and function of COX-1 in primates

Species	Reference	Meterial	Method	Location	Functional study	Suggested role in the kidney
Human	Komhoff et al. 1997	• Adult kidney (age not stated)	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Glomerulus • Thin limb of loop of Henle • Collecting duct • Vasa recta • Medullary interstitial cells	-	• Regulation of Na^+ and water homeostasis
		• Foetal kidney (gestation age 17-24 wk)	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Glomerulus • Collecting duct	-	• Regulation of Na^+ and water homeostasis • Involved in nephrogenesis
	Khan et al. 1998	• Adult kidney (20-50 y)	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Afferent arteriole • Collecting duct • Medullary interstitial cells	-	• Regulation of Na^+ and water homeostasis • Inhibition of COX-1 may cause renal papillary necrosis
	Zidar et al. 2008	• Adult kidney (2-50 y)	• Immunohistochemistry (protein) • Western blooting (protein) • RT-PCR (mRNA)	• Afferent arteriole • Glomerulous • Collecting duct	-	-
	Nantel et al. 1999	• Adult kidney (17-97 y)	• Immunohistochemistry (protein)	• Thin limb of Henle • Collecting duct • Medullary interstitial cell	-	-
	Hebert et al. 1998	• Adult kidney (age not stated)	• Immunohistochemistry (protein) • Western blooting (protein)	• Collecting duct	-	-
Monkey	Khan et al. 1998	Normal kidney	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Afferent arteriole • Collecting duct • Medullary interstitial cell	• PRA increased in low salt diet group • No change in COX-1 expression at any site	• Regulation of Na^+ and water homeostasis • Inhibition of COX-1 may cause renal papillary necrosis

Table 2 Renal localization and function of COX-1 in dogs and mice

Species	Reference	Meterial	Method	Location	Functional study	Suggested role in the kidney
Dog	Khan et al. 1998	Normal kidney	• Immunohistochemistry (protein) • Western blooting (protein) • RT-PCR (mRNA)	• Afferent arteriole • Collecting duct	• PRA increased in low salt diet group • No change in COX-1 expression at any site	• Regulation of Na^+ and water homeostasis • Inhibition of COX-1 may cause renal papillary necrosis
Mouse	Campean et al. 2003	• Wild-type mice • COX-1 knockout mice	• Immunohistochemistry (protein) • Western blooting (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Glomerulus • Distal tubule • Collecting duct	-	-
	Meskell and Ettarh 2009	Normal kidney	Immunohistochemistry (protein)	• Macula densa • Glomerulus • Proximal tubule • Distal tubule • Collecting duct	-	-
	Radi and Ostroski 2007	Normal kidney	Immunohistochemistry (protein)	• Macula densa • Glomerulus • Distal tubule • Thick ascending limb of Henle • Collecting duct	-	-
	Ye et al. 2006	COX-1 knockout mice	• Immunohistochemistry (protein) • Telemetry implantatio (mean arterial pressure) • EIA (PGE_2) • RT-PCR (mRNA)	• Collecting duct • Medullary interstitial cel • COX-1 knockout mice develop hypertension during salt loading • Urinary PGE_2 production decreased after high- salt intake	• High-salt loading caused no change in COX-1 expression	• Medullary COX-1 derived -PGE_2 regulation of sodium homeostasis, protecting against sodium loading leading to hypertension.

Table 3 Renal localization and function of COX-1 in rabbits and rats

Species	Reference	Meterial	Method	Location	Functional study	Suggested role in the kidney
Rabbit	Schumacher et al. 2002	• Neonatal kidney • Cultured embryonic collecting duct epithelium	• Immunohistochemistry (protein) • Western blooting (protein) • Perfusion culture	• Afferent arteriole • Glomerulus • cortical collecting duct (only in embryonic zone) • Medullary collecting duct • Medullary interstitial cell	• Collecting ducts COX-1 expression was not changed after salt loading	• Involved in tubulogenesis
		• Adult kidney	Immunohistochemistry (protein)	• Glomerulus • Medullary collecting duct	-	-
Rat	Khan et al. 1998	Normal kidney	• Immunohistochemistry (protein) • Western blooting (protein) • RT-PCR (mRNA)	• Afferent arteriole • Collecting duct • Medullary interstitial cell	• PRA increased in low salt diet group • No change in COX-1 expression at any site	• Regulation of Na^+ and water homeostasis • Inhibition of COX-1 may cause renal papillary necrosis
	Campean et al. 2003	Normal kidney	• Immunohistochemistry (protein) • Western blooting (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Glomerulous • Distal tubule • Collecting duct	-	-
	Harris et al 1994	Normal kidney	• Immunohistochemistry (protein) • Western blooting (protein) • northern blooting (protein) • In situ hybridization (mRNA)	• Medullary collecting duct • Medullary interstitial cell	-	-
	Te et al. 2006	Normal kidney	• Immunohistochemistry (protein) • Western blooting (protein) • Telemetry implantation (mean arterial pressure) • EIA (PGE_2)	• Collecting duct • Medullary interstitial cell	• Renal medulla infusion of COX-1 inhibitor induced salt-sensitive hypertension	• Involved in natriuretic and antihypertensive

Table 4 Renal localization and function of COX-2 in human subjects

Reference	Meterial	Method	Location	Functional study	Suggested role in the kidney
Komhoff et al. 1997	• Adult kidney (age not stated)	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Afferent arteriole • Glomerulus • Vasa recta	-	• Regulation of renal haemodynamics
	• Foetal kidney (gestation age 17-24 wk)	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Glomerulous • JGA	-	• Regulation of glomerular haemodynamics
Khan et al. 1998	• Adult kidney (<50 y)	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Afferent arteriole • Glomerulus	-	• Regulation of glomerular haemodynamics
Khan et al. 2001	• Foetal kidney (gestation age 15-23 wk)	Immunohistochemistry (protein) • Thick ascending limb of loop of Henle	• Macula densa	-	• Involved in nephrogenesis
Zida et al. 2008	• Adult kidney (<50 y)	• Immunohistochemistry (protein) • Western blooting (protein) • RT-PCR (mRNA)	• Glomerulous • Proximal tubule	-	-
Nantel et al. 1999	• Adult kidney (17-97 y)	Immunohistochemistry (protein)	• Macula densa • Afferent arteriole • Glomerulous • Thick ascending limb of Henle • Medullary interstitial cell	-	• Mediating renin secretion
Hebert et al. 1998	• Adult kidney (age not stated)	• Immunohistochemistry (protein) • Western blooting (protein) • RT-PCR (mRNA)	• Afferent arteriole • Glomerulus	• COX-2 was upregulated in renal arterial stenosis • COX-2 co-located with EP_4 receptor in the afferent arteriole	• Vascular COX-2/EP_4 induced PGs synthesis under conditions of low renal blood flow • Vascular COX-2 derived PGs contribute to the macula densa-renin secretion in low salt diet
	• Foetal kidney (age not stated)	• Immunohistochemistry (protein) • Western blooting (protein) • RT-PCR (mRNA)	• Afferent arteriole • Glomerulus • Macula densa • Thick ascending limb of loop of Henle	-	• Involved in nephrogenesis

Table 5 Renal localization and function of COX-2 in dogs, rabbits and mice

Species	Reference	Meterial	Method	Location	Functional study	Suggested role in the kidney
Dog	Khan et al. 1998	Normal kidney	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Afferent arteriole • Thick ascending limb of loop of Henle • Macula densa	• PRA increased in low salt diet group • COX-2 expression increased in the macula densa and thick ascending limb of loop of Henle	• PGs/COX-2 regulation of renin secretion
Rabbit	Schumac-her et al. 2002	• Neonatal kidney • Cultured embryonic collecting duct epithelium	• Immunohistochemistry (protein) • Western blotting (protein) • Perfusion culture	• Glomerulus • Macula densa • Medullary collecting duct • Medullary interstitial cell	• Collecting ducts COX-2 expression increased after salt loading	• Medullary PGs/COX-2 involved in water re-absorption and sodium regulation
		Adult kidney	Immunohistochemistry (protein)	• Glomerulus • Medullary collecting duct	-	-
	Fuson et al 2003	Normal kidney	Immunohistochemistry (protein)	Macula densa	• COX-2 and PGE_2 synthase expression increased in the macula densa with dietary salt restriction	• PGE_2 generated from COX-2 stimulated renin release from the macula densa • Macula densa COX-2/ PGE_2 upregulation in response to low salt diet
Mouse	Ampean et al. 2003	Normal kidney	• Immunohistochemistry (protein) • Western blooting (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Macula densa • Thick ascending limb of loop of Henle	-	• Mediating renin secertion • Involved in Na_+ and water regulation
	Radi and Ostroski 2007	Hypertensive kidney	Immunohistochemistry (protein)	• Macula densa • Afferent arteriole • Proximal tubule • Distal tubule • Thick ascending limb of loop of Henle • Collecting duct • Interstitial cell	-	• Mediating renin secertion

Table 6 Renal localization and function of COX-2 in monkeys and rats

Species	Reference	Meterial	Method	Location	Functional study	Suggested role in the kidney
Monkey	Khan et al. 1998	Normal kidney	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Afferent arteriole • Glomerulus	• PRA increased in low salt diet group • No change in COX-2 expression at any site	• COX-2 not involved renin secretion • Little relevance to normal renal physiology
Rat	Khan et al. 1998	Normal kidney	• Immunohistochemistry (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Thick ascending limb of loop of Henle • Macula densa	• PRA increased in low salt diet group • COX-2 expression increased in the macula densa and thick ascending limb of loop of Henle	• PGs/COX-2 regulation of renin secretion
	Campean et al. 2003	Normal kidney	• Immunohistochemistry (protein) • Western blooting (protein) • In situ hybridization (mRNA) • RT-PCR (mRNA)	• Thick ascending limb of Henle • Macula densa • Medullary interstitial cell	-	-
	Harris et al. 1994	Normal kidney	• Immunohistochemistry (protein) • Western blotting (protein) • Northern blotting (protein) • In situ hybridization (mRNA)	• Macula densa • Thick ascending limb of loop of Henle • Medullary interstitial cell	• COX-2 expression in the cortex was not altered in the high salt diet group • COX-2 expression in the macula densa and thick ascending limb increased in low salt diet group	• Constitutive COX-2 in the kidney was regulated by dietary salt alteration • PGs/COX-2 regulation of renin secretion and sodium balance
	Vio et al. 1997	Normal kidney	Immunohistochemistry (protein)	• Thick ascending limb of loop of Henle	-	-
	Ye et al. 2006	Normal kidney	• Immunohistochemistry (protein) • Western blotting (protein) • Telemetry implantation (mean arterial pressure) • EIA (PGE_2)	Medullary interstitial cell	• PGE2 production in the inner medulla increased in high- salt intake • COX-2 expression in the medullary interstitial cells increased in high- salt intake • Intramedullary selective COX-2 inhibitor administration led to elevated mean arterial pressure	• Medullary interstitium COX-2/PGE_2 mediating blood pressure homeostasis during chronic salt loading

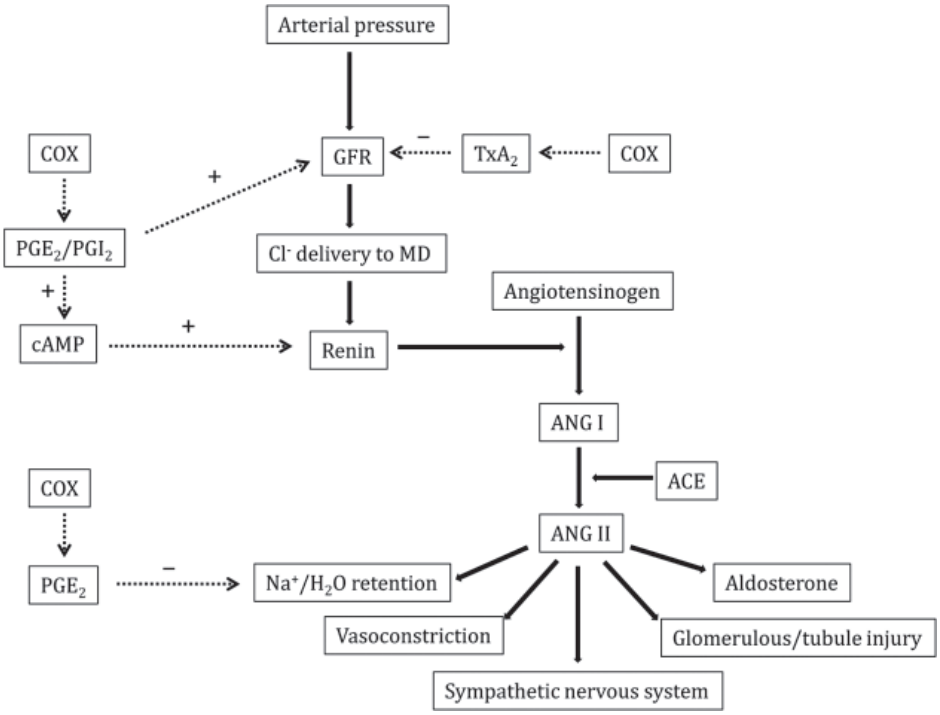

Figure 1. Summary pathways through which the COX system is thought to be involved in regulating renal function. The COX/prostanoid system may involved in renal haemodynamic regulation in both physiological and pathophysiological situations. In the cortex, COX-derived prostanoids may induce renin production. The arteriole may be dilated or constricted by different prostanoids to maintain GFR. Prostanoids from the COX system may regulate salt and water homoestasis in the renal medulla, facilitating natriuresis, dieresis and protecting the medullary interstitial cells in situations where water deprivation occurs. GFR, glomerular filtration rate; MD, macula densa; COX, cyclooxygenase; PGE_2, prostlandin E2; PGI_2, prostacyclin; cAMP, cyclic adenosine-monophosphate; TxA2, thromboxane A2; ANG, angiotensin; ACE, angiotensin converting enzyme

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