

Local cyclic adenosine monophosphate signalling cascades—Roles and targets in chronic kidney disease

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Abstract

The molecular mechanisms underlying chronic kidney disease (CKD) are poorly understood and treatment options are limited, a situation underpinning the need for elucidating the causative molecular mechanisms and for identifying innovative treatment options. It is emerging that cyclic 3',5'-adenosine monophosphate (cAMP) signalling occurs in defined cellular compartments within nanometre dimensions in processes whose dysregulation is associated with CKD. cAMP compartmentalization is tightly controlled by a specific set of proteins, including A-kinase anchoring proteins (AKAPs) and phosphodiesterases (PDEs). AKAPs such as AKAP18, AKAP220, AKAP-Lbc and STUB1, and PDE4 coordinate arginine-vasopressin (AVP)-induced water reabsorption by collecting duct principal cells. However, hyperactivation of the AVP system is associated with kidney damage and CKD. Podocyte injury involves aberrant AKAP signalling. cAMP signalling in immune cells can be local and slow the progression of inflammatory processes typical for CKD. A major risk factor of CKD is hypertension. cAMP directs the release of the blood pressure regulator, renin, from juxtaglomerular cells, and plays a role in Na⁺ reabsorption through ENaC, NKCC2 and NCC in the kidney. Mutations in the cAMP hydrolysing PDE3A that cause lowering of cAMP lead to hypertension. Another major risk factor of CKD is diabetes mellitus. AKAP18 and AKAP150 and several PDEs are involved in insulin release. Despite the increasing amount of data, an understanding of functions of compartmentalized cAMP signalling with relevance for CKD is fragmentary. Uncovering functions will improve the understanding of physiological processes and identification of disease-relevant aberrations may guide towards new therapeutic concepts for the treatment of CKD.

KEYWORDS

AKAP, AQP2, AVP, cAMP, CKD, hypertension, PDE

1 | CHRONIC KIDNEY DISEASE, AN INTRODUCTION

More than 700 million people worldwide suffer from chronic kidney disease (CKD),^{1,2} and the prevalence of the

disease is further increasing. In 1990, CKD was ranked 27th in the list of causes of the total number of global deaths, whereas in 2010 it was already placed 18th.³ In 2017, CKD was the 12th leading cause of death worldwide (1.2 million deaths).⁴ The epidemiological characteristics of CKD vary

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widely. For instance, it affects more women than men.⁵ However, among patients starting renal replacement therapy, there are more men than women. The geographical stratification revealed the highest number of CKD patients in Europe, North America and Australia, the economically most developed countries and with a higher percentage of old people in the population.¹ The investigation of racial predisposition to CKD showed that black Americans are at higher risk of morbidity and mortality compared to white Americans.⁶ This phenomenon could be related to the presence of certain variations in the genes encoding for myosin heavy chain 9 (MYH9) and apolipoprotein L1 (APOL1) in individuals of African origin.^{7,8}

CKD is characterized by a progressive loss of kidney function,⁹ which is associated with an increase in the pressure in the glomerular capillaries, podocyte injury and an increase in the glomerular basement membrane permeability. These changes lead to other pathological events, such as an increase in cell proliferation, accumulation of extracellular matrix molecules and inflammatory responses, which altogether promote further kidney injury including fibrosis.¹⁰

The Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group defined CKD as a disease accompanied by the decrease in the estimated glomerular filtration rate (eGFR) to values lower than 60 mL/min/1.73 m² for at least 3 months and albuminuria (≥ 30 mg/g).¹¹ CKD progresses through distinguishable stages. Stages 1 and 2 are defined by the single assessments of albuminuria (ie, no persistence) and eGFR ≥ 90 and 60-89 mL/min/1.73 m² respectively; Stages 3 and 4 are defined by 30-59 and 15-29 mL/min/1.73 m² respectively. The final stage of CKD is end stage renal failure (ESRD), which is equivalent to the loss of 85%-90% of kidney function and an eGFR lower than 15 mL/min/1.73 m². The patients require haemodialysis, peritoneal dialysis or kidney transplantation.¹² Recently, the Global Burden of Disease Kidney Disease Collaboration suggested even five stages of CKD that precede ESRD. The stages were defined by low eGFR, elevated albumin-to-creatinine ratio or both, and independent of the 3-month persistence of low glomerular filtration rate (GFR).¹³

CKD can arise independently or as a sequel of a primary disease. The list of risk factors (Figure 1) includes common

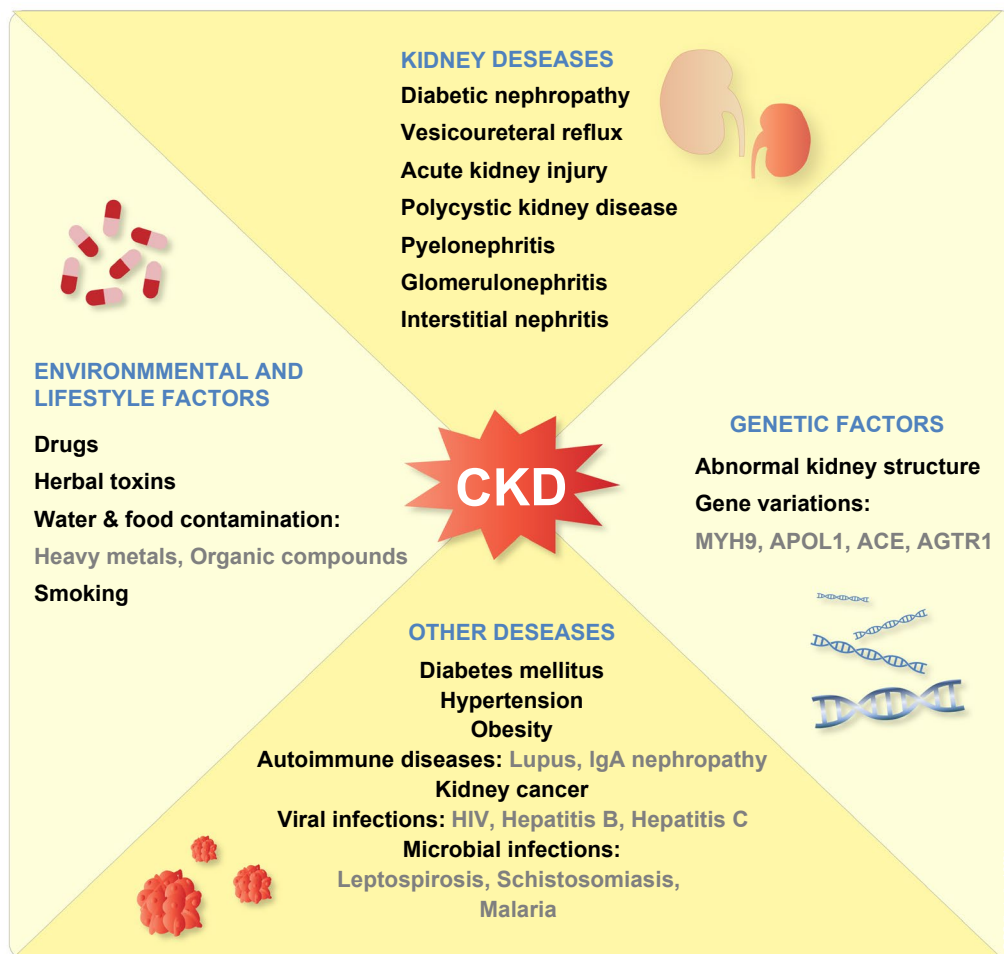


FIGURE 1 An overview of risk factors of CKD. ACE1, angiotensin converting enzyme; AGTR1, angiotensin II receptor type 1; APOL1, apolipoprotein L1; CKD, chronic kidney disease; HIV, human immunodeficiency virus; MYH9, myosin, heavy chain 9

diseases such as diabetes mellitus (DM),^{14,15} hypertension,¹⁶ glomerulonephritis,¹⁷ polycystic kidney disease (PKD),¹⁷ obesity⁷ and infections,¹⁸ as well as specific factors, in particular, herbal toxins.¹⁹

The molecular mechanism causing CKD and its progression is largely unclear. Accordingly, a rational treatment of CKD is lacking. Thus, elucidating the molecular mechanisms underlying CKD and finding innovative treatment concepts is urgently required. Surprisingly, the role of cyclic adenosine monophosphate (cAMP) in the development of CKD has been hardly considered.

cAMP is a ubiquitous second messenger, which controls a plethora of physiological processes. Dysregulation of cAMP signalling causes or is associated with various diseases, including kidney diseases, inflammatory responses, fibrosis and hypertension and DM, the major risk factors for CKD. The aim of this review is to discuss cAMP functions in cellular signalling processes that control specific kidney functions and which play a role in kidney diseases, inflammation and DM and hypertension. Options for targeting cAMP signalling for the treatment of CKD are evaluated. A focus will be on compartmentalized cAMP signalling.

2 | THE COMPARTMENTALIZATION OF cAMP SIGNALLING

The second messenger cAMP is a central molecule in signal transduction. It is generated in response to a plethora of extracellular stimuli such as catecholamines, neurotransmitters,

peptide hormones, lipids and chemical or mechanical cues and elicits specific cellular responses to each stimulus.²⁰ Several stimuli and their cognate receptors that mediate their actions in the kidney through cAMP and which are discussed further below are listed in Table 1. A generic cAMP signalling cascade is illustrated in Figure 2.

cAMP signalling is initiated upon binding of an extracellular ligand to its cognate seven-transmembrane G protein-coupled receptor (GPCR).²¹ GPCRs are mainly located in the plasma membrane but also reside in intracellular compartments such as endosomal membranes and the Golgi apparatus. Ligand binding leads to activation of a co-localized heterotrimeric G protein.^{22–26} G proteins consist of an α -subunit and dimerized β - and γ -subunits. G protein activation causes an exchange of GDP for GTP on the α -subunit and a conformational change that promotes the release of the α -subunit. The α -subunits of the stimulatory G protein, G_s , stimulate adenylyl cyclases (AC) to synthesize cAMP from ATP. The $\beta\gamma$ -dimers can also stimulate some AC isoforms. The α -subunits of the inhibitory G protein family, G_i , inhibit ACs. Therefore, G_s and G_i proteins are the key regulators of the cellular cAMP synthesis. There are further families of G proteins, such as G_q and G_{12} , which mainly control signalling other than cAMP-induced.²⁷

In mammals, 10 AC isoforms have been identified. AC1–9 are transmembrane G protein-regulated isoforms.²⁴ In addition to G_s and G_i , some other factors can modulate AC1–9 activities; for example, calmodulin can stimulate AC1 and AC8, and Ca^{2+} inhibits AC5 and AC6.²⁴ AC10 is soluble (sAC), G protein-independent, and activated by Ca^{2+} , ATP, and intracellular bicarbonate.²⁸ ACs are expressed in a tissue-specific

TABLE 1 Agonists and receptors stimulating cAMP signalling cascades in the kidney that are relevant for CKD

Agonist	Receptor	Target cell	Relevant effects	Reference
AVP	V2R	Collecting duct principal cells	Water reabsorption NKCC, ENaC-based Na^+ reabsorption	Bachmann and Mutig, ¹⁹⁰ Rosenthal et al ³⁰¹ Birnbaumer et al ³⁰²
ADM	ADM-R	Collecting duct principal cells	Inhibition of water reabsorption Natriuresis	Ma et al ⁵¹
PGE_2	EP2, EP4	Podocytes VSMC Juxtaglomerular cells	Glomerular filtration Renal blood flow Renin release	Mangelsen et al ¹¹² Kim et al ²¹⁸ Purdy and Arendshorst ³⁰³ Kurtz ¹⁷¹
Prostacyclin	PGI2	Juxtaglomerular cells VSMC	Renin release Renal blood flow	Kurtz ¹⁷¹ Cao et al ³⁰⁴
ATP	P2Y4	Podocytes	Actin remodelling	Szrejder et al ¹¹⁶
VIP	VPAC ₁ , VPAC ₂	Fibroblasts	Antifibrosis	Duggan et al ¹⁵⁸
Adenosine	AR2B	Fibroblasts	Fibrosis	Wilkinson et al ¹⁵⁹
Angiotensin II	AT1R	VSMC	Vasoconstriction	Santos et al ³⁰⁵

Note: ADM-R is formed by a complex of calcitonin-receptor-like receptor (CRLR) and receptor-activity-modifying protein 2 or 3 (RAMP2 or RAMP3).

Abbreviations: ADM, adrenomedullin; AR2B, adenosine receptor 2B; AT1R, angiotensin II receptor; AVP, arginine-vasopressin; EP1–EP4, PGE_2 receptors; P2Y₄, P2 purinergic receptor; PGE_2 , prostaglandin E₂; V2R, vasopressin receptor type 2; VIP, vasointestinal peptide.

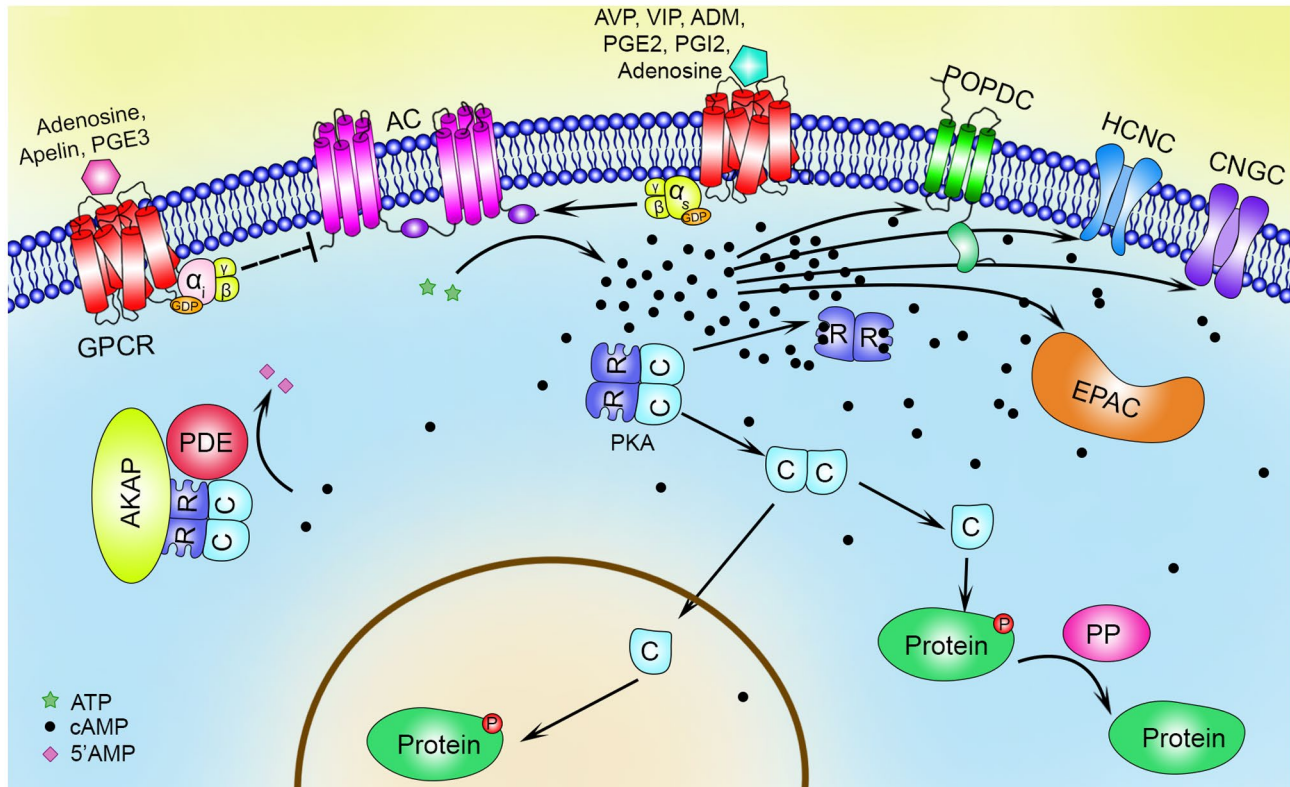


FIGURE 2 A generic cAMP signalling cascade. For details, see main text. GPCR, G protein-coupled receptor; α , β , γ , subunits of the stimulatory (G_s) and inhibitory (G_i) G proteins. Ligands for GPCRs: 5' AMP, 5'-adenosine monophosphate; AC, adenylyl cyclase; Adenosine; ADM, adrenomedullin; AKAP, A-kinase anchoring protein; ATP, adenosine triphosphate; AVP, arginine vasopressin; C, catalytic subunit of protein kinase A; cAMP, 3',5'-adenosine monophosphate; CNGC, cyclic nucleotide-gated ion channel; EPAC, exchange protein activated by cAMP; HCNC, hyperpolarization-activated cyclic nucleotide-gated channel; PDE, phosphodiesterase; PGE₂, prostaglandin E₂; PGE₃, prostaglandin E₃; PGI₂, prostaglandin I₂; PKA, protein kinase A; POPDC, popeye domain-containing protein; PP, protein phosphatase; R, regulatory subunit of protein kinase A; VIP, vasointestinal peptide. Solid arrow and dotted line from GPCR indicate activation (G_s) and inhibition (G_i) of AC, respectively

manner. Their distribution along the nephron is indicated in Table 2. An increase in the intracellular cAMP level leads to activation of its effector proteins. cAMP directly binds to effectors that regulate vital functions including transcription, metabolism, differentiation, and proliferation. The effectors are exchange proteins activated by cAMP (Epa1 and 2),²⁹ Popeye domain-containing (Popdc) proteins,³⁰ cyclic nucleotide-gated ion (CNGC) and hyperpolarization-activated cyclic nucleotide-gated (HCNC) channels,³¹ and the main effector, cAMP-dependent protein kinase (protein kinase A, PKA).³²

PKA is a serine/threonine protein kinase with broad substrate specificity. PKA holoenzyme consists of homodimers of either regulatory RI (RI α or RI β) or RII (RII α or RII β) subunits and two catalytic subunits (C α , C β or C γ), each bound to a R protomer. The combination of different isoforms of regulatory and catalytic subunits creates variants of PKA that differ in cAMP affinity, activity or cell type-specific expression providing a certain level of specificity to PKA signalling.³³ Upon binding of two molecules of cAMP to each regulatory subunit, catalytic subunits dissociate and phosphorylate targets in close proximity.^{34,35} However, PKA holoenzyme can

also be active. The dissociation of the C subunits may not be required for phosphorylation of targets within 150-250 Å, for example, for PKA tethered by an A-kinase anchoring protein (AKAP) (see below), AKAP79.³⁶⁻³⁸

The termination of cAMP signalling occurs through several mechanisms: dephosphorylation of PKA substrate proteins by protein phosphatases and removal of cAMP to the extracellular space via ABC-transporters (for instance, Multidrug resistance protein 4 in fibroblasts³⁹ or spermatozoa⁴⁰). A key mechanism of termination is cAMP hydrolysis by phosphodiesterase (PDE). There are more than 100 different PDEs belonging to 11 families (PDE1-PDE11). Depending on their substrate specificity, they are divided into three groups: cAMP-specific (PDE4, PDE7, PDE8), cyclic guanosine monophosphate (cGMP)-specific (PDE5, PDE6, PDE9) and dual-specific enzymes hydrolysing both cAMP and cGMP (PDE1-PDE3, PDE10, and PDE11).⁴¹⁻⁴³

In the kidney, PDE1-PDE5 are the most abundant PDEs, among them, PDE1, PDE3 and PDE4 are considered the predominant forms. However, other PDEs are also expressed in the kidney, for example, PDE8 and PDE9.^{44,45} Although the expression patterns of several PDEs along the nephron

TABLE 2 Expression of adenylyl cyclases (ACs) in cells and segments along the nephron

Isoform	Localization	Reference	Isoform	Localization	Reference
AC1	Podocytes	Xiao et al ³⁰⁶	AC6	Glomerulus	Bek et al ³⁰⁷ Chabardes et al ³⁰⁸
AC2	Glomerulus	Bek et al ³⁰⁷		Juxtaglomerular cells	Friis et al ¹⁷² Bek et al ³⁰⁷
	Tubules	Bek et al ³⁰⁷		Tubules	Choi et al ¹⁰⁸ Bek et al ³⁰⁷ Chabardes et al ³⁰⁸
	Collecting ducts	Bek et al ³⁰⁷		Thin limb of Henle	Bek et al ³⁰⁶ Chabardes et al ³⁰⁷
AC3	Glomerulus	Bek et al ³⁰⁷		Thick ascending limb	Bek et al ³⁰⁷ Chabardes et al ³⁰⁸ Erdorf and Seifert ³⁰⁹
	Tubules	Sherpa et al ⁶⁵ Bek et al ³⁰⁷		Collecting ducts	Sherpa et al ⁶⁵ Gonzalez et al ¹⁷⁶ Bek et al ³⁰⁷ Chabardes et al ³⁰⁸
	Thin limb of Henle	Bek et al ³⁰⁷		Kidney vessels	Sherpa et al ⁶⁵ Pluznick et al ³¹⁰
	Collecting ducts	Sherpa et al ⁶⁵ Hoffert et al ³¹¹	AC7	Glomerulus	Bek et al ³⁰⁷
	Kidney vessels	Sherpa et al ⁶⁵ Pluznick et al ³¹⁰		Proximal tubule	Bek et al ³⁰⁷
AC4	Glomerulus	Bek et al ³⁰⁷ Chabardes et al ³⁰⁸ Erdorf and Seifert ³⁰⁹	AC9	Glomerulus	Bek et al ³⁰⁷
	Thin limb of Henle	Bek et al ³⁰⁷		Proximal tubules	Bek et al ³⁰⁷
	Distal tubules	Bek et al ³⁰⁶		Thin limb of Henle	Bek et al ³⁰⁷
	Collecting ducts	Bek et al ³⁰⁷		Thick ascending limb	Bek et al ³⁰⁷
AC5	Glomerulus	Bek et al ³⁰⁷ Chabardes et al ³⁰⁸ Erdorf and Seifert ³⁰⁹		Collecting ducts	Bek et al ³⁰⁷
	Juxtaglomerular cells	Friis et al ¹⁷² Ortiz-Capisano et al ¹⁸⁵	AC10 (sAC)	Thick ascending limb	Hallows et al ³¹² Pastor-Soler et al ³¹³
	Tubules	Choi et al ¹⁰⁸		Distal tubules	Hallows et al ³¹² Pastor-Soler et al ³¹³
	Collecting ducts	Sherpa et al ⁶⁵ Bek et al ³⁰⁷ Chabardes et al ³⁰⁸ Erdorf and Seifert, ³⁰⁹ Shen et al ³¹⁴		Collecting ducts	Hallows et al ³¹²
	Kidney vessels	Sherpa et al ⁶⁵			

Note: AC3, AC5 and AC6 are the most abundant ACs in kidney (highlighted in italic), whereas AC8 was not detectable.³¹⁴

has been analysed (Table 3), the subcellular localization of PDEs in kidney cells has only been analysed for a few PDEs. As an example, PDE1C is located in the cytoplasm of juxtaglomerular cells and kidney vessels.⁴⁶ PDE3B is detected in cytoplasmic vesicles of distal convoluted tubular cells,⁴⁷ and various PDE4 isoforms were found in collecting ducts; for example, PDE4D was found on aquaporin-2 (AQP2)-bearing vesicles,⁴⁸ PDE4C in primary cilia.⁴⁹

As many of the cAMP signalling cascade components are ubiquitously expressed, the key question is how each of the different cAMP-utilizing stimuli elicits a specific cellular response. For example, in kidney collecting duct principal cells, arginine-vasopressin (AVP, antidiuretic hormone) stimulates the G_s-coupled vasopressin type 2 receptors (V2R) and an elevation of cAMP, which, in turn, causes water reabsorption.⁵⁰ Adrenomedullin also stimulates cAMP synthesis in the principal cells but has the opposite effect. It reduces water reabsorption. Adrenomedullin acts through a phospholipase C pathway involving protein kinase C. A likely explanation for these opposite effects is that different pools of cAMP are activated by the two receptors.⁵¹ Indeed, it is beginning to

emerge that cAMP-mediated signalling occurs within defined intracellular nano-scale compartments,⁵²⁻⁵⁴ enabling even multiple cellular responses to occur simultaneously.⁵⁵⁻⁵⁸

The interplay of cAMP synthesis and degradation by the constitutively active and strategically positioned PDEs establishes gradients and local pools of cAMP that are sensed by cAMP effectors located at defined cellular compartments. The formation of the gradients involves the “buffering” of cAMP, that is, binding to targets to slow diffusion; otherwise synthesis would exceed PDEs' hydrolysis capacity and cAMP would evenly flood the cells.⁵² Establishing of gradients and signalling compartments often requires direct protein-protein interactions of scaffolding proteins such as those of the around 50 AKAPs, of which several are expressed in the kidney (Table 4). AKAPs tether protein complexes to defined cellular compartments. They possess a conserved domain for the interaction with PKA, unique domains for direct interactions with further signalling proteins such as ACs, PDEs, phosphatases, other kinases, kinase substrates and anchoring domains.⁵⁹⁻⁶² This engagement of direct protein-protein interactions and assembly of protein complexes that are specific

TABLE 3 Expression pattern of the most abundant PDEs in the different parts of the kidney

Isoform	Localization in kidney	Reference
PDE1	Juxtaglomerular cells, Kidney vessels	Ortiz-Capisano et al ⁴⁶
	Glomeruli	Sandner et al ¹⁷⁸ Dousa, ²⁷² Matousovich et al ³¹⁶
	Distal convoluted tubules, collecting ducts	Cheng and Grande, ²⁷⁰ Dousa ²⁷²
PDE2	Glomeruli	Sandner et al ¹⁷⁸ Matousovich et al ³¹⁶
	Thick ascending limb	Ares et al ³¹⁷
	Distal convoluted tubules	Theilig and Wu ³¹⁸
PDE3	Kidney vessels; Juxtaglomerular cells	Friis et al ¹⁷² Sandner et al ¹⁷⁸
	Mesangial cells	Zhu et al ³¹⁹
	Distal convoluted tubules, collecting ducts	Sandner et al ¹⁷⁸ Cheng and Grande, ²⁷⁰ Dousa, ²⁷² Matousovich et al ³¹⁶
PDE4	Kidney vessels, Juxtaglomerular cells	Friis et al ¹⁷²
	Distal convoluted tubules, collecting ducts	Stefan et al ⁴⁸ Cheng and Grande, ²⁷⁰ Dousa, ²⁷² Matousovich et al ³¹⁶
	Mesangial cells	Zhu et al ³¹⁹
	Thick ascending limb	Haque et al ¹⁹⁷
PDE5	Glomeruli	Dousa, ²⁷² Pofi et al ²⁸⁴ Braun et al ³²⁰
	Kidney vessels	
	Mesangial cells	Pofi et al ²⁸⁴
	Cortical tubules	Pofi et al ²⁸⁴ Polzin et al ³²¹
	Collecting ducts	Dousa, ²⁷² Pofi et al ²⁸⁴

for a particular cellular environment enhances the specificity of cAMP signalling and allows for specific responses to each extracellular stimulus. Regulatory mechanisms modulating AC and PDE activities cause changes in local cAMP concentrations and make cAMP signalling a highly dynamic process.⁶³ Recently, it was found that PKA can undergo phase separation, that is, PKA forms droplets inside cells and thereby a signalling compartment.⁵⁴

3 | COMPARTMENTALIZED CAMP SIGNALLING COORDINATES SPECIFIC KIDNEY FUNCTIONS—IMPLICATIONS FOR KIDNEY-ASSOCIATED DISORDERS AND CKD

In the following section, we discuss examples underpinning that local cAMP signalling in defined kidney cells is crucial for physiological kidney function and illustrate that dysregulation is associated with or causes kidney disease.

3.1 | Collecting duct principal cells and AVP

The functional unit of the kidney is the nephron, consisting of defined segments, the terminal part being the collecting duct (Figure 3). The collecting duct has a crucial role in the regulation of water and electrolyte homeostasis and acid-base balance.⁶⁴ The majority of studies of compartmentalized cAMP signalling in the kidney concentrated on the investigation of its role in the AVP system in the collecting duct. AVP binds to V2R on the surface of principal cells, which leads to AC3/AC5/AC6-mediated elevation of cAMP and activation of PKA.⁶⁵⁻⁶⁷ PKA activation triggers a redistribution of the water channel AQP2 from intracellular vesicles into the plasma membrane of the cells.^{68,69} The plasma membrane accumulation promotes water reabsorption from the tubular fluid (primary urine). Water enters the principal cells from the lumen of the collecting duct and exits the cells through AQP3 and AQP4 constitutively present in the basolateral plasma membrane.

The AVP-stimulated cAMP/PKA signalling that controls AQP2 proceeds in defined compartments. Primary cilia are cellular protrusions of the plasma membrane of many cells. They function as antennae that sense the environment and initiate the signalling to transduce input into a cellular response.⁷⁰ Components of cAMP signalling compartments, GPCRs, ACs and PKA are present, and cAMP controls cilia disassembly through a local protein complex comprising PKA, the kinase NEK10 and an E3 ubiquitin ligase.⁷¹ In cultured mouse inner medullary collecting duct principal cells (IMCD3 cells), V2R is found in primary cilia together with AC5/6, and stimulation of V2R by AVP induces a local increase in cAMP in the cilia, underpinning the requirement for local cAMP signalling for proper water reabsorption.⁶⁵ In the primary cilia of another kidney epithelial cell model, LLC-PK1, V2R and AC5/6 also colocalize and V2R stimulation causes a cAMP increase.⁷² AQP2 is found in the ciliary shaft and in the subapical compartment in normal cilia.⁷³ Surprisingly, in rat primary inner medullary collecting (IMCD) cells, AVP causes activation of a pool of PKA in the perinuclear region where the majority of AQP2-bearing vesicles resides under resting conditions.⁴⁸ How the cAMP signal generated in primary cilia or other plasma membrane regions activates perinuclear PKA, and how that initiates the accumulation of AQP2 in the plasma membrane is unclear.

It is clear though that the interaction of PKA with AKAPs is a prerequisite for the AVP-induced redistribution of AQP2 to the plasma membrane, as the global uncoupling of PKA from AKAPs with peptides prevents the redistribution.⁷⁴ Several AKAPs are present in the principal cells. AKAP18 coordinates a signalling module on AQP2-bearing vesicles comprising PKA and PDE4D that locally tunes the cAMP level and PKA activity.^{48,75} Under resting conditions, the constitutively active PDE4D

TABLE 4 AKAPs in the kidney

AKAP	Localization in kidney	Intracellular localization	Reference
AKAP1	Podocytes	Cytosolic side of the outer mitochondrial membrane	Flippo et al ¹¹⁴
AKAPLbc (AKAP13)	Inner medullary collecting duct principal cells	Cytoplasm	Schrade et al ⁸² Klussmann et al ³²²
AKAP18 (AKAP7)	Inner medullary collecting duct principal cells	Cytosolic AQP2-bearing vesicles	Stefan et al ⁴⁸ Henn et al ^{75,323} Klussmann et al ³²⁴
AKAP95 (AKAP8)	Principal cell	Nucleus	Orellana et al ³²⁵
AKAP150 (AKAP5)	Nephron epithelial cells	Primary cilium	Choi et al ¹⁰⁸
AKAP220 (AKAP11)	Inner medullary collecting duct principal cells	Subapical cytoplasmic region	Whiting et al ⁷⁶ Okutsu et al ⁷⁷
mAKAP (AKAP6)	Principal cell	Nuclear membrane	Orellana et al ³²⁴
Ezrin	Principal cell	Apical cytoplasmic region	Orellana et al ³²⁵
Moesin	Principal cell	Actin cytoskeleton	Tamma et al ³²⁶
STUB1 (CHIP)	Principal cell	AQP2-bearing vesicles	Dema et al ⁸³

Note: Alternative names of AKAPs are indicated in brackets. The AKAP function of Ezrin, Moesin and STUB1 was recognized after they had been named. Therefore, no AKAP acronym is available. Ezrin and Moesin are members of the ERM family.³²⁶ STUB1 (STIP1 homology and U-box containing protein 1) also termed CHIP (C-terminal Hsc70 interacting protein) is a ubiquitin E3 ligase.⁸³

maintains a low level of cAMP and thus of PKA activity in close proximity of AQP2. This inhibitory effect prevents an inappropriate redistribution of AQP2 into the plasma membrane and thus an inappropriate water reabsorption. AVP stimulation induces a rise of cAMP above a threshold level that exceeds the cAMP hydrolysing capacity of PDE4D and allows for activation of PKA followed by the redistribution of AQP2 into the plasma membrane facilitating water reabsorption. PKA phosphorylates PDE4D thereby increasing PDE4D activity and introducing a negative feedback loop for termination of the signal.⁴⁸

Another AKAP on AQP2-bearing vesicles is AKAP220. It contributes to coordinating the localization of the vesicles through tethering of PKA and the small GTPase RhoA.^{76,77} A PKA-dependent inhibition of RhoA facilitates the redistribution of AQP2-bearing vesicles to the plasma membrane. RhoA inhibition causes a depolymerization of F-actin and thereby removes a physical barrier preventing AQP2-bearing vesicles from reaching the plasma membrane under resting condition. Thus, an intact F-actin prevents inappropriate water reabsorption in the absence of AVP.⁷⁸⁻⁸⁰ In addition to the interaction of RhoA with AKAP220, the interaction of RhoA with AKAP-Lbc participates in the control of AQP2.⁸¹ Disruption of the AKAP-Lbc-RhoA interaction causes a depolymerization of F-actin and a redistribution of AQP2-bearing vesicles to a sub-plasma membrane region.⁸²

Recently, a signalosome on AQP2-bearing vesicles comprising CDK18, the E3 ubiquitin ligase, STUB1 (also termed CHIP), PKA and AQP2 was identified that participates in the control of the localization and abundance of AQP2. STUB1 functions as an AKAP anchoring PKA and connecting AQP2 and CDK18. STUB1-mediated ubiquitination of AQP2 contributes to regulate its abundance and CDK18 controls AQP2 through phosphorylation.⁸³ CDK18 is one of the kinases that phosphorylates Ser261 of AQP2 under resting conditions. Phosphorylated Ser261 both maintains AQP2 ubiquitinated and thereby promotes its proteasomal degradation, and it restrains it to an intracellular localization. AVP causes the dephosphorylation of Ser261 promoting a plasma membrane localization.^{83,84} Therefore, with AKAP18, AKAP220, AKAP-Lbc and STUB1, at least four AKAPs are involved in keeping AQP2 under tight control.

Dysregulation of the AVP/cAMP/PKA axis causes or is associated with diseases. Mutations in the genes encoding AVP, V2R and AQP2 cause congenital diabetes insipidus (DI). The mutations interfere with the ability of the principal cells to respond to AVP.⁵⁰ Although the mutations are rare, the most frequent cause of DI is inhibition of the system during here no new line

the treatment of bipolar disorders with lithium-containing drugs. Hypercalcaemia, hypercalciuria and obstructive uropathy can be involved in disease progression.⁸⁵⁻⁸⁸

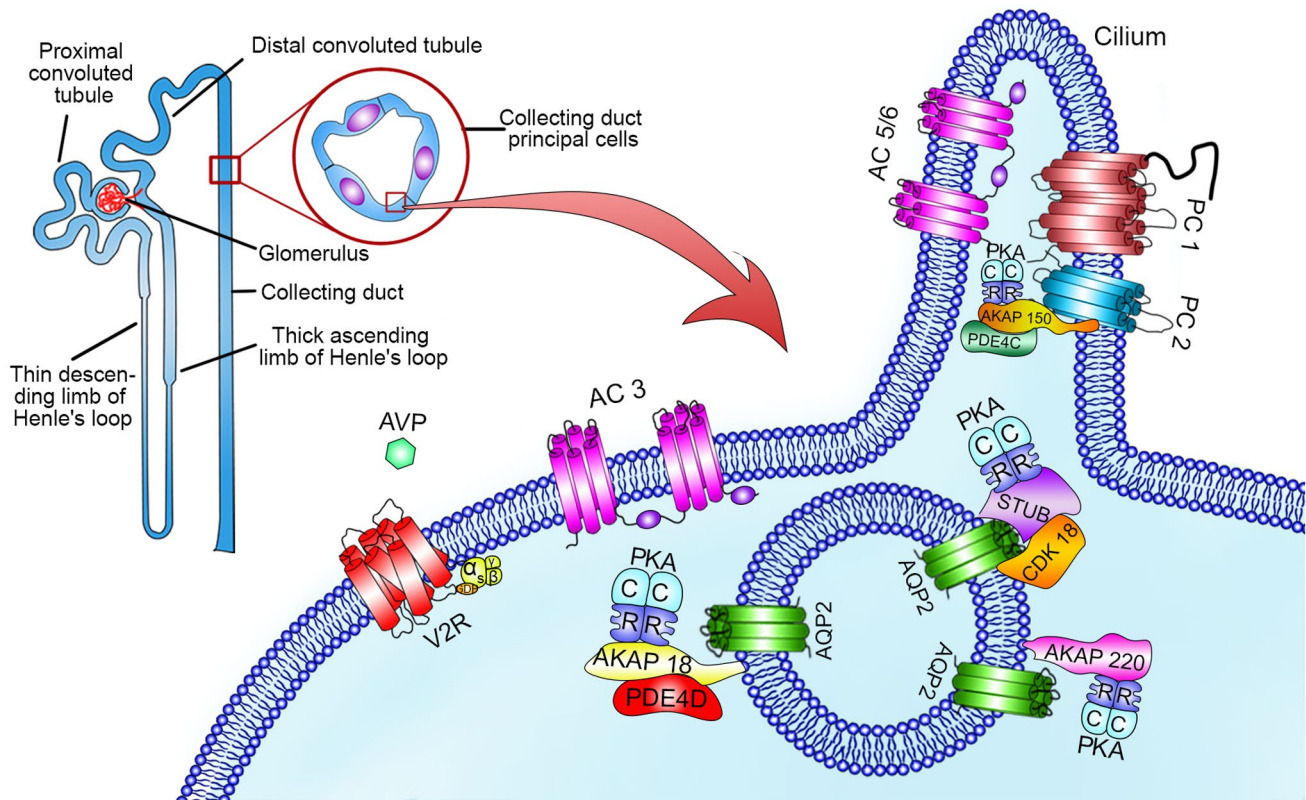


FIGURE 3 AKAP-based signalosomes in collecting ducts principal cells. Upper left, segments of the nephron and localization of collecting ducts cells within the nephron. Magnified view showing a principal cell plasma membrane region and AQP2-bearing vesicles. Depicted are plasma membrane protein complexes and AKAP-based signalosomes on AQP2-bearing vesicles. AC, adenylyl cyclase; AKAP150, A-kinase anchoring protein 150; AKAP18, A-kinase anchoring protein 18; AKAP220, A-kinase anchoring protein 220; AQP2, aquaporin-2; AVP, arginine vasopressin; C, catalytic subunit of protein kinase A; CDK18, cyclin-dependent kinase 18; PC1, polycystin 1; PC2, polycystin; PDE4C, phosphodiesterase 4C; PDE4D, phosphodiesterase 4D; R, regulatory subunit of protein kinase A; STUB, STIP1 homology and U-Box containing protein 1; V2R, vasopressin receptor 2

The direct detection of AVP as a disease marker in AVP-dependent fluid disorders is difficult for various reasons; for example, AVP has a short half-life of <30 minutes, a large fraction is bound to vasopressin V1 receptors (V1R) on platelets and the detection is technically complex. Because AVP is synthesized on the same precursor as the stable copeptin, copeptin serves as a surrogate for AVP and as a marker for the progression of diseases (see below).⁸⁹

Hyperactivation of the AVP system is associated with kidney damage, such as glomerular hyperfiltration and kidney hypertrophy and CKD progression, as initially recognized in rats.⁹⁰ Rats respond to 5/6 nephrectomy with an increase in vasopressin V1a and V1b receptors (V1aR and V1bR), as well as with elevated V2R and AVP mRNA levels in the kidney cortex.⁹¹ An increase in serum AVP and excessive stimulation of V2R leads to the progression of CKD.^{90,92} Brattleboro rats cannot produce AVP, and Brattleboro rats with 5/6 nephrectomy display a milder course of CKD compared to control animals that express AVP; kidney hypertrophy, hyperfiltration, proteinuria and progression of CKD are less pronounced if AVP is absent.⁹⁰ Moreover, treatment of Brattleboro rats

with CKD using the V2R agonist dDAVP (desmopressin) aggravates disease progression.⁹³ Based on such findings, it seemed that dampening of the AVP system activity could be an option for CKD treatment. Indeed, treatment with V1R and V2R antagonists separately or in combination with renin-angiotensin-aldosterone system (RAAS) antagonists promotes renoprotective effects during CKD development in rats.^{94,95} However, using the combination of V1/2R blockers with antagonists of RAAS system or only RAAS inhibitors were more effective than treatment with V1/2R antagonists alone.⁹⁴ Thus, the RAAS system mediates the renoprotective effects.

Tolvaptan is the first approved V2R blocker approved for the treatment of autosomal dominant polycystic kidney disease (ADPKD).⁹⁶ Blocking of the V2R with tolvaptan is successfully used for the treatment of ADPKD. ADPKD accounts for 7 %-10 % of patients with ESRD and is the fourth most common cause for renal replacement therapy worldwide.^{97,98} Serum AVP increases progressively with advancement of the disease.⁹⁹ The aim of the tolvaptan treatment is the reduction of cAMP, which is a driver of ADPKD. Mutations in the genes encoding polycystin-1 (PC1) and polycystin-2 (PC2) are responsible for

ADPKD.¹⁰⁰⁻¹⁰⁴ PC1 is a transmembrane protein with similarities to unusual adhesion GPCRs, and it interacts with PC2, a cation channel.¹⁰⁵ Together, PC1 and PC2 form a complex, which is functioning as a Ca²⁺ channel. PC1 and PC2 are located in the primary cilia of principal and other epithelial cells, not just of the nephron. Mutant PC1 and PC2 cause a decrease in intracellular Ca²⁺, which is associated with activation of Ca²⁺-inhibited AC6 and inhibition of the Ca²⁺-calmodulin-activated PDE1. PDE1 hydrolyses cGMP. The consequence of its inhibition is an increased cGMP level. As cGMP inhibits PDE3, the outcome is the elevation of cAMP promoting the formation and growth of cysts by stimulation of epithelial cell proliferation. Once cysts are formed, elevated cAMP levels lead to excessive activation of cystic fibrosis transmembrane conductance regulator (CFTR)-mediated chloride driven fluid secretion into the cysts, which leads to their swelling.^{100,106} The AKAP Ezrin tethers PKA to CFTR and PKA phosphorylates the channel to increase Cl⁻ and hence water entry into the cysts. Knock out of PDE1A, PDE1C and PDE3A is associated with an increase in the cAMP level, activation of PKA and aggravation of polycystic kidney disease development in mouse models.¹⁰⁰ In polycystic kidney disease patients, PDE3 and PDE4, but not PDE1 expression is decreased.¹⁰⁷ Inhibition of PDE4 promotes activation of cAMP signalling both under basal conditions and upon AVP stimulation and activates the Cl⁻ secretion in polycystic kidney disease cells, whereas PDE1 downregulation mediates stimulation of extracellular signal-regulated kinase (ERK) and cell proliferation. PDE1 co-immunoprecipitates with B-Raf, AKAP79 and forms a nanodomain involved in the regulation of local cAMP levels. AVP stimulation increases the interaction between those proteins, but only in cells derived from polycystic kidney disease patients, not in cells from healthy individuals.¹⁰⁷ In primary cilia of mouse kidney epithelial cells, PC2, AC5, PKA and AKAP150, the rodent orthologue of AKAP79, form a complex with PDE4C that is dysregulated in ADPKD.¹⁰⁸ All of the cAMP-dependent molecular mechanisms are most likely inhibited by tolvaptan treatment and their inhibition contributes to slowing the progression of ADPKD. However, a side effect of tolvaptan is diuresis due to blocking the plasma membrane accumulation of AQP2 in the principal cells, which decreases the compliance of the patients. An alternative for such patients may be the targeting of specific compartmentalized cAMP signalling processes. The conclusion that adrenomedullin stimulates a cAMP pool that is different from the V2R-directed pool (see above)⁵¹ hints towards the possibility to target a V2R-independent cAMP pool for modulation of water reabsorption if V2R is blocked.

3.2 | Podocytes

Podocytes are involved in the development of CKD.^{109,110} They maintain the filtration barrier integrity and prevent protein loss with the glomerular filtrate. One of the main CKD features is

severe proteinuria due to podocyte injury that is associated with loss of their structure and podocyte detachment from the glomerular basal membrane. Glomerular hyperfiltration exposes podocytes to excessive fluid flow shear stress and is one of the factors underlying the development of albuminuria. Excessive fluid flow shear stress causes podocyte injury, which is associated with elevated prostaglandin E₂ (PGE₂) synthesis and upregulation of cyclooxygenase 2 (COX2).¹¹¹ This upregulation and an autocrine/paracrine pathway between COX2 and PGE₂ that engages the PGE₂ receptors EP₂ and EP₄ exists in human podocytes, and PGE₂ levels are elevated in glomeruli of Munich Wistar Frömter rats, a model with glomerular hyperfiltration.¹¹² The stimulation of EP₂ and EP₄ receptors induces cAMP synthesis.¹¹² However, the involved cAMP signalling compartments are unknown. Elucidation of the podocyte cAMP pathways may provide novel targets for renoprotection against mal-adaptations of podocytes to hyperfiltration.

Recently, a first PKA compartment in human podocytes has been recognized.¹¹³ AKAP1 tethers PKA to the cytosolic face of the outer mitochondrial membrane and regulates mitochondrial fusion and fission through interaction with dynamin-related protein 1 (Drp1). Streptozotocin (STZ)-induced diabetes in rats causes podocyte damage that is associated with upregulation of AKAP1. High glucose promotes phosphorylation of Drp1 at Ser637 and its recruitment to AKAP1. The AKAP1/Drp1 complex decreases the mitochondrial membrane potential, ATP synthesis, and leads to an elevation of reactive oxygen metabolites generation as well as apoptosis. Thus, the increased interaction of AKAP1 with Drp1 compromises the mitochondrial dynamic homeostasis in podocytes and contributes to podocyte injury. AKAP1 knock-down protected the kidney from diabetes-induced injury.¹¹³

AKAP1 can also bind Src kinase, protein phosphatase 1, calcineurin (CaN) and PDE4,¹¹⁴ and the use of knockout mice has revealed roles of AKAP1 and its interactions in supporting cardiovascular, lung and neuronal cell survival in a post-ischemic environment.¹¹⁵ ATP, via stimulation of P2Y purinoceptor 4 receptors (P2Y4), initiates PKA activation and PKA phosphorylation and thus inhibition of RhoA signalling to modulate the podocyte contractile apparatus and glomerular filtration. This signalling axis represents a renoprotective mechanism for the glomerular barrier against oxidative stress and for maintaining an appropriate energy balance.¹¹⁶ A detailed understanding of the functioning of AKAP1- and PKA-directed signalling compartments may guide to novel targets for promoting physiological podocyte function in diseases, including CKD.

3.3 | Immune cells, fibroblasts and inflammation and fibrosis

Inflammation is an important feature of CKD.¹¹⁷⁻¹²⁰ Inflammatory processes are driven by various immune cells,

including neutrophils, monocytes, macrophages, as well as endothelial and smooth muscle cells; recent single cell RNA sequencing data show an association of CKD with increases of tissue-resident IL-33R+ and IL-2Ra+ regulatory T cells whose transcription pattern indicates excessively expressed hyperactivation and fibrosis markers. During regeneration, the expression profile shows upregulation of regenerative and proangiogenic pathways.¹²¹ The levels of cytokines and chemokines change in CKD.¹²¹ For example, proinflammatory interleukin-1 β (IL-1 β), IL-6, Tumour necrosis factor- α (TNF- α), C-reactive protein (CRP) and fibrinogen release is increased in CKD patients,^{120,122-124} whereas anti-inflammatory cytokines such as IL-2, IL-4, IL-5, IL-12 are reduced.^{122,124}

cAMP is involved in slowing the progression of inflammatory processes.^{125,126} Chemokine receptors are usually G_{i/o}-coupled and thus responsible for decreasing cAMP levels during inflammation¹²⁷; an elevation of cAMP level decreases levels of proinflammatory chemokines such as CCL3, CXCL1, CCL2, CCL4 and CCL11.¹²⁶ Early work has shown that elevation of cAMP in neutrophils prevents oxidative bursts induced by granulocyte-monocyte colony-stimulating factor.¹²⁸ The accumulation of cAMP with subsequent activation of PKA and Epac1/2 also decreases the expression of TNF and IL-1 β ,^{129,130} two inducers of NF- κ B signalling. As a consequence, NF- κ B-induced proinflammatory cytokines and signalling declines.^{120,124,126} In addition, T cell activation and responses of neutrophils to oxidative stress as well as migration of eosinophils are reduced by elevation of cAMP.¹³¹⁻¹³³ However, an excessive accumulation of cAMP can lead to proinflammatory chemokine release from macrophages in vitro.¹²⁶

A growing body of evidence indicates that cAMP signalling in immune cells occurs in compartments. For example, T cells express at least eight AKAPs. In effector T cells, Ezrin binds PKA, Ezrin-radixin-moesin-binding phosphoprotein 50 (EBP50), phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG) and the tyrosine-protein kinase Csk in lipid rafts. Activation of EP₂ or EP₄ receptors increases the cAMP level, activates PKA, which phosphorylates Csk on S364. Csk phosphorylates another Tyrosine-protein kinase, Lck, on Y505 and inhibits its activity. The inhibition prevents further signal transmission in effector T cells.^{134,135} In regulatory T cells, Ezrin-based complexes can be associated with connexin 43 (Cx43) to create an immune synapse and allow cAMP flow from regulatory to effector T cells.¹³⁵ Another AKAP domain, identified in T cell¹³⁶ and dendritic cell lipid rafts¹³⁷ consists of AKAP79, PKA RII, PKC and protein phosphatase2B/CaN.^{138,139} In this complex, the phosphatase activity of CaN is inhibited, which prevents the Nuclear factor of activated T cells (NFAT) dephosphorylation and downregulates the production of IL-2 and T cell proliferation. Disruption of the PKA/AKAP79 interaction

abolishes the inhibition of CaN and downstream effects. The AKAP79/PKA/CaN compartment is associated with β 2AR. β 2AR stimulation and the subsequent increase in local cAMP is important for CaN inhibition and prevents the aforementioned effects.¹⁴⁰ A similar role has AKAP450, which interacts with Serine/threonine-protein kinase N1 (PKN) and PKA RII α , phosphatases (PP1 and PP2A)^{141,142} and PDE4D3.¹⁴³ The complex is required for T cell activation and IL2 production.¹⁴⁴ The AKAPs MTG8 and MTG16b belong to the myeloid translocation gene family. They anchor PKA RII subunits to the Golgi apparatus and centrosomes^{138,145} and can bind PDE4.¹⁴³ MTG8 interacts with PDE7A in immune cells. Immune cells express additional AKAPs such as AKAP95 and D-AKAP1. Both of them interact with PDE4, however, their function and further interaction partners are unclear.^{135,143,146}

PDE4, expressed in neutrophils, eosinophils, cytotoxic T cells and macrophages, plays a major role in the regulation of inflammation.¹²⁶ Inhibition of PDE4, and thus elevation of cAMP, leads to a reduced recruitment of inflammatory leukocytes to tissues and is already successfully applied for the treatment of inflammatory diseases, such as chronic obstructive pulmonary disease (COPD), inflammatory bowel diseases and neuroinflammation.^{147,148} The PDE4 inhibitor, roflumilast, protected against cadmium-induced kidney damage and oxidative stress by modulation of NF- κ B activation in rats.¹⁴⁹

Kidney fibrosis, a hallmark of both CKD and diabetic nephropathy, is the last step in CKD manifestation. Fibrosis is characterized by the excessive production and deposition of extracellular matrix proteins by activated fibroblasts and associated with podocyte death, inflammation and monocyte infiltration.¹⁵⁰ cAMP has antifibrotic effects. Specialized pro-resolving mediators (SPM) exhibit renoprotective properties and attenuate CKD-associated fibrosis progression by promoting the resolution of inflammation.^{151,152} Antifibrotic effects of SPM depend on the intracellular cAMP level. For instance, SPM RvD1 stimulates the G_s-coupled GPCR N-formyl peptide receptor 2/lipoxin A4 receptor (FPR2/ALX) to increase cAMP levels in leukocytes and non-immune cells.¹⁵³ Moreover, RvD1 together with RvD5 decreases PDE4B, thus elevates cAMP, in human macrophages upon inflammation induced by *Escherichia coli*.¹⁵⁴ Lipoxines (LX), produced by neutrophils, platelets and resident tissue immune cells at the sites of inflammation, act as inflammation breaking molecules.¹⁵² LXs also increase cAMP levels, possibly indirectly through activation of purine receptors (for instance P2RY11).¹⁵⁵ An elevation of cAMP activates PKA, which phosphorylates and thus activates CREB, and it activates Epac. Whereas CREB inhibits TGF β -mediated profibrotic gene transcription, Epac blocks TGF β -mediated Smad-dependent profibrotic gene transcription.¹⁵⁶ In line, cAMP elevation through butaprost, a selective agonist of the

G_s -coupled EP_2 receptor, attenuates kidney fibrosis in human kidney slices and in a mouse model, unilateral ureteral obstruction.¹⁵⁷ Similarly, vasoactive intestinal peptide (VIP) stimulates cAMP synthesis in the macrophage cell line, RAW 264, and its infusion in spontaneous hypertensive rat (SHR), a model of interstitial fibrosis without glomerulosclerosis, reduces fibrosis.¹⁵⁸

However, cAMP can also have fibrotic effects. Fibrosis is associated with an increase in extracellular adenosine levels. Kidney fibroblasts express the G_s -coupled adenosine receptor, AR2B. Activation of AR2B induces cAMP signalling in cultured kidney NRK-49F fibroblasts and increases in the levels of profibrotic and proinflammatory molecules such as SMA- α , IL-6, TGF- β , CTGF, and fibronectin twofold to fourfold.¹⁵⁹ Thus, different GPCRs and presumably different cAMP pools have opposite effects in the development of kidney fibrosis. Elucidating the relevant cAMP signalling compartments may lead to novel strategies for targeting fibrosis in CKD.

In cardiac fibrosis, cAMP promotes antifibrotic effects through PKA and Epac activation,¹⁶⁰ whereas an AKAP, AKAP-Lbc, promotes fibrosis.¹⁶¹ However, this effect does not involve the tethering of PKA. It is the intrinsic Rho-specific guanine nucleotide exchange factor (GEF) activity of AKAP-Lbc that activates RhoA and transduces profibrotic signals downstream of type I angiotensin II receptors (AT1Rs) in cardiac fibroblasts. The knockdown of AKAP-Lbc reduces angiotensin II-mediated RhoA activation, differentiation of cardiac fibroblasts to myofibroblasts, collagen deposition as well as myofibroblast migration.¹⁶¹ In patients with idiopathic pulmonary fibrosis (IPF), a variant of AKAP-Lbc represents a susceptibility gene. It is highly expressed in fibrotic lung regions.¹⁶² It is suspected that it acts through RhoA.¹⁶² In the liver of AKAP12 knockout mice, the mRNA expressions of some fibrosis-related genes such as those encoding epithelial cell adhesion molecule, collagen type 1 $\alpha 1$ and elastin are upregulated.¹⁶³ Such initial findings indicate roles of AKAPs in the development of fibrosis. However, the precise function of these AKAPs and whether their role in compartmentalizing cAMP signalling plays a role in kidney fibrosis is mostly unclear.

4 | A ROLE OF CAMP FOR THE CKD RISK FACTORS HYPERTENSION AND DM

4.1 | Hypertension

Hypertension is a major risk factor for CKD. It affects around 1.4 billion people worldwide,¹⁶⁴ and around 90% of patients with CKD at stages 3-5.¹⁶⁵ Hypertension and CKD are considered a cause and a consequence of each other. The most

frequent scenario of the hypertension-CKD pathway includes the long-term increase in blood pressure, subsequent elevation of intraglomerular pressure and, as a result, damage of kidney vessels, impairment of glomerular filtration and proteinuria^{166,167}; vice versa, CKD-related changes lead to a decrease in the glomerular filtration, an increase in the blood volume and, consequently, an elevation of the blood pressure. Thus, one aim of CKD treatment is to reach blood pressure values lower than 130/80 mmHg.¹⁶⁸ However, the commonly used antihypertensive drugs at best slow the progression of hypertension, and at least 25% of CKD patients have a treatment-resistant hypertension.¹⁶⁹ It is emerging that cAMP signalling compartments are involved in controlling blood pressure from inside and outside the kidney. They could lay a foundation for novel treatments.

4.2 | cAMP control of blood pressure from inside the kidney

Kidneys modulate the blood pressure by participating in the control of vessel tonus and blood volume.¹⁷⁰ A decrease in blood volume and pressure stimulates the secretion of renin from juxtaglomerular cells into the blood.¹⁷¹⁻¹⁷³ Renin cleaves angiotensinogen to angiotensin I, which, in turn, kidney or lung angiotensin-converting enzyme (ACE) hydrolyses to yield angiotensin II. Angiotensin II elevates the blood pressure by activation of Angiotensin II receptor type 1 (AT1) on vascular smooth muscle cells to cause vasoconstriction. It also stimulates aldosterone synthesis and secretion from the zona glomerulosa of the adrenal cortex. Aldosterone stimulates Na^+ and water reabsorption.^{172,173} An increase in angiotensin II, and also a decrease in blood volume, blood pressure or an increase in plasma osmolality causes AVP secretion from the neurohypophysis. AVP induces vasoconstriction through V1R on the surface of vascular smooth muscle cells, and it drives water reabsorption in the collecting duct (see above) and thereby volume replenishment. The consequence of these processes is a rise of the blood pressure.

Renin secretion is modulated by several factors. The stimulation of the juxtaglomerular cells, for example, with norepinephrine,¹⁷⁴ prostaglandin I_2 or PGE_2 stimulates G_{α_s} -coupled GPCRs¹⁷¹ and AC5- and AC6-dependent production of cAMP, which activates PKA. The catalytic subunits of PKA translocate to the nucleus where they phosphorylate CREB. CREB then induces renin gene transcription.^{175,176} The rate-limiting step of renin action is its cAMP-induced exocytic secretion.¹⁷¹ Mice with G_{α_s} deficiency in juxtaglomerular cells display lower renin stores and plasma renin concentration.¹⁷⁷ Both PDE3 and PDE4 hydrolyse cAMP and are expressed in kidney vessels and juxtaglomerular cells.¹⁷⁸ Global inhibition of PDE3 in humans or of PDE4 in rabbits increases cAMP levels and stimulates renin secretion.^{179,180}

However, recently mutations in the PDE3A gene were identified that lead to enzyme hyperactivation and lower cAMP levels in second-order mesenteric arteries. The mutations cause autosomal dominant hypertension with brachydactyly (HTNB).¹⁸¹ Most surprisingly, the mutations are not associated with changes in the serum renin level or changes of other RAAS system components.¹⁸² It is unclear why global inhibition and activation of PDE3A do not have opposite effects. An explanation may be that defined pools of PDEs direct renin synthesis and secretion. The exocytosis-like redistribution of AQP2 into the plasma membrane is also cAMP/PKA-triggered and tuned by PDEs. This regulation occurs locally and requires the anchoring of PKA to AKAPs.^{74,183} Several AKAPs bind PDEs.^{43,61,184} Renin secretion may also involve AKAP-directed local PDE and cAMP signalling.

Renin secretion is modulated indirectly by cGMP and Ca^{2+} . Ca^{2+} inhibits renin secretion because it attenuates AC-induced cAMP synthesis and it enhances cAMP degradation, in particular by Ca^{2+} -activated PDE1.^{172,185} In the macula densa, neuronal nitric oxide synthase (nNOS) synthesizes NO,¹⁸⁶ which leads to elevation of cGMP in juxtaglomerular cells where it suppresses PDE3 and thus elevates the cAMP level and renin secretion in isolated perfused rat kidney.¹⁸⁷

Aldosterone acts through mineralocorticoid receptors and promotes Na^+ reabsorption mainly through stimulation of Epithelial Na^+ channels (ENaC),^{188,189} Na-K-2Cl cotransporters (NKCC2),^{190,191} NaCl cotransporters (NCC)¹⁹⁰; they are regulated by cAMP. NKCC2 is predominantly located in the apical plasma membrane of the epithelial cells lining the lumen of the thick ascending limb of the loop of Henle. NKCC2 mediates the uptake of Na^+ , K^+ and two Cl^- .¹⁹⁰ Na^+ reabsorption is complemented by Na^+/K^+ -ATPase in the basal plasma membrane,¹⁹² whereas Cl^- is transferred to the extracellular space by Cl^- channels of the basal membrane.¹⁹³ K^+ is secreted back into the lumen by the outer medullary potassium channel (ROMK; Kir1.1). NKCC2 is cAMP-regulated both on the transcriptional and the posttranslational level. Stimulation of V2R promotes the cAMP-induced trafficking of NKCC2-bearing vesicles to and their fusion with the plasma membrane of collecting duct principal cells.¹⁹⁴ In addition, AVP stimulates the phosphorylation of Ser126 and Ser874 of NKCC2 by PKA, which increases its activity.¹⁹⁵ Prolonged V2R stimulation enhances NKCC2 transcription and biosynthesis through CREB.¹⁹⁶ Isoproterenol-induced stimulation of β -adrenoceptors of the thick ascending limb increases surface expression of NKCC2 via activation of the cAMP signalling pathway in a mouse kidney lysate. The inhibition of PDE4 with the selective inhibitor rolipram enhances the isoproterenol-mediated effects in rats.¹⁹⁷

Na^+ reabsorption in distal convoluted tubules is mainly orchestrated by members of the electroneutral cation-coupled chloride cotransporter family, namely, NCC.¹⁹² NCC activity is regulated by various hormones, in particular, aldosterone,

glucocorticoids and AVP.¹⁹⁸ Activation of V2R induces NCC phosphorylation at Thr53 and Thr58; the likely kinases being SPAK (SPS1-related proline/alanine-rich kinase) and OSR1 (oxidative stress-responsive kinase 1).^{199,200} In AC6 knockout mice, AVP stimulation does not affect the level of phosphorylated Thr58, which means that AVP activates NCC via a V2R-cAMP pathway²⁰¹; direct evidence that PKA is involved in the phosphorylation is lacking.²⁰² The level of surface NCC expression is independent of cAMP signalling¹⁹⁸ and is probably regulated by the RAAS.¹⁹⁶ Deactivation of both NKCC2 and NCC occurs via dephosphorylation, predominantly by the calcium/calmodulin-dependent phosphatase CaN or protein phosphatase 1.²⁰³

ENaC is found in the apical plasma membrane of distal tubules and collecting duct principal cells. In humans, the channel consists of four subunits (α - δ), among which β - δ are expressed constitutively, whereas the level of α -subunits can be regulated.^{188,204,205} AVP and aldosterone control ENaC activity in a synergistic manner.²⁰⁶ AVP modulates a fast response, whereas aldosterone is responsible for long-term effects.²⁰² Aldosterone enhances the expression of the α -subunits cAMP-independently through activation of mineralocorticoid receptors, and enhances channel trafficking to the apical plasma membrane.^{189,207-209} AVP binding to the V2R and AC3- and AC6-mediated elevation of cAMP and activation of PKA facilitates through phosphorylation of the ubiquitin E3 ligase, Nedd4-2, the maintaining of ENaC in the plasma membrane.²¹⁰ In addition, AVP induces an increase in the open probability of ENaC.²⁰²

So far, only a few studies point to an involvement of compartmentalized cAMP signalling or components of compartmentalized cAMP signalling cascades in Na^+ reabsorption. For example, AKAP18 co-purifies with PKA and voltage-dependent sodium channel from rat brain.^{211,212} In *Xenopus laevis*-derived A6 cells, eicosapentanoic acid activates ENaC in a cAMP/PKA-dependent manner through serum and glucocorticoid regulated kinase (SGK) in membrane-bound compartments containing an AKAP, activated PKA, and a PDE. The identity of the AKAP is unknown.²¹³ Experiments in oocytes suggested that AKAP18-directs a PKC pathway that reduces the amiloride-sensitive, whole-cell conductance in high and low Na^+ conditions.²¹⁴ Determining the phosphorylation state of a protein by the interplay of kinases and phosphatases such as that of NKCC2 and NCC, requires close proximity of the enzymes and their substrate. There are several AKAPs that form the platforms for such kinase-phosphatase interplay; for example, AKAP79 binds CaN and PKA and thereby controls glutamate receptors in neurons.²¹⁵ Such AKAP-based signalling compartments may be expected to also regulate kidney Na^+ reabsorption.

The endogenous vasodilators such as prostaglandins or NO and vasoconstrictors such as angiotensin II control kidney perfusion and the kidney perfusion pressure in a similar

manner as other peripheral vessels. Hypertension particularly affects kidney microvessels. Angiotensin II and adenosine cause the generation of reactive oxygen species (ROS) and oxidative stress, leading to vascular remodelling and increases of pre-glomerular resistance, which, in turn, are key features of hypertension.²¹⁶ The reperfusion of ischemic kidneys and the subsequent re-oxygenation also causes the generation of ROS. Such kidney ischemia-reperfusion injury (IRI) initiates a cascade of cellular responses leading to inflammation and cell death that can cause acute kidney injury (AKI).²¹⁷ AKI represents an important risk factor for CKD. There are indications that upregulation of cAMP has nephroprotective effects in AKI. For example, SW033291, an inhibitor of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), prevents AKI in a murine model of IRI by activation of PGE₂/EP₄ signalling and an elevation of cAMP in the kidney.²¹⁸ A peptidomimetic ligand of the EP₄ receptor, THG213.29, also improved kidney function including perfusion in an acute kidney failure rat model.²¹⁹ cAMP released from kidney cells is converted to adenosine in the extracellular space and stimulates adenosine receptors, which, in turn, has pleiotropic effects as it controls glomerular vascular resistance, renin release and also ROS production (see above) or fibrosis (see below).²²⁰ However, whether cAMP compartmentalization plays a role is unknown. Of utmost importance for the control of kidney perfusion is the NO/sGC/cGMP systems in kidney blood vessels and vascular smooth muscle cells. The signalling cascade has vasodilatory and renoprotective effects. Therefore, various approaches are taken to stimulate the cascade. They include increasing cGMP through NO-donors, direct stimulation of sGC with sGC activators, or by inhibition of cGMP PDEs, such as PDE5, which is abundant in the kidney (Table 3).²²¹

4.3 | Control of blood pressure by cAMP from outside the kidney

A main feature of hypertension is a vascular smooth muscle cell (VSMC)-mediated elevation of blood vessel contraction and increased vascular resistance.²²² The three main mechanisms for the initiation of VSMCs contraction, physical stretching, depolarization and activation of GPCRs by certain ligands (eg, norepinephrine, angiotensin II, AVP), are based on increases of intracellular Ca²⁺. Ca²⁺ binds calmodulin and the complex activates myosin light chain kinase (MLCK), which phosphorylates myosin light chains (MLC) that promote contraction.²²³ cAMP plays a major role in controlling VSMC contractility. cAMP induces vasodilatation via MLCK inhibition (and, in addition, through activation of NO synthesis in endothelial cells).^{223,224} Accordingly, the activation of G_i-coupled receptors is associated with an increase in VSMC

contractility through decreasing the cAMP level, whereas a stimulation of G_s-coupled receptors is responsible for muscle relaxation via cAMP level elevation. Indeed, the G_i level in the heart and aorta increases in rats with deoxycorticosterone acetate-induced hypertension, whereas G_s significantly decreases. In SHRs, accumulation of cAMP in VSMCs lowers blood pressure and peripheral vascular resistance.²²⁵ Additionally, activation of β_{1/2}-adrenoceptors with propranolol or inhibition of G_i-mediated signalling by pertussis toxin decreased peripheral vascular resistance in these animals. Moreover, the hypertensive animals demonstrate a decreased AC activity and an impaired response to AC activation with forskolin.²²⁶

PDEs play an important role in the control of cAMP in VSMCs. Pre-treatment with cAMP analogues or PDE3 inhibitors prevents the increase in blood pressure and peripheral vascular resistance. Indeed, the PDE3 inhibitor, cilostazol, acts as a vasodilator and is approved for the treatment of intermittent claudication in peripheral vascular disease. Cilostazol decreases the negative effects of CKD in the kidney via protecting VSMCs from injury.²²⁷ However, the beneficial effects of cAMP elevation are time and strength dependent. Chronic elevation of intracellular cAMP is associated with pathological cardiac remodeling, arrhythmias, as well as apoptosis, symptoms that ultimately can progress to heart failure.²²⁸ Mutations in the PDE3A gene that lead to hyperactivity of the enzyme and lower cAMP content in second-order mesenteric arteries cause hypertension in HTNB (see above).^{181,182} Therefore, global modulation of cAMP levels for therapeutic purposes appears counter-productive.

cAMP signalling in blood vessels occurs in nanodomains. In the sarcolemma of arterial VSMCs and in the vicinity of AC5, AKAP150 anchors PKA, PKC, and CaN and binds the pore-forming subunit (αC1) of the Cav1.2 L-type Ca²⁺ channel.²²⁹ In response to several stimuli, in particular an increase in glucose in patients with diabetes, PKA phosphorylates Cav1.2 at Ser1928, which increases their open probability and thereby the intracellular Ca²⁺ promoting excessive vasoconstriction.^{230,231}

Nanodomains identified in vessels can also be involved in the regulation of blood pressure in kidney arteries. The interaction between Kv7.4, G_{βγ}-subunits and AKAP-anchored PKA is responsible for kidney artery relaxation. Downregulation of Kv7.4 with siRNA as well as preventing the Kv7.4-G_{βγ}-subunit interaction is associated with vascular dysfunction, hypertension and the inability of kidney vessels to respond to isoproterenol stimulation.²³²⁻²³⁴ The protein complex has not been investigated in detail, yet, and may include additional proteins, in particular PDEs. This example suggests that such complexes represent attractive therapeutic targets for the treatment of hypertension and, therefore, also of CKD.

4.4 | cAMP signalling in DM

DM is another major risk factor for CKD. DM type 2 alone affects more than 400 million people.^{14,15,235} The number of DM type 2-associated CKD cases increased worldwide from 1.4 million in 1990 to 2.4 million in 2017.²³⁶ Around 25% of patients with DM are affected by diabetic nephropathy.²³⁷ Diabetic nephropathy depends on characteristic glomerular changes with Kimmelstiel-Wilson bodies and mesangial expansion, is associated with the disruption of the glomerular barrier permeability, albuminuria and a reduced GFR,²³⁸ and it is the leading cause of CKD and ESRD. The underlying molecular mechanisms remain elusive.^{239,240} Progression of CKD in DM can be slowed by tight serum glucose control with antidiabetic drugs and by attenuating the activity of the RAAS with antihypertensive drugs.²⁴¹

Kidneys are involved in maintaining glucose homeostasis. They can supply glucose to the circulation through gluconeogenesis, and the glomeruli filter glucose and, mainly the proximal tubules, mediate glucose reabsorption through sodium-glucose co-transporters (SGLT1 and SGLT2).²⁴² Various signalling pathways are involved in the regulation of SGLT activity and trafficking to the plasma membrane. In a kidney cell model, LLC-PK₁ cells, glucose decreases cAMP and PKA activation, leading to decreased SGLT2 accumulation in the plasma membrane and thus reduced glucose uptake. This inhibitory effect is apparently mediated by p38 MAPK.²⁴³ As opposed to pancreatic β -cells, it is largely unknown whether compartmentalized cAMP signalling is involved in kidney control of the glucose homeostasis.

In the β -cells, a rise of serum glucose activates its uptake by Glucose transporters, GLUT1 in humans, GLUT2 in rodents. Then glucose promotes an elevation of intracellular ATP and an inhibition of K_{ATP}-channels. This, in turn, leads to plasma membrane depolarization, an increase in the open probability of L-type Ca²⁺ channels (Cav1.2) and Ca²⁺ influx, which triggers insulin secretion.²⁴⁴⁻²⁴⁸

cAMP signalling can amplify insulin secretion. Glucagon, and incretins such as glucose-dependent insulinotropic polypeptide (GIP) or glucagon-like peptide-1 (GLP1) through stimulation of G_s-coupled GIP and GLP-1 receptors, respectively, stimulate increases of cAMP and PKA activity. PKA phosphorylates K_{ATP}-channels (S1448),²⁴⁹ Cav1.2 (the phosphorylation site is unclear)²⁵⁰ and GLUT2²⁵¹ to stimulate insulin release. PKA can also promote insulin exocytosis via phosphorylation of secretory granule proteins.²⁵² Some of the mutations that affect cAMP signalling are considered as risk factors of DM; mutations that cause lowering of AC5 expression in pancreatic islets are an example.²⁵³ Another example is a mutation in the α 2A-adrenoceptor-encoding gene that leads to receptor overexpression, subsequent downregulation of cAMP signalling and inhibition of insulin secretion.²⁵⁴ Heterozygosity for an inactivating mutation in the gene

encoding PKA regulatory RI subunits, an endogenous inhibitor of the catalytic subunits, increases insulin release.²⁵⁵ Expression of constitutively active PKA in pancreatic β cells activates insulin release,²⁵⁶ whereas ablation of α -subunits of G_s leads to severe hypoglycaemia and glucose intolerance.²⁵⁷

For the tight control of serum glucose, several agonists inhibit insulin secretion through stimulation of G_i-coupled GPCRs and AC inhibition, for example, adrenalin and noradrenalin stimulate α ₂-adrenoceptors, somatostatin type 1, 2 and 5 receptors, and melatonin MTNR1B receptors. Leptin mediates PKA-dependent blocking of K_{ATP}-channels and thus inhibits insulin secretion.²⁵⁸ This depends on the interaction of PKA with AKAP79/150.²⁵⁹

Glucose and incretins promote cAMP elevations near the plasma membrane with pronounced oscillations, which contribute to the pulsatile secretion of insulin.²⁶⁰ The sub-plasma membrane oscillations are thought to result from Ca²⁺-mediated modulations of AC and PDE activities and involve spatial orchestration by AKAPs.²⁴⁴ AKAP150 or the human orthologue AKAP79 interact with Ca²⁺-sensitive AC8, store-operated Ca²⁺ channels, Epac2 and CaN and anchor the complex at the plasma membrane. AKAP150 null-mice show a decrease in cAMP production, insulin secretion and aggravated glucose intolerance, which underpins the key role of AKAP150 in cAMP signalling and the maintenance of glucose homeostasis.^{244,261,262} An elevation of cAMP induces translocation of Epac from the cytoplasm to the plasma membrane.²⁶³ Among the AKAP18 variants (α , β , γ , δ),²⁶⁴ siRNA knockdown of AKAP18 α or AKAP18 γ in β -cells lowered and elevated insulin secretion in animal studies, respectively.^{265,266} AKAP18 α tethers PKA to L-type Ca²⁺ channels, facilitates its phosphorylation by PKA and thereby enhances Ca²⁺ entry.²⁶⁵

cAMP compartments require molecules that can regulate the cAMP level, such as PDEs. PDE3B is the quantitatively dominant isoform regulating insulin-induced glucagon suppression.²⁴⁴ PDE1, PDE3, PDE4 and PDE8 are also expressed in the pancreas and involved in controlling the cAMP level.

Based on the ample evidence for a cAMP involvement in insulin secretion, stimulation of cAMP signalling seems to be a valid approach for activation of insulin release in DM. Indeed, incretin effects are impaired in DM and stimulation of GLP-1 receptor signalling is established as a successful therapeutic approach. GLP-1 receptor agonists, exenatide being the first, have been introduced. They have been further developed and are now available as combinations of GLP-1 and GIP. They lead to activation of PKA and increase insulin secretion. However, they cause side effects in the gastrointestinal tract. Another option would be elevation of the cAMP level by PDE inhibition, for example, the PDE4 inhibitor roflumilast and roflumilast-N-oxide improve glucose homeostasis in diabetic mice and diabetic nephropathy.^{267,268} Global inhibition of PDEs would also likely cause side effects.

Collectively, the role of cAMP signalling in insulin release suggests that targeting disease-relevant β -cell compartments to locally increase cAMP signalling may effectively activate insulin release, cause fewer side effects than those caused by the commonly prescribed drugs and may overall improve the outcome for patients with DM and diabetic nephropathy.

5 | PDE MODULATION: AN OPTION FOR CKD TREATMENT?

Among all cAMP signalling components, PDEs have probably been evaluated the most as potential targets for the treatment of kidney diseases, and they may have value for the treatment of CKD (Table 5). Indeed, the non-selective PDE inhibitor pentoxifylline in combination with blockers of the RAAS decreases the GFR in DM type 2 patients who suffer from CKD and postpone their progression to ESRD.²⁶⁹ Pentoxifylline alone improves the status of rats with 5/6 subtotal nephrectomy (a model that recapitulates CKD) via decreasing proteinuria, glomerulosclerosis, interstitial inflammation, and fibrosis.²⁷⁰

Despite treatment with non-selective PDE inhibitors provides promising results, using specific inhibitors could be

more effective and cause less side effects. Along these lines, inhibition of PDE3 with olprinone hydrochloride that is used for the treatment of acute heart failure reduces kidney dysfunction in the development of multi organ dysfunction syndrome in a mouse model.²⁷¹ The PDE3 inhibitor, cilostamide, provides anti-inflammatory effects by slowing reactive oxygen metabolite generation.^{272,273} Another PDE3 inhibitor, cilostazol, inhibits diabetes-induced hypertrophy of glomeruli and activation of an inflammatory response, including the elevation ICAMs and VEGF levels in the kidney.²⁷⁴ Therapeutic effects of cilostazol, which is approved for the treatment of intermittent claudication,²⁷⁵ are based on dilating the arteries and decreasing local blood pressure. Similar mechanisms and signalling pathways could be involved in declining the blood pressure in kidney arteries in CKD patients.

The inhibition of PDE4 improves kidney function in mouse models of acute kidney injury.²⁷⁶ The inhibition of PDE4 by cilomilast protects kidneys from nephrotoxic effects of cisplatin via antagonizing the reactive oxygen metabolites and alleviating the inflammatory processes.²⁷⁶ Another PDE4 inhibitor, rolipram, suppresses the generation of reactive oxygen metabolites in glomeruli upon phorbol myristate acetate (PMA) stimulation in mice.²⁷³ However, because of the many side effects,

TABLE 5 Effects of PDE inhibitors on the indicated kidney diseases and models

Enzyme	Compound	Effect	Disease, organism	Reference
PDE1-PDE11	Pentoxifylline	Decreased GFR	T2D and CKD patients	Chen et al ²⁶⁹
	Pentoxifylline	Decreased proteinuria, glomerulosclerosis, interstitial inflammation and fibrosis	5/6 subtotal nephrectomy, rats	Cheng and Grande ²⁷⁰
PDE3	Cilostamide	Inhibited reactive oxygen species generation	PMA stimulation, rats	Dousa, ²⁷² Chini et al ²⁷³
	Olprinone hydrochloride	Decreased creatinine plasma level	Zymosan-induced multiple organ dysfunction syndrome, mice	Mazzon et al ²⁷¹
	Cilostazol	Declined blood pressure in kidney arteries	CKD patients	Wang et al ²⁷⁴
PDE4	Cilomilast	Improved kidney function, kidney tubular injury, tubular cell apoptosis, and inflammation	Cisplatin-induced acute kidney injury, mice	Xu et al ²⁷⁶
	Roflumilast	Reduced proteinuria, attenuated kidney injury, improved podocyte differentiation	HIV-associated nephropathy, mice	Zhong et al ²⁷⁷
	Roflumilast	Prevented toxic kidney injury	Cadmium (Cd)-induced nephrotoxicity, rats	Ansari et al ¹⁴⁹
	Rolipram	Suppressed generation of reactive oxygen species	PMA stimulation, mice and rats	Chini et al ²⁷³
PDE5	Sildenafil	Prevented the progression of diabetic nephropathy	Streptozotocin-induced diabetes, mice	Pofi et al ²⁸⁴
	Sildenafil	Decreased proteinuria and serum creatinine levels	5/6 subtotal nephrectomy, rats	Tapia et al ²⁸²
	PF-00489791	Reduced albuminuria and the urine albumin-to-creatinine	Diabetic nephropathy patients	Scheele et al ²⁸⁵

rolipram has not reached the clinic but represents a valuable pharmacological tool. Treatment with the PDE4 inhibitor roflumilast prevents the development of cadmium (Cd)-induced nephrotoxicity in rats.¹⁴⁹ Roflumilast also decreases proteinuria, attenuates kidney injury, and enhances differentiation of podocytes upon nephropathy induced by Human Immunodeficiency Virus Type 1 in mice,²⁷⁷ and it reduces inflammatory and fibrotic processes, and fosters podocyte survival in rats with subtotal nephrectomia²⁷⁸

CKD is associated with a decrease in NO bioavailability.²⁷⁹⁻²⁸¹ Therefore, consequences of PDE5 inhibitors and their cGMP- and NO-elevating effects in CKD prevention and treatment were evaluated.^{270,279,282,283} For example, inhibition of PDE5 with sildenafil prevents the progression of diabetic nephropathy and associated hypertension via improving hemodynamic parameters in mice with streptozotocin-induced diabetes.²⁸⁴ Another PDE5 inhibitor, PF-00489791, has nephroprotective properties and has already completed clinical phase II trials. PF-00489791 in combination with RAAS blockers reduces albuminuria and the urine albumin-to-creatinine ratio in diabetic nephropathy patients.²⁸⁵ The evaluation of the effects of PDE5 inhibition needs to consider the crosstalk between cGMP and cAMP. PDE5 inhibition leads to elevation of the cGMP level, which in turn inhibits PDE3; the affinity of PDE3 for cAMP and cGMP is similar (K_m values from 0.1-0.8 $\mu\text{mol/L}$) the V_{max} for cAMP is 4-10 times higher than for cGMP.²⁸⁶ Therefore, renoprotective effects of PDE5 inhibitors are most likely at least in part mediated by PDE3 inhibition.

Some kidney disorders require lowering of cAMP levels and could thus be treated with specific PDE activators. A recent example stems from the development of the small-molecule, MR-L2, for the treatment of polycystic kidney disease. The molecule activates long forms of PDE4 and inhibits the formation of cysts in a cell culture model, that is, MDCK cells, as well as in primary cell cultures derived from PKD patients.²⁸⁷ A renoprotective effect of cAMP lowering may also be conferred by hyperactivation of PDE3A, as in HTNB patients where hyperactivation of PDE3A is the cause of the disease but where no hypertensive kidney damage has been observed.^{181,182,288-290}

Overall, the examples illustrate that using PDE modulators could be a promising direction for CKD treatment. However, the available inhibitors target all isoforms of a PDE family but not individual PDE isoforms, for example, milrinone inhibits both PDE3A and PDE3B.²⁹¹ An improvement are the new PDE4 activators; they only target the long isoforms of the PDE4 family.²⁸⁷ The still limited specificity of the available PDE modulators in the light of the wide expression of PDE family members is considered the reason for side effects of interference with PDE activity. Specificity and simultaneous modulation of local cAMP

levels in defined cellular compartments may be achieved by targeting defined PDE protein interactions such as interactions of PDEs with AKAPs.⁴³

6 | SUMMARY AND OUTLOOK

CKD treatment includes taking antihypertensive drugs and lifestyle modification, for example, dietary restriction and an increase in daily physical activity.^{279,292-294} However, these approaches only slow progression to ESRD. The currently limited understanding of the molecular mechanisms underlying CKD is in line with the limited therapeutic options. Accordingly, the medical need for innovative treatment concepts persists and CKD remains a global burden.¹³

cAMP is a central signalling molecule, and it is becoming increasingly clear that cAMP signalling proceeds in nanodomains in specific cellular environments.⁵³ The compartmentalization of cAMP signalling is a prerequisite for the proper function of various kidney cell types such as principal cells or podocytes. Moreover, it is emerging that aberrant cAMP signalling is involved in the pathogenesis of various kidney diseases and aspects of CKD, such as hypertension, diabetes, inflammation and fibrosis. Therefore, dissecting cAMP signalling compartments, that is, identifying their components and delineating their physiological roles in the kidney and their disease relevance in CKD, will not only provide further mechanistic insight into kidney functioning but can also lay the foundation for the discovery of novel CKD-relevant pharmacological targets. For example, AKAPs act as local scaffolds and play a pivotal role in compartmentalizing cAMP signalling.^{61,295} They engage in direct protein-protein interactions with components of cAMP signalling cascades, for example, PDEs, and thereby coordinate their actions. The identification of altered cAMP signalling and protein-protein interactions in these compartments will facilitate precise pharmacological interference. The required methodology for such an endeavour is in place or is being developed. cAMP signalling in nanodomains can be visualized by novel imaging technology both in living cells and animals.^{296,297} Large signalling complexes can be analysed at the atomic level by modern electron microscopy, for example, how AKAP79 provided access of phosphatases to their substrates.²⁹⁸ Using small molecules for disruption of defined protein-protein interactions within cAMP signalling compartments is possible.^{82,299,300}

In summary, a thorough understanding of compartmentalized cAMP signalling in the kidney will pave the way towards a better understanding of kidney physiology and pathophysiology.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.

AUTHOR CONTRIBUTIONS

AS and EK analysed the data and wrote the manuscript. Both authors read and approved the manuscript.

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