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Role of G protein coupled receptors in acute kidney injury

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Abstract
Acute kidney injury (AKI) is a clinical condition characterized by a rapid decline in kidney function, which is associated with local inflammation and programmed cell death in the kidney. The G protein-coupled receptors (GPCRs) represent the largest family of signaling transduction proteins in the body, and approximately 40% of drugs on the market target GPCRs. The expressions of various GPCRs, prostaglandin receptors and purinergic receptors, to name a few, are significantly altered in AKI models. And the role of GPCRs in AKI is catching the eyes of researchers due to their distinctive biological functions, such as regulation of hemodynamics, metabolic reprogramming, and inflammation. Therefore, in this review, we aim to discuss the role of GPCRs in the pathogenesis of AKI and summarize the relevant clinical trials involving GPCRs to assess the potential of GPCRs and their ligands as therapeutic targets in AKI and the transition to AKI-CKD.

Keywords G protein-coupled receptors (GPCRs), Acute kidney injury, GPCR ligands

Introduction

Acute kidney injury (AKI) is a significant public health problem that is associated with high morbidity and mortality. Clinically, AKI is characterized by a sustained 7-day reduction in urine output and/or a significant increase in serum creatinine levels [1]. The prevalence of AKI is 10–15% in hospitalized patients and can be as high as 50% in intensive care unit patients, with 10–20% requiring renal replacement therapy [2]. The average pooled mortality rate for AKI is 23%, which can increase up to 49.4% in those requiring KRT [1]. AKI can be classified into pre-renal, renal and post-renal injury, depending on the site and etiology of the lesion. Pre-renal factors include volume depletion, hypotension and other ischemia-reperfusion injuries. Renal factors include nephrotoxic drugs and sepsis, and approximately 20% of AKI cases are related to nephrotoxic drug exposure. Post-renal AKI is mainly caused by urinary tract obstruction, which accounts for about 5% of AKI cases [3, 4]. Although the pathological mechanisms may differ among different causes of AKI, they all ultimately lead to the loss of renal function. The kidney has the ability to repair damage, and the degree of AKI injury can affect the outcome. Recent advances in technology, such as single-cell RNA sequencing and chromatin accessibility analysis, have provided new insights into the mechanisms of AKI injury, and emerging mechanisms, such as metabolic reprogramming and iron death, are being explored [1]. However, most of these studies are still at the preclinical stage, and clinical treatment of AKI mainly focuses on managing symptoms, as effective and feasible therapeutic measures are still lacking.

G protein-coupled receptors (GPCRs) are the most extensive family of cell membrane receptors associated

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with signal transduction, and they are widely distributed throughout the body. These receptors have various endogenous ligands such as odors, hormones, neurotransmitters, and chemokines, which have diverse forms such as photons, lipids, and peptides [5, 6]. Based on their amino acid sequences, GPCRs can be classified into different subfamilies, including Class A (retinoid), Class B (secretin and adhesion), Class C (glutamate), and Class F (coiled-coil). These subfamilies have some structural commonness, such as the presence of seven transmembrane structures, but they also have their unique structural characteristics, as shown in Fig. 1. The diverse structure of GPCRs determines the uniqueness and diversity of their functions. GPCR activation methods are diverse and include classical "GPCR-G protein" activation, biased activation, and dimerization activation (Fig. 2). Different receptor activation modes exert unique biological functions through various downstream pathways, including G protein-dependent and non-G protein-dependent pathways (Fig. 3).

GPCRs are implicated in many diseases, including depression, Alzheimer's disease, and cancer. Presently, approximately 40% of available drugs target GPCRs, and GPCRs are the focus of around 60% of ongoing clinical trials [7]. The emergence of cryo-electron microscopy and crystallography techniques has shed new light on the number of GPCR crystal structures, and advancements in cross-disciplinary technologies, such as nuclear magnetic resonance spectroscopy and artificial intelligence, have provided new insights into the structure and function of GPCRs. Consequently, GPCR-based drug research has entered a new stage. However, research on GPCRs related to AKI is relatively limited and dispersed when compared to studies on neurological and cancer-related GPCRs, which somewhat limits the structural advantages of GPCR in drug development for AKI. Therefore, this paper aims to review newly discovered GPCRs, such as metabolism-related receptors, cannabinoid receptors and orphan receptors, that have important roles in AKI pathogenesis, and briefly summarize the existing AKI-related GPCRs, such as Ang receptors, chemokines and complement receptors (Supplementary Table 1).

Role of GPCR in AKI

The kidney is a vital organ that maintains homeostasis by regulating blood pressure, electrolyte balance, and blood components. It performs excretory and endocrine functions and consists of functional units called nephron. These units are composed of glomeruli, capillaries, and tubules, which are comprised of different cell types. The number of nephron is established at birth and decreases with age, particularly after 25 years of age [1]. Although the mechanism of injury may vary, all forms of AKI can ultimately lead to loss of kidney function. Mild renal impairment can be repaired by the kidneys themselves, while severe AKI injury can result in atypical repair, leading to CKD or even ESRD [8].

Renal blood flow is abundant, accounting for 25% of cardiac output in the resting state, and 90% of renal blood flow is perfused to the cortex. The countercurrent

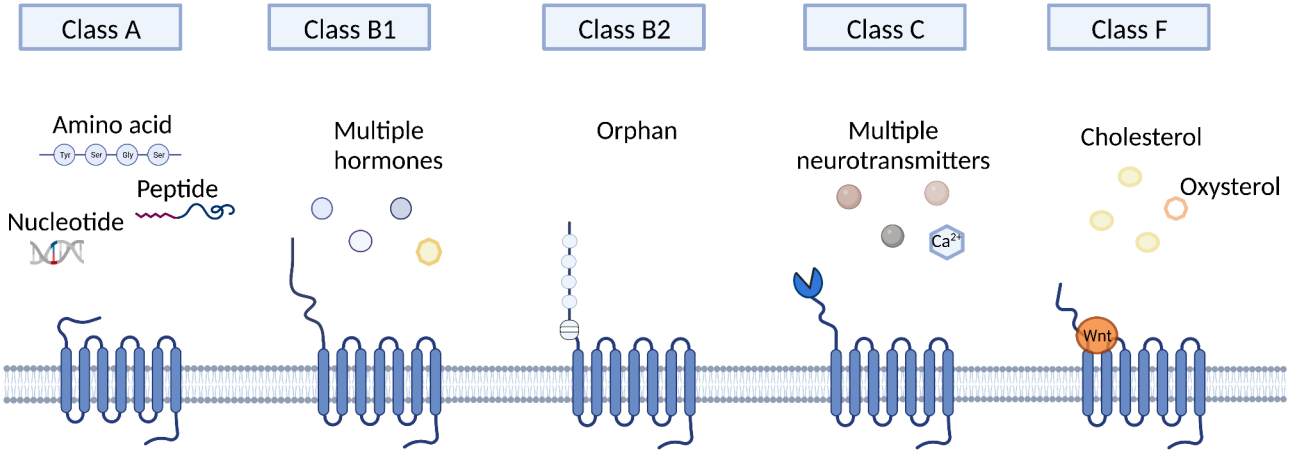

Fig. 1 Structural characteristics and classification of GPCRs. The structures of various GPCR subfamilies are different. For **class A**, the extracellular N-terminus is short. Their native ligands directly bind to the transmembrane region or indirectly affect their conformation by binding to extracellular loop structures. Of note, chemokines and glycoprotein hormone receptors have long N-terminal domains. For **class B1**, the extracellular N-terminus is long, which binds to hormones such as vasoactive intestinal peptide (VIP), adrenocorticotropic hormone-releasing factor (CRF), and calcitonin gene-related peptide (CGRP), respectively. For **class B2**, the extracellular N-terminus is long, with multiple adhesion domains and a GPCR auto-proteolytic site(GPS site). aGPCR is unique in that the extracellular GPS site cleavage exposes the stachel fragment to bind to the transmembrane region and thus activates itself. For **class C**, there is a larger double-lobe N-terminus, also known as the "dreamcatcher" structure, which can form a dimeric structure with a unique activation pattern. **Class F** subfamily contains 10 frizzled receptors (FZD1-10) and 1 smoothened receptor (SMO). The extracellular domain contains approximately 120 amino acids (FZ domain, also known as cysteine-rich domain, CRD). FZD-GPCRs transmit signals via the Wnt pathway, while SMOs transmit signals via the Hedgehog pathway

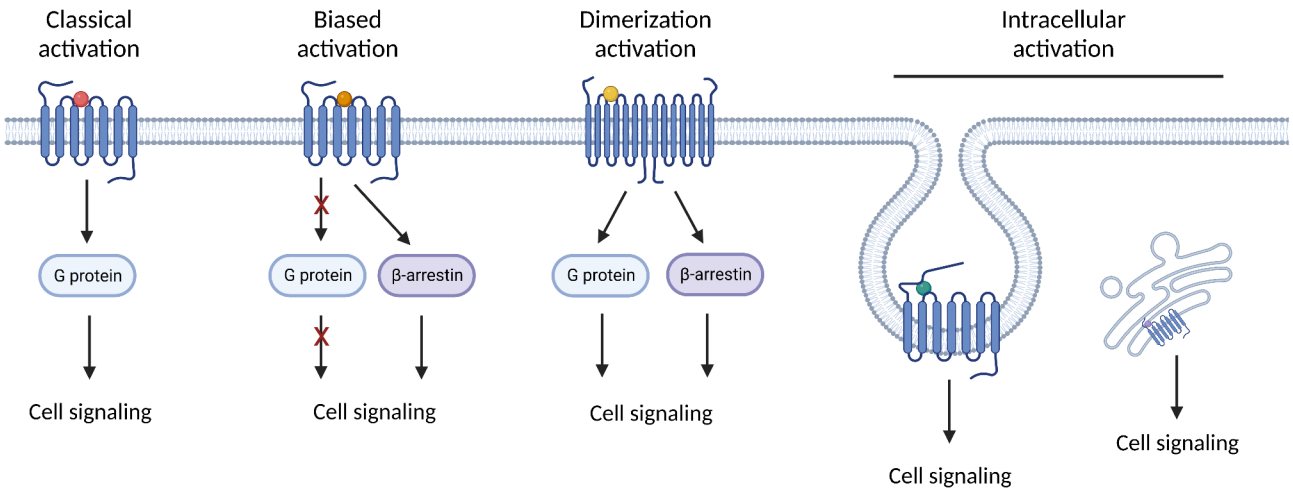

Fig. 2 Activation mode of GPCRs. The activation of membrane receptor GPCR depends on the binding of its ligand. In **classic "GPCR-g protein" activation mode**, GPCR undergoes conformational changes after binding, and then interacts with intracellular G protein. And the activated G protein transducts and amplifies GPCR signals through the second messenger, producing a variety of cellular responses. In **biased activation**, ligands selectively activate the activation mode mediated by the β-arrestin pathway. As for **dimerization activation**, GPCRs do not always exist in monomeric form, and dimerization is also important for certain functions and activation of GPCR signaling pathways. Some GPCRs can be conjugated as either monomers or dimers, and both can activate different downstream signaling pathways. Of note, some GPCR dimerization can be understood as a switch of the conjugated G protein or arrestin molecule. Besides, some GPCRs can be activated within cells and trigger specific downstream effects, so-called "**intracellular activation**". There are at least two explanations for the activation of intracellular GPCRs: First, GPCRs can continue to signal after internalization with their agonists. Second, GPCRs located on different organelle membranes, such as GPR78, can be activated intracellularly

arrangement of the microvasculature allows for urine concentration, but also makes renal tissue particularly sensitive to hypoxia, which affects tissue oxygenation [9]. In addition, the kidney has high energy demands due to its metabolic activity in reabsorbing electrolytes and nutrients from tubular fluid into the blood and secreting waste products from the blood into tubular fluid [10]. The high energy demand renders renal tissue more sensitive to hypoxia, particularly the proximal tubular cells, which are primarily supplied by fatty acid oxidation in the physiological state. In AKI, there is a disruption of the energy balance, enhancement of glycolysis and pentose phosphate pathways, and immunometabolic reprogramming of intrarenal cells [11]. These changes further link hemodynamic changes and cause a series of injuries.

Hemodynamics

The kidney plays a crucial role in regulating blood pressure and fluid homeostasis in the body. Inadequate renal perfusion due to factors such as volume depletion and hypotension can lead to a decrease in the glomerular filtration rate. This alteration can activate the renin-angiotensin system (RAS) when macula densa sense the changes in NA+concentration in the lumen of the distal convoluted tubule. Continuous activation of the RAS system can cause hemodynamic alterations that promote a series of injuries, including hypoxia, metabolic disorders, and inflammation.

Angiotensin II Receptors and Mas Receptors

Angiotensin is a crucial component of the RAS, which plays a significant role in regulating blood pressure and fluid homeostasis. The RAS system's involvement in AKI has garnered considerable attention in research field [12–14]. The RAS system operates through two axes in the kidney, namely the classical axis, which comprises Angiotensin II (Ang II), Angiotensin-Converting Enzyme (ACE), and Angiotensin II Type 1 Receptor (AT1R), and the non-canonical axis, which consists of Angiotensin [1–7] (Ang 1–7), Angiotensin-Converting Enzyme 2 (ACE2), and MasR. These two axes function differently in AKI, with the former increasing blood pressure, promoting inflammation, and causing endothelial dysfunction [15], while the latter reduces blood pressure and exerts anti-inflammatory and anti-fibrotic effects. The angiotensin receptors AT1R, AT2R and MasR are class A GPCRs (Supplementary Table 1). Their expression in the kidney is shown in Table 1 (mouse) and Supplementary Table 2 (human). When renal ischemia-reperfusion injury occurs, the dynamic balance between the two axes is disrupted. **The role of the classical axis in AKI has long been established and numerous clinical studies have shown the protective effect of its inhibition in AKI** [16]. For example, RAS system inhibitors such as losartan can reduce the risk of secondary CKD in cardiac surgery-related AKI [17], reducing severe mortality in AKI patients at 1 year by approximately 52% [18].

On the contrary, the protective role of the non-canonical axis against AKI has received attention in recent years. **Based on data from preclinical studies,**

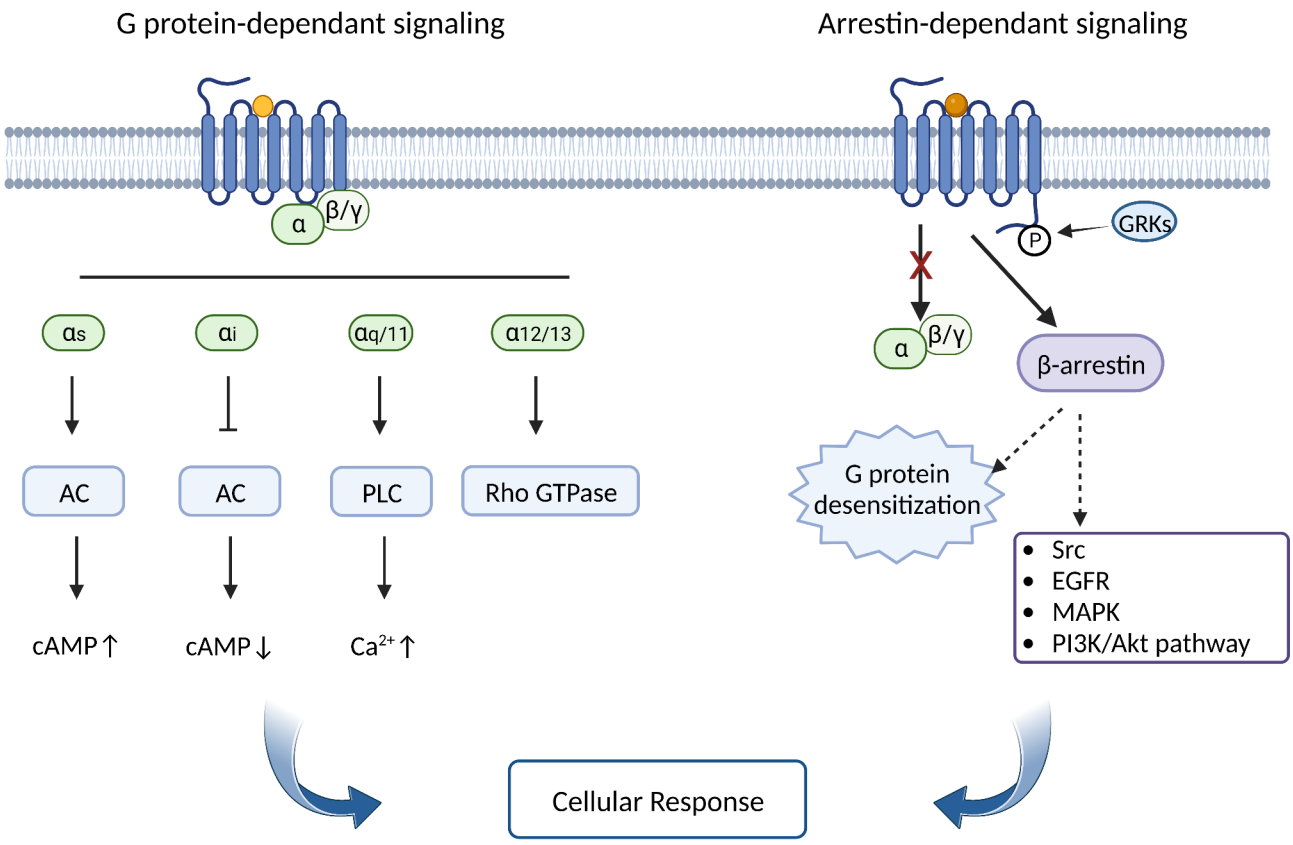

Fig. 3 GPCRs downstream signalings. GPCRs downstream pathways of can be roughly divided into two categories: G protein-dependent signaling pathways and non-G protein-dependent (β-arrestin-dependent) signaling pathways. **G protein-dependent signaling pathways** require G protein involvement, in short, the human body has 16 Gα, 5 Gβ and 13 Gγ subunits that can combine to form a variety of heterotrimeric G proteins. Each Gα subunit is able to signal independently, while the Gβ subunit and Gγ subunit are obligate heterodimers as a single unit (Gβγ). The 16 Gα subunits can be divided into 4 major Gα families (Gs, Gi/o, Gq/11, and G12/13), which regulate the function of key effector factors(adenosine cyclase(AC), phospholipase C(PLC)) that affect the generation of secondary messengers (cAMP, Ca2+, etc.), which in turn triggers different signaling cascades. Many different GPCRs can be conjugated to the same Gα protein, and the same GPCR can also be conjugated to multiple Gα proteins. As for **non-G protein-dependent signaling pathways**, ligands-activated or self-activated GPCRs integrate and transduce extracellular signals by β-arrestin. Phosphorylation of GPCRs by GRK results in the recruitment of β-arrestin, a key molecule of signaling of GPCRs, which can mediate the desensitization of GPCRs, recruit enzymes for second messenger degradation and mediate the internalization of GPCRs, and can also mediate a variety of signal transduction including Src, EGFR, MAPK, PI3K/Akt signaling pathways

the expression of AT2R decreases during growth and development [19], **and is only found in some organs after birth, but is overexpressed in pathological states** [20]. Compared to AT1R, AT2R plays a protective role in the organism by counteracting the various effects of AT1R [21–23]. In ischemic reperfusion injury, AT2R agonist C21 protects renal tubular cells and alleviates injury through the GTPase/RhoA/Cdc42 pathway [24]. In LPS-induced injury, C21 down-regulates the expression of inflammatory factors such as IL-6 and TNF-α and alleviates kidney injury; while this effect is lost locally in the kidney after IL-10 neutralizing antibody treatment, suggesting that the protective effect of AT2R agonist C21 is mediated by IL-10 [25]. MasR is also a member of the descending axis and is presented in various tissues such as heart, kidney, lung, and liver [16], and its ligand Ang [1–7] is protective in the kidney. Accordingly, Ang [1–7] alleviates oxidative stress, inflammation, and apoptosis via MasR in renal injury induced by rhabdomyolysis in rat [26]. Nevertheless, the role of MasR in the kidney is controversial. Studies have shown MasR expression is increased in tubule after IRI in rat [27]; AVE0991 (MasR antagonist) ameliorates IRI-induced tubular injury such as tubular vacuolization and tubular necrosis; however, in MasR knockout mice, ischemia-reperfusion injury on kidney is no significantly different from that of WT mice [28]. In lipotoxic nephropathy, Mas receptor-mediated palmitic acid (PA)-induced renal autophagy and ER stress [29]. Nevertheless, in the UUO model, renal inflammation and apoptotic damage were exacerbated in Mas knockout mice compared to WT mice [30]. Further studies are needed to investigate the role of MasR in AKI and the possible biased signaling of MasR.

Table 1 Expression of GPCRs related to renal hemodynamics in mouse

Gene_symbol	Glomeruli	PTS1	PTS2	PTS3	DTL1	DTL2	DTL3	ATL	MTAL	CTAL	DCT	CNT	CCD	OMCD	IMCD
Agtr1a	396.0	51.6	22.8	7.9	3.4	3.8	1.2	1	0.6	2	0.8	0.2	0.4	0.8	0.3
Agtr1b	0.4	0	0	0	0.4	0	0.1	0	0	0	0	0	0	0	0
Agtr2	0.5	0	0	0	0.8	0.3	0.7	0.3	0	0.5	0	0	0	0	0
Ptger1	4.6	0.4	0.5	0.5	3.7	3	4.6	15.5	2.1	2	1.2	29.5	86.4	494.5	336.3
Ptger2	7.4	0.1	0	0	2	1.9	32.3	0.3	0.1	0	0	0	0	0.3	0
Ptger3	2.1	7.3	0.2	0	4.5	1.3	1.5	36.4	729.4	511.5	18.3	64.5	26.9	1.3	0.2
Ptger4	97.0	0.2	0.1	0.4	20.7	5.8	7.4	2.7	0.5	4.4	0.7	13.4	19.2	11	0.4

The expression of GPCRs mentioned above is extracted from the database providing the mean gene expression values (transcripts per million, TPM) for micro-dissected mouse renal glomeruli (https://esbl.nhlbi.nih.gov/MRECA/G/) and tubule segments (https://esbl.nhlbi.nih.gov/MRECA/Nephron/). GlOM, glomerulus; PTS1, the initial segment of the proximal convoluted tubule; PTS2, the proximal straight tubule in cortical medullary rays; PTS3, the last segment of the proximal straight tubule in the outer stripe of outer medulla; DTL1, the short descending limb of the loop of Henle; DTL2, the long descending limb of the loop of Henle in the outer medulla; DTL3, the long descending limb of the loop of Henle in the inner medulla; ATL, the thin ascending limb of the loop of Henle; MTAL, medullary thick ascending limb of the loop of Henle; CTAL, cortical thick ascending limb of the loop of Henle; DCT, the distal convoluted tubule; CNT, the connecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct; IMCD, inner medullary collecting duct

Prostaglandin receptors

Prostaglandins (PGs) are hormone-like metabolites of arachidonic acid (AA). PGE2, one of the most abundant prostaglandins in the kidney, is produced by all kinds of renal cells and can serve as a chemical signal regulator involved in various biological functions such as blood pressure regulation and fluid homeostasis [31]. Due to its short half-life, PGE2 is released extracellularly in an autocrine or paracrine manner and binds to specific receptor to exert various biological functions. There are four PGE2 receptors (EP1-4) and their expression in the kidney is shown in Table 1 (mouse) and Supplementary Table 2 (human). Physiologically, the regulation of hemodynamics of PGE2 through EPs is closely related to the water channel protein AQP2 [31, 32]. In AKI, EP4 receptors are of great importance due to high expression in immune cells such as macrophages in renal interstitials [33, 34]. There is growing evidence that PGE2/EP4 ameliorates renal I/R injury through various antioxidant, anti-apoptotic and anti-inflammation effects [35, 36]. In our previous study, we also found, in AKI mouse model, EP4 was significantly increased mainly in macrophages but not tubular cells. Activated EP4 inhibited macrophage polarization (decreased M1/M2 ratio) by inducing carnitine palmitoyltransferase 2 (CPT2)-mediated macrophage lipid autophagy to delay AKI progression to CKD [37]. Furthermore, we recently found in gentamicin-induced zebrafish kidney single-cell RNA sequencing data that renal interstitial cells(RICs) secrete PGE2, which promotes proliferation and regeneration of renal cells by activating EP4 on renal progenitor cells [38]. Notably, different EP4 agonists may exert different effects. For example, CAY10598 inhibits IRI-induced mitochondrial dysfunction and alleviates apoptosis [39], while EP4-selective agonist (ONO-AE1-329) increases neutrophil infiltration exacerbating IRI injury [40].

Intercellular stress

Renal tubular cells are the most abundant cell type in the kidney and are critical for substance transport and reabsorption of glomerular filtrate. Renal tubular cells, especially proximal tubular cells, have high mitochondrial content, high energy requirements, and metabolism-related signaling that is essential for the proper functioning of TECs, which also makes them susceptible to oxidative and metabolic stress [1]. Both ischemia-reperfusion injury and cytotoxicity caused by drugs such as cisplatin disrupt tubular cell mitochondrial function and metabolism, especially glycolysis and fatty acid oxidation processes. Long-term abnormalities in metabolic homeostasis lead to tubular cell death and subsequent development of CKD [1].

Purine metabolism and adenosine receptors.

ATP is a crucial energy source for intracellular reactions. However, its negative charge prevents it from crossing the cell membrane freely, resulting in a concentration of extracellular ATP (eATP) that is 1000 times lower than intracellular ATP (iATP) under normal physiological conditions [41]. In response to cellular stress or injury, iATP is released extracellularly via exocytosis or active transport, and exerts signaling functions by binding membrane-anchored ionotropic receptors P2XRs and metabotropic P2YRs [42, 43], which belong to class A GPCRs. Their expression in the mouse and human kidney is shown in Table 2 and Supplementary Table 2, **respectively.** eATP can be degraded to AMP/ADP by the ectonucleotidase CD39, and AMP/ADP can be further degraded to adenosine by the ectonucleotidase CD73 [42, 43]. In the kidney, CD39 exhibits greater enzymatic efficiency than CD73, resulting in a higher local production of AMP/ADP than adenosine [41]. Various types of renal injury lead to increased extracellular ATP concentrations, as well as deficient expression of proximal tubular CD73 and increased concentrations of eAMP/ADP, resulting in sustained activation of purinoceptors [41]. Our previous study [44] found that P2×7R expression was upregulated in renal tubular cells of mice with cisplatin-induced AKI. Blocking P2×7R ameliorated injury by decreasing inflammatory vesicle components, oxidative stress, and caspase-3 activity. Accordingly, P2×7R is a major factor in NLRP3 inflammatory vesicle activation in IRI in mouse [45] and sepsis-induced AKI in rat [46]. In addition, studies have shown that elevated extracellular UDP concentrations activate P2Y14 receptors, promoting chemokine expression and renal infiltration of neutrophils and monocytes in IRI mice [47]. The expression of P2Y4 is associated with inflammatory injury in tubular cells in sepsis-AKI. P2Y4 knockdown ameliorates sepsis-induced kidney injury in mice by inhibiting the NF-κB/MMP-8 axis activation [48].

Adenosine is an important signaling molecule with a protective role in various physiological processes. Its action is mediated through four different adenosine receptors [49, 50]. Adenosine receptors belong to class A GPCRs. Their expression in the mouse and human kidney is shown in Table 2 and Supplementary Table 2, respectively. However, adenosine has a short half-life under normal physiological conditions due to rapid removal by nucleotidases, adenosine kinase, and adenosine deaminase. Hypoxia disrupts several key enzymes involved in adenosine production and degradation, leading to an overall increase in extracellular adenosine levels [51]. Adenosine receptors are expressed in innate immune cells such as macrophages, dendritic cells, and natural killer cells [52]. The activation of different subtypes of adenosine receptors (A1AR, A2aAR, A2bAR, and A3ARs) regulates various cellular responses [53, 54]. A1AR and A2AR are high-affinity adenosine receptors, while A2BR and A3R are 100-fold lower affinity for adenosine than A1AR. Studies have shown that A1AR activation upregulates the protective factor IL-11 through activation of ERK and hypoxia-inducible factor 1-α, as well as induces cytoprotective heat shock protein 27 (HSP27) synthesis through p38 MAPK activation phosphorylation, thereby reducing renal tubular apoptosis and inflammation [51]. Moreover, in mouse models of sepsis-AKI, the absence of A1aR resulted in a more rapid decline in GFR, indicating the importance of A1AR in regulating renal function [55]. Macrophage A2AR activation reduces inflammatory cell infiltration [56],exerting a renoprotective effect. These protective effects are dependent on receptors on bone marrow-derived immune cells rather than receptors on renal intrinsic immune cells [57]. Furthermore, in IRI mice, renal endothelial A2AR activation not only increases medullary blood flow and oxygen partial pressure, but also decreases medullary transport activity, mediating the protective effects of nuclear transporter protein 1ENT1 inhibitor [58].

Lysophospholipid receptors(LPAR/S1PR)

Phospholipids are the main components of biological membranes and usually have two fatty acid chains. Phospholipids with a single fatty acid are called lysophospholipids. Lysophospholipids, such as lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), are produced by the metabolism and perturbation of biological membranes. Both molecules are established extracellular lipid mediators that signal through specific G protein-coupled receptors and have important roles in cellular stress signaling, inflammation, resolution, and host defense responses [59].

LPA receptors belong to GPCR class A subfamily, often been activated classically and trigger G-protein dependent signaling (Supplementary Table 1), and their expression in mouse and human kidney are shown in Table 2 and Supplementary Table 2, respectively. It can be divided into two subgroups based on their different protein homologies. LPAR1-3 are homologous to protein sequences in the endothelial differentiation gene (Edg) family [60], and LPAR4-6 are homologous to the sequences of P2Y purinergic receptor protein(LPA4 / GPR23 / P2Y9, LPA5 / GPR92 and LPA6 / P2Y5) [61]. Here we focus on LPAR1-3. The role of LPA depends on the exact receptor being activated. Accordingly, in IRI mouse model, simultaneous blockade of LPA1 and LPA3 receptors improves renal function, and the protective effect of the dual antagonist is reversed after the use of OMPT, an LPA3 agonist, suggesting that LPAR3 activation may promote renal injury in IRI [62]. Other findings suggest that the ligand LPA exerts a protective effect in the kidney [63, 64], but no study investigates the specific

Table 2 Expression of GPCRs related to renal intercellular stress in mouse

Gene_symbol	Glomeruli	PTS1	PTS2	PTS3	DTL1	DTL2	DTL3	ATL	MTAL	CTAL	DCT	CNT	CCD	OMCD	IMCD
P2rx1	104.5	0.1	0	0	2.4	0.9	0.6	1.1	0.7	0.2	0	0.2	0.1	0.5	0.2
P2rx2	6.8	0.1	0.1	0	0.5	0.3	0.4	0.1	0.3	0.1	0.1	0.1	0	0.3	0
P2rx3	13.1	2.8	0.5	0.2	15.5	11.3	14	15.5	1	1	0.8	0.5	1	8.4	3.3
P2rx4	212.4	48.6	95.3	53.6	55	52.6	52.3	70.6	27.8	39	81.1	87.4	77.5	61.8	57.1
P2rx5	0.6	0.4	18.3	16	1.2	0.1	0.4	15.5	45.7	50	1.3	0.1	0.1	0.1	0
P2rx6	2.4	0.9	0	0	1.6	0.4	0.9	0.6	0	0.1	0	0.2	0.2	0.4	0.1
P2rx7	22.5	0.5	0.3	0	13.1	2.9	3.3	3.2	1	1.5	1	0.9	1.5	2.4	1
P2ry1	75.1	3.6	3.4	1.1	0.9	0.4	0.8	0.1	1.2	0.6	4.1	7.9	2.1	0.3	0.2
P2ry10	0.3	0	0	0	0	0.1	0	0	0	0	0	0	0	0	0
P2ry10b	4.4	0.2	0.1	0	3.8	2.1	0.9	0	0.2	0.6	0.5	0.4	0.4	0.5	0
P2ry12	0.8	0.1	0	0	0.1	0.5	0.2	0	0	0.3	0.1	0.2	0.1	0.4	0.2
P2ry13	0.9	0.1	0	0	1	0.1	0.4	0.3	0.2	0.2	0.1	0.1	0	0.3	0.3
P2ry14	8.2	0.9	0.1	0	9.6	1.4	3.8	2.3	0.3	0.3	2.9	20.5	53.9	236.5	146
P2ry2	7.9	0.4	7.6	5.3	23.4	89.1	102.3	22.2	54.1	36	2.6	8.7	19.4	34.8	16.7
Adora1	10.6	0.4	0.1	0	32.6	190.2	163.3	62.7	0.7	0.9	0.3	15.5	37.8	149.9	96.2
Adora2a	10.3	0.2	0.1	0.1	3.8	2.1	2.4	3.4	2	0.6	0.2	0.2	0.2	1	1.1
Adora2b	2.9	0.8	3.6	3.5	0.7	0.3	0.8	4.7	0.4	9.9	15.7	3	2.2	0.4	0.4
Adora3	3.5	0.5	0	0	7.4	1.1	2.4	2	0.1	0.1	0	0.1	0	1	0.2
Lpar1	3.2	0.5	0.3	0	4.6	0.8	4.7	12.4	1	2.4	3.3	3.9	8.7	20.8	22.7
Lpar2	0.2	0.3	0.4	0.6	1.1	0.3	0.3	0.3	0.1	0.2	0.2	0.2	0.2	0.3	0.3
Lpar3	1.5	94	26.4	19.9	1.5	0.2	0.6	0.2	0	0	0.3	0.1	0.1	0.1	0
Lpar4	3.9	0.1	0	0	3.7	1.8	0.5	1.2	0.1	0.2	0.3	0.8	0.4	0.7	0.1
Lpar5	1.3	0.1	0	0	0.8	1.8	8	5.8	0	0.2	0.1	0.2	0.2	0.7	0.1
Lpar6	8.8	4.1	12.5	15.2	6	4.5	6.2	2.6	3.2	4.8	5.8	7.2	7.9	3	4.6
S1pr1	95.7	1.1	1.1	1.7	36.3	20.9	22.1	3.7	3	5.8	4.6	5.6	2.2	6.2	1.8
S1pr2	14.5	1.2	1	1	7.7	4	6	2.7	0.8	1.2	1.2	2	2.4	2.8	0.2
S1pr3	219.3	0.2	0.1	0.2	8.2	2	3.3	3.8	2.8	1.1	0.4	13.7	21.8	1.4	0.6
S1pr4	4.5	0.2	0.1	0.1	3.3	1.8	1.4	2.5	0.2	0.2	0.2	0.2	0.1	1.3	0.2
S1pr5	4.1	0.4	0	0	2.8	1.1	2.1	0.8	0.2	0.1	0.1	0.2	0.1	1	0.1
Gpbar1	8.6	1.3	0.2	0.2	13.6	3.6	4	6.5	0.1	0.2	0.2	0.7	1.2	4.2	0.6
Ffar1	1.1	0.2	0	0	2.6	0.8	0.9	1.2	0	0	0	0	0.1	0.5	0.1
Ffar2	1.0	0.1	0	0	0.9	0.2	1.8	0.1	0	0	0	0.1	0.3	0.6	0.3
Ffar3	1.0	1.4	1.7	0	1.4	0.3	0.3	0	0	0	0	0	0	0.1	0.1
Ffar4	1.1	0	0	0	4	0.3	0.3	0.8	2.4	2.5	0.1	0	0.1	0.4	0.1

The expression of GPCRs mentioned above is extracted from the database providing the mean gene expression values (transcripts per million, TPM) for micro-dissected mouse renal glomeruli (https://esbl.nhlbi.nih.gov/MRECA/G/) and tubule segments (https://esbl.nhlbi.nih.gov/MRECA/Nephron/). GlOM, glomerulus; PTS1, the initial segment of the proximal convoluted tubule; PTS2, the proximal straight tubule in cortical medullary rays; PTS3, the last segment of the proximal straight tubule in the outer stripe of outer medulla; DTL1, the short descending limb of the loop of Henle; DTL2, the long descending limb of the loop of Henle in the outer medulla; DTL3, the long descending limb of the loop of Henle in the inner medulla; ATL, the thin ascending limb of the loop of Henle; MTAL, medullary thick ascending limb of the loop of Henle; CTAL, cortical thick ascending limb of the loop of Henle; DCT, the distal convoluted tubule; CNT, the connecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct; IMCD, inner medullary collecting duct

LPA receptor that this beneficial effect is based on [64]. Another study found that in IRI rats, LPA1 receptors promote the production and secretion of the pro-fibrotic factor PDGFB/CTGF in proximal tubular cells through EGFR/ERK1/2/AP-1 signaling [65]. Collectively, LPAR3 may have an important role in the acute phase of AKI injury while LPAR1 promotes the AKI to CKD fibrotic process.

Sphingosine 1-phosphate (S1P) is a naturally occurring lysophospholipid that is present at high nanomolar (nm) concentrations in serum [66]. S1P activates S1P receptors(S1PR), also belong to class A GPCR (Supplementary Table 1), to regulate a variety of important cellular functions, including cell survival, cytoskeletal rearrangement, and cell motility [67]. In kidney, S1PR1 and S1PR2 are expressed in proximal tubular cells, endothelial cells, and immune cells [68, 69]. Also, they are the major S1P receptors expressed in the embryonic kidney. S1PR1 expression increases during kidney development, while S1PR2 expression decreases [70]. In renal IRI, S1P provides functional and structural protection through S1PR1 by maintaining endothelial barrier function, reducing apoptosis and promoting regeneration by increasing angiogenesis and proliferation [71]. S1PR2 activation promotes apoptosis and proinflammation through Rho kinase and ROCK1 activation [72]. S1P3 and S1P4 receptors play a central role in the initiation of the immune response. S1PR3 is essential for dendritic cell function and NKT cell activation, while S1PR4 exerts anti-inflammatory by increasing IL-10 release and inhibiting T cell proliferation through the IL-2 / IFNγ pathway [73, 74]. The nonspecific S1PR agonist FTY720 alleviates cisplatin induced kidney injury by enhancing proximal tubular cell mitochondrial function [75]; and regulates mitochondrial biogenesis in DCs to prevent kidney from ischemic reperfusion injury [76]. Oral fingolimod is an S1PR modulator that has been approved by the FDA for the treatment of relapsing multiple sclerosis. Considering the immune-regulating effect and renal tubular protective effects, S1P and its receptors are thought to have therapeutic potential in AKI. The use of fingolimod in a clinical phase II trial in renal transplantation improved creatinine levels but, unfortunately, the increased incidence of macular edema limited the advancement of the trial [77, 78].

Bile acid receptors

Bile acids, the major organic constituents of bile, are mainly several structurally similar steroidal acids. In addition to hepatic and intestinal fat absorption, circulating bile acids regulate a wide range of metabolic pathways, including glucose and lipid metabolism regulation, energy expenditure, and immune responses by activating bile acid receptors, acting as signaling molecules. There are two main bile acid receptors in the kidney: the nuclear receptor farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5) [79, 80]. TGR5 belong to class A GPCRs (Supplementary Table 1), and its expression in kidney is shown in Table 2 (mouse). Previous studies have mostly focused on TGR5 in diabetes/obesity-related renal inflammation and fibrosis. But the protective role of TGR5 activation in IRI kidneys has recently been found. Farnesiferol B could protect kidney function from I/R-induced damage by attenuating inflammation through activating TGR5 in macrophages [81]. Renal tubular TGR5 activation increased renal AQP2 expression and ameliorated lithium-induced uremia, which was reversed in TGR5 knockout mice, suggesting that TGR5 is involved in regulating renal water metabolism [82]. Besides, activation of TGR5 by lithocholic acid (LCA) in collecting duct master cells is found to ameliorate IRI-induced loss of aquaporin-2 (AQP2) through upregulation of hypoxia-inducible factor HIF-1α; also, it may directly inhibit NF-kB pathway and attenuate renal inflammation [83]. Nevertheless, studies on TGR5 receptors in kidneys are currently limited. Considering that its ligand originates from the hepatic-intestinal circulation, whether the role of that intestinal flora metabolites in AKI is associated with TGR5 needs further investigation.

Fatty acids receptors

Fatty acids serve as both energy substrates and signaling molecules in various biological processes. Long- and medium-chain fatty acids obtained from dietary triglycerides, as well as short-chain fatty acids (SCFAs) produced from fermentation of indigestible dietary fibers by intestinal microorganisms, are the primary sources of free fatty acids (FFAs) in the metabolic network. Emerging evidence suggests that FFAs not only provide energy, but also act as signaling molecules that link metabolism and immunity through free fatty acid receptors (FFARs), which are class A GPCRs with classical signaling (Supplementary Table 1). The expression of FFARs in kidney are shown in Table 2 (mouse). FFAR4, for example, is downregulated in cisplatin-induced acute kidney injury (AKI), and the FFAR4 agonist TUG891 has been shown to effectively alleviate injury by regulating endoplasmic reticulum stress-related apoptosis [84]. Knockdown of FFAR4 systemically or specifically in renal tubular epithelial cells exacerbates AKI injury, while activation of renal tubular FFAR4 with TUG891 ameliorates cisplatin-induced renal tubular cell senescence through the Gq subunit of CaMKKβ/AMPK signaling [85]. Furthermore, FFAR4 (GPR120) is expressed in macrophages, and activation of GPR120 on macrophages has been shown to alleviate renal fibrosis in rat models of unilateral ureteral

obstruction when autologously returned to the kidney via intrarenal injection in rat [86].

GW9508, the FFAR1(GPR40) agonist, reduced cisplatin-induced apoptosis in human renal proximal tubular epithelial HK-2 cells [87]. PBI-4050, a synthetic analogue of medium-chain fatty acids that not only agonizes GPR40 but also antagonizes the synthetic ligand of GPR84, has been found to be able to ameliorate renal fibrosis in three types of kidney disease (unilateral ureteral obstruction, ischemic reperfusion injury, and adenine-induced chronic kidney disease) [88]. PBI-4050 ameliorates renal fibrosis by ameliorating adenine-induced endoplasmic reticulum (ER) stress and apoptosis, which was reversed after GPR40 knockdown [89].

Cellular stress

Cannabinoid receptors

Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are essential components of the endogenous cannabinoid system, and are considered to be major ligands for CB1R and CB2R. CB1R and CB2R are class A GPCR (Supplementary Table 1), and their expression in kidney are shown in Table 3 (mouse). CB1R has a high affinity for AEA, while CB2R preferentially binds to 2-AG. These compounds are synthesized from lipid precursors on demand, act locally in an autocrine or paracrine manner, and are rapidly degraded [90]. Activation of CB1R not only regulates cAMP levels via Gαs and Gαi proteins, but also modulates intracellular Ca2+concentration through Gαq proteins. CB1R and CB2R are often co-expressed on the same or adjacent cells and exhibit antagonistic effects. CB1R activation promotes oxidative stress and inflammation, leading to apoptosis and fibrosis, whereas CB2R activation has anti-inflammatory effects and reduces inflammation-driven fibrosis. In cisplatin-induced AKI, endogenous cannabinoids promote inflammation and tubular cell death via CB1R activation and downstream MAPK signaling. However, these injuries can be reversed by CB1R knockdown [91]. Conversely, HU-308, a selective CB2R agonist, ameliorates cisplatin-induced injury by reducing inflammation, oxidative stress, and renal cell death. CB2R knockdown, on the other hand, exacerbates cisplatin-induced renal inflammation and tissue damage [92]. Additionally, URB602, an enzyme that generates 2-AG, plays a protective role in renal ischemia-reperfusion injury (IRI) by scavenging ROS and reducing inflammatory mediators via CB2R in rat [93]. Notably, a common hydrolysis product of endogenous cannabinoids is arachidonic acid (AA), which can generate PGE2 through a series of enzymatic reactions. PGE2 also affects renal perfusion and inflammatory regulation in renal IRI [94]. Whether there is a linkage between cannabinoid receptors and PGE2 receptors in the kidney requires further investigation.

In addition to CB1R and CB2R, cannabinoids can activate many other GPCRs in vivo, such as GPR55, which are classified as members of the novel cannabinoid receptor family [95]. Studies have shown that antagonists of GPR55 can significantly alleviate sepsis-induced renal injury, embodying as reducing KIM-1, NGAL, creatinine and urea nitrogen levels [96].

Adhesion-like G protein-coupled receptors (aGPCRs)

aGPCRs, class B2 GPCRs, are the second largest GPCR subfamily after the retinoid family, and they consist of nine subclasses (I to IX), including 33 members. These receptors have a distinct structure with a long extracellular N-terminal and a self-hydrolysis site known as the GPS motif that enables their self-activation without ligand binding. Their expression in kidney are shown in Table 3 (mouse) and Supplementary Table 2 (human). aGPCRs are widely expressed in vivo and have been implicated in various biological processes, such as inflammation [97] and cell proliferation [98]. The activation of aGPCRs and their downstream signaling pathways are involved in several physiopathological processes, but their role in the pathogenesis of AKI is still limited.

Among the aGPCRs, Gpr116 is one of the most abundant in the kidney and is closely associated with H+secretion in the renal collecting duct, regulating ATPase transport and urinary acidification. Knockdown of Gpr116 causes enhanced tubular H+secretion and leads to tubular alkalosis [99]. ELTD1-Gpr116 double-knockout mice develop severe glomerulosclerotic lesions, and 80% of double-knockout mice do not survive past eight weeks [100]. Furthermore, Gpr97 expression is upregulated in kidneys of AKI mice and patients with acute tubular necrosis. Systemic knockout of Gpr97 in mice, compared to wild-type mice, showed significantly less renal injury and inflammation. Gpr97 activation increases sema3A expression by upregulating the RNA-binding protein HuR, which enhances sema3A stability and participates in AKI tubular apoptosis and inflammation [101].

Despite recent advancements in elucidating the crystal structure of aGPCRs, most of these receptors are orphan receptors. Their relatively high expression in kidneys and unique ability to self-hydrolyze for cleavage activation suggests a potential role in kidney physiology and pathology. Further investigation is warranted to unravel the precise role of aGPCRs in the kidney.

Inflammation and immune responses

Chemokine receptor

Chemokines are a diverse group of cytokines that play a vital role in the recruitment of leukocytes during both

Table 3 Expression of GPCRs related to renal cellular stress in mouse

Gene_symbol	Glomeruli	PTS1	PTS2	PTS3	DTL1	DTL2	DTL3	ATL	MTAL	CTAL	DCT	CNT	CCD	OMCD	IMCD
Cnr1	1.4	0.2	0	0	1.6	0.6	0.6	1.2	0	0	0	0	0	0.5	0.1
Cnr2	18.5	0.1	0.2	0	3.3	2.3	0.5	0.1	0.3	0.7	0.7	0.7	0.4	0.4	0.1
Gpr55	0.5	0.1	0	0	0.7	0.1	0.1	0	0	0	0	0	0	0.1	0.1
Adgra1	1.3	0.1	0	0	1.5	0.7	0.9	0.8	0	0	0	0	0	6.1	8.2
Adgra2	10.8	2.8	0.2	0	2.4	0.4	1	0.4	0.2	0.1	0.1	0.1	0.1	0.4	0.1
Adgra3	35.7	23.3	58.4	27.4	52.9	58.4	32.1	35	39.2	81.4	42.6	27.4	21.2	17.9	24.4
Adgrb1	0.6	0.1	0	0	2.2	0.1	0.4	0.6	0	0	0	0	0	0.2	0.2
Adgrb2	2.8	0.1	0	0	3.1	0.9	2.6	1.1	0	0	0.1	0.1	0.2	0.8	0.3
Adgrb3	5.1	0.8	0	0	8.8	1.9	2.8	3.9	0	0.1	0.1	0.1	0.1	1.7	0.3
Adgrd1	3.6	0.3	0.2	0.2	3.9	1.3	1.7	1	0.3	0.1	0.1	0.1	0.2	1.2	0.2
Adgrd2-ps	0.1	0	0	0	0.1	0	0.1	0	0	0	0	0	0	0	0
Adgre1	2.3	0.6	0.7	0	0.7	1.2	0.1	0.6	2.6	6.6	3.7	4.1	2.3	1.3	0
Adgre4	4.8	0.1	0	0	0.4	0.3	0.4	0.4	0	0.4	0.2	0.1	0.1	0.1	0
Adgre5	421.6	1.5	51.9	24.5	35.1	18.3	10.3	120.4	6	8.2	6	18.8	28.1	37	6.6
Adgrf1	0.5	0.2	0	0	0.8	0.1	0.6	1.2	0	0	0.5	0.4	0.2	3.2	121.6
Adgrf2	2.6	0.2	0	0.1	1.6	2.7	1.2	2.1	0	0.1	0	0.1	0.1	1	0.1
Adgrf3	1.5	0.2	0.1	0	3.2	1.4	1.2	3.7	0.1	0.1	0	0.2	0.2	1.3	0.2
Adgrf4	0.6	0.1	0	0	1.2	0.3	0.1	0.1	0.1	0.1	0	0.1	0.1	0.2	0.2
Adgrf5	231.2	1	2.5	3.7	111.3	70.6	51.2	13.3	8.5	12.1	48	155.4	186.2	406	6.3
Adgrg1	71.0	96.9	63.3	35.8	1054.9	830.1	1136.4	644.8	599.7	928.4	302.8	1055.3	1304	1242	187.2
Adgrg2	0.7	0.4	0.3	0	0.8	0.4	0.7	0.3	0	0.1	0.1	3	3.9	0.3	0
Adgrg3	10.9	0.3	0.2	0.9	25.9	15.8	15.1	15.9	2.8	3.6	1.7	16.6	12.4	10.6	2.5
Adgrg4	1.0	1.8	7	13.1	1.6	0.5	0.7	0.2	0	0	0	0	0.1	0.1	0
Adgrg5	0.9	0	0	0	0.2	0.1	0.2	1.6	0	0.1	0.1	0.1	0.1	0.1	0.1
Adgrg6	5.3	0.1	0	0	31.1	0.8	8	0.4	0.1	0.2	0.1	5.3	12.2	17.2	8.6
Adgrg7	0.3	0	0	0	0.2	0.3	0.3	0.1	0	0	0	0	0	0.1	0
Adgrl1	8.6	6.8	2.3	1.8	7.1	2.9	2.4	3.5	1.4	2.1	1.4	2.7	3.3	3.9	2
Adgrl2	112.0	6	13.1	3.6	38.6	20.5	14.8	9.7	18.9	21.2	16.8	11	13.8	22.7	1
Adgrl3	27.3	1.7	0	0	22.6	5.4	7.9	8	0.2	0.3	0.1	0.1	0.3	3.3	1
Adgrl4	158.9	4.1	3	6.7	261.2	173.7	59.4	9.5	14.8	18.5	23.7	20.9	13.7	43.2	1.6
Adgrv1	9.1	1.1	0.2	0.4	34.7	6.6	7.2	3.6	0.8	0.4	0.1	0.8	1.4	1.9	0.6

The expression of GPCRs mentioned above is extracted from the database providing the mean gene expression values (transcripts per million, TPM) for micro-dissected mouse renal glomeruli (https://esbl.nhlbi.nih.gov/MRECA/G/) and tubule segments (https://esbl.nhlbi.nih.gov/MRECA/Nephron/). GlOM, glomerulus; PTS1, the initial segment of the proximal convoluted tubule; PTS2, the proximal straight tubule in cortical medullary rays; PTS3, the last segment of the proximal straight tubule in the outer stripe of outer medulla; DTL1, the short descending limb of the loop of Henle; DTL2, the long descending limb of the loop of Henle in the outer medulla; DTL3, the long descending limb of the loop of Henle in the inner medulla; ATL, the thin ascending limb of the loop of Henle; MTAL, medullary thick ascending limb of the loop of Henle; CTAL, cortical thick ascending limb of the loop of Henle; DCT, the distal convoluted tubule; CNT, the connecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct; IMCD, inner medullary collecting duct

acute and chronic inflammation. There are four subfamilies of chemokines, including CCL, CXCL, CX3CL, and CL, which bind to a total of 19 known class A GPCRs [102]. Their expression in mouse and human kidney are shown in Table 4 and Supplementary Table 2, **respectively.** The importance of the chemokine family in AKI has been extensively reviewed [11, 103–105]. Depending on their cell-specific expression, chemokine receptors play distinct roles in AKI pathogenesis. For instance, neutrophils primarily bind to chemokines CXCL1, CXCL8, and others via CXCR1 and CXCR2 receptors on their surface, whereas monocytes and macrophages mainly bind to chemokines CCL2, CCL8, and others via membrane surface CCR1, CCR2, and CCR5 receptors, leading to various signaling pathways that contribute to AKI injury.

Complementary receptor

Complement activation is a crucial component of innate immunity, generating biologically active fragments (such as C3a, C5a, and C3b) that exert diverse effects through interactions with their respective receptors. C5aR1 and C3aR1 are class A GPCRs (Supplementary Table 1), expressed not only on myeloid cells (e.g., neutrophils, monocytes/macrophages, mast cells) but also on some non-myeloid cells (e.g., endothelial cells, tubular epithelial cells) [106]. Their expression in mouse and human kidney are shown in Table 4 and Supplementary Table 2, **respectively.** In acute kidney injury, C3a and C5a deposition is increased in the kidney, and attenuating C3aR and/or C5aR expression can ameliorate renal ischemia-reperfusion injury, although C5a seems to play a more predominant role in the pathogenesis of this injury [107]. The important role of complement in renal disease has been thoroughly reviewed previously [106, 108–110]. Notably, the roles of C5aR and C3aR differ in urinary tract infections. In the uropathogenic E. coli (UPEC) model, C5a activates C5aR on renal tubules, promoting bacterial adhesion and colonization by affecting the exposure of mannose sites on tubular cells, while also promoting the release of inflammatory factors and amplifying inflammation [111, 112]. In contrast, the C3a/C3aR1 signaling pathway exhibits a nephroprotective role in urinary tract infections. In the UPEC model, C3a activates C3aR on macrophages, down-regulating inflammatory factors, enhancing macrophage phagocytosis, and reducing bacterial load and renal tissue damage [113].

Therapeutic potential of GPCRs and ligands in AKI

Numerous animal studies have demonstrated the therapeutic potential of targeting GPCRs in AKI. As such, this section will delve into the clinical translation and potential application of GPCRs and their ligands in the treatment of AKI.

Angiotensin is a crucial component of the RAS system in vivo, and its inhibitory agents such as losartan, targeting the AT1R receptor, are widely used in the clinical management of blood pressure. While the use of ARBs was previously discontinued during AKI clinical practice, recent clinical studies have shown that timely initiation of ARBs after the acute phase can improve the prognosis of patients with AKI. A dual-center parallel cohort study conducted in Sweden and the UK, which included 7303 hospitalized AKI patients with a median follow-up of 1.1 years, demonstrated that continuing previous ACEI/ARB therapy after an AKI episode did not increase the risk of heart failure and recurrent AKI compared to discontinuers [114]. Similar results were found in a Taiwan cohort of Asian patients with AKI/AKD requiring dialysis, which included 17,141 patients with a mean follow-up of 1.23 years. Patients who continued ARB treatment after withdrawal from dialysis apparatus had a lower risk of all-cause mortality and no increased risk of re-dialysis compared to those who did not use ARB [115]. It is important to note that the use of ACEI/ARB is not recommended in the acute phase of AKI; rather, fluid supplementation and vasopressors are preferred to improve the patient's circulating blood volume. However, the most effective vasopressor for treating general shock or specific AKI remains unclear [116]. Currently, six ongoing clinical trials investigated the efficacy of angiotensin II in AKI from various causes, such as sepsis and post-liver transplantation. For instance, a study comparing angiotensin II with standard therapy (midodrine, octreotide, and albumin) to improve renal injury in patients with hepatorenal syndrome is still in the patient recruitment or pre-recruitment phase (see Table 5). Concerning ligands, Ang [1–7] is a critical member of the hypotensive axis of the RAS system (Ang 1–7/ ACE2/MasR). Wagener et al. [117]. conducted an RCT study ($n=22$, including patients with COVID-19) to investigate the effect of recombinant protein TXA-127 on AKI in critically ill patients. The results indicated that TXA-127 was safe to use in patients with severe COVID-19 infection and that the incidence of AKI was low. Nevertheless, larger studies are needed to provide more substantial evidence on this issue.

Prostaglandins (PGs) are hormone-like metabolites of arachidonic acid (AA) that act as both hormones and chemical signal modulators. They play important roles in various biological functions, including blood pressure regulation and fluid homeostasis. A double-blind, placebo-controlled randomized trial investigated the effect of prostaglandin E1 infusion on the prognosis of patients during the perioperative period of living liver transplantation. The study's secondary endpoints included AKI. The results showed a significantly lower incidence of AKI in the PGE1 treatment group compared to the control group (8.2% vs. 28%; $P=0.02$), as well as lower peak and

Table 4 Expression of GPCRs related to renal inflammation and immune responses in mouse

Gene_symbol	Glomeruli	PTS1	PTS2	PTS3	DTL1	DTL2	DTL3	ATL	MTAL	CTAL	DCT	CNT	CCD	OMCD	IMCD
Ccr1	3.0	0.2	0	0	2.5	1	1	0.4	0.1	0.3	0.1	0.1	0.1	0.8	0.1
Ccr10	0.7	0	0	0	1.3	0.5	0.5	0	0.2	0.2	0.6	0.6	0.6	0.3	0.1
Ccr1l1	0.8	0.1	0	0	0.6	0.3	0.4	0.6	0	0	0	0	0.1	0.4	0.1
Ccr2	7.8	0.5	0.1	0	4.2	1.3	2.2	1	0.1	3.8	2.3	1.6	1	0.6	0.2
Ccr3	0.4	0	0	0	0.4	0.1	0.4	0	0	0	0	0	0	0.2	0
Ccr4	3.6	0.5	0	0	6.6	1.5	2.5	3.7	0.1	0.1	0.1	0.3	0.2	2.2	0.3
Ccr5	1.1	0.2	0.2	0	1.9	0.7	1.4	1.1	0.7	1.7	0.6	1	0.7	0.4	0
Ccr6	2.7	0.9	0.3	1.2	5.5	2.6	2.8	2.3	0	0	0	0.1	0	0.9	0.2
Ccr7	4.7	0.1	0	0	1.9	0.9	1	0.5	0	0	0	0	0	0.2	0.3
Ccr8	3.4	0.5	0	0	4.4	0.9	1.9	0.9	0.1	0	0	0	0	0.8	0.1
Ccr9	4.1	0.7	0.1	0.3	7.4	2.1	3.5	2.7	0.1	0.1	0.1	0.1	0.2	1.4	0.4
Ccrl2	133.5	1.3	1.3	0.5	12	9.9	2.6	0.6	1.4	6.1	6.1	6.2	2.4	2.2	0.3
Cmklr1	6.6	0.2	0	0.1	18.8	2	1.1	0	0.1	0.2	0.1	0.2	0.2	0.6	0.5
Cx3cr1	6.3	0.5	0.5	0	3	0.9	1.1	2	2.1	6	2.3	2.7	2.1	1.2	0.2
Cxcr1	0.3	0.1	0	0	0	0.2	0.1	0	0	0	0	0	0	0	0
Cxcr2	3.0	0.2	0	0	2.7	1	2.4	0.9	0	0	0	0	0.1	0.2	0.1
Cxcr3	0.7	0.1	0	0	0	0.2	0.1	0	0	0.4	0.2	0.3	0.2	0.1	0
Cxcr4	4.5	0.2	0	0	2.5	0.6	4.8	0.2	0.1	1	1	3.6	2.8	0.5	0.2
Cxcr5	1.5	0	0	0	1.6	0.3	0.9	0.1	0	0	0	0	0	0.5	0.1
Cxcr6	1.6	0.2	0.1	0	1.7	1.2	2.1	1.5	0.2	0.7	0.2	0.3	0.4	0.3	0.4
Xcl1	0.3	0.1	0	0	0.1	0	0.1	0.2	0	0.1	0	0.1	0	0.2	0
Xcr1	1.9	0.1	0	0	0.7	0.4	0.7	0.2	0	0.1	0	0.2	0.1	0.2	0
C3ar1	3.0	0.6	0.1	0	3.9	1	1.7	1.6	0.7	1.6	0.8	0.9	0.6	1.2	0.2
C5ar1	3.9	0.6	0.3	0.1	5.5	3	1.6	2.3	2	2.9	0.9	1.1	0.8	2.3	0.3
C5ar2	3.4	0.3	0	0	5	1.2	2.7	1.7	0.2	0.1	0.1	0.1	0.1	0.8	0.4

The expression of GPCRs mentioned above is extracted from the database providing the mean gene expression values (transcripts per million, TPM) for micro-dissected mouse renal glomeruli (https://esbl.nhlbi.nih.gov/MRECA/G/) and tubule segments (https://esbl.nhlbi.nih.gov/MRECA/Nephron/). GlOM, glomerulus; PTS1, the initial segment of the proximal convoluted tubule; PTS2, the proximal straight tubule in cortical medullary rays; PTS3, the last segment of the proximal straight tubule in the outer stripe of outer medulla; DTL1, the short descending limb of the loop of Henle; DTL2, the long descending limb of the loop of Henle in the outer medulla; DTL3, the long descending limb of the loop of Henle in the inner medulla; ATL, the thin ascending limb of the loop of Henle; MTAL, medullary thick ascending limb of the loop of Henle; CTAL, cortical thick ascending limb of the loop of Henle; DCT, the distal convoluted tubule; CNT, the connecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct; IMCD, inner medullary collecting duct

Table 5 Pharmacological agents targeting GPCR ligands currently reported to be in clinical trials of AKI

NCT number	Product Name	Class	Status	Study Phase	Conditions	Interventions	Locations
NCT00711789	Angiotensin II	Angiotensin II	Unknown status	**Phase 2**	Acute Renal Failure|Sepsis|Septic Shock	Drug: Angiotensin II|Drug: Saline placebo	Northern Hospital, Epping, Victoria, Australia|The Western Hospital, Footscray, Victoria, Australia
NCT04592744	Angiotensin II	Angiotensin II	Enrolling by invitation	**Phase 4**	Cirrhosis, Liver|End Stage Liver DIsease|Acute Kidney Injury|Liver Transplant; Complications	Drug: Angiotensin II|Drug: Norepinephrine	Michael Y Lin, Los Angeles, California, United States
NCT04901169	Angiotensin II	Angiotensin II	Recruiting	**Phase 2**	Liver Transplant; Complications|Vasoplegia	Drug: Angiotensin II|Drug: Saline	University of California, San Francisco, San Francisco, California, United States
NCT05475717	Alprostadil	PGE1	Recruiting	**Phase 2**	Contrast-induced Acute Kidney Injury	Drug: Alprostadil liposome injection	Beijing University First Hospital, Beijing, Beijing, China
NCT03892447	Alprostadil	PGE1	Unknown status	**Phase 4**	Children AKI Patients	Drug: Alprostadil|Drug: Sodium Ferulate|Drug: Dopamine	Shenjing Hospital, Shenyang, Liaoning, China
NCT01722513	Alprostadil	PGE1	Unknown status	**Phase 4**	Kidney Diseases|Diabetes Mellitus|Acute Kidney Injury|Kidney Failure, Chronic|Renal Insufficiency	Drug: Alprostadil & control	Department of Cardiology, Shanghai Tenth People's Hospital, Shanghai, Shanghai, China
NCT05524051	TIN816	Recombinant human CD39 enzyme	**Recruiting**	**Phase 2**	Acute Kidney Injury Following Cardiac Surgery	Drug: TIN816|Other: Placebo	Unknown

Table 5 (continued)

NCT number	Product Name	Class	Status	Study Phase	Conditions	Interventions	Locations
NCT04570397	Ravulizumab	humanized monoclonal antibody that inhibits complement C5	**Active, not recruiting**	**Phase 3**	Covid19|Thrombotic Microangiopathies|Acute Kidney Injury	Drug: Ravulizumab	Brigham and Women's Hospital, Boston, Massachusetts, United States
NCT04743804	Ravulizumab	humanized monoclonal antibody that inhibits complement C5	**Terminated**	**Phase 3**	Thrombotic Microangiopathy	Biological: Ravulizumab|Other: Placebo|Other: Best Supportive Care	Clinical Trial Site, Tucson, Arizona, United States|Clinical Trial Site, Orange, California, United States|Clinical Trial Site, Gainesville, Florida, United States|Clinical Trial Site, Lexington, Kentucky, United States|Clinical Trial Site, Boston, Massachusetts, United States|Clinical Trial Site, Boston, Massachusetts, United States|Clinical Trial Site, Boston, Massachusetts, United States|Clinical Trial Site, New York, New York, United States|Clinical Trial Site, Valhalla, New York, United States|Clinical Trial Site, Cleveland, Ohio, United States|Clinical Trial Site, Columbus, Ohio, United States|Clinical Trial Site, Philadelphia, Pennsylvania, United States|Clinical Trial Site, Pittsburgh, Pennsylvania, United States|Clinical Trial Site, Salt Lake City, Utah, United States|Clinical Trial Site, Morgantown, West Virginia, United States|Clinical Trial Site, Bruxelles, Belgium|Clinical Trial Site, Leuven, Belgium|Clinical Trial Site, Liege, Belgium|Clinical Trial Site, Montreal, Canada|Clinical Trial Site, Toronto, Canada|Clinical Trial Site, Bordeaux, France|Clinical Trial Site, Chambery, France|Clinical Trial Site, Lille, France|Clinical Trial Site, Montpellier, France|Clinical Trial Site, Paris, France|Clinical Trial Site, Tours, France|Clinical Trial Site, Bergamo, Italy|Clinical Trial Site, Rome, Italy|Clinical Trial Site, Iruma-gun, Japan|Clinical Trial Site, Miyagi, Japan|Clinical Trial Site, Miyazaki City, Japan|Clinical Trial Site, Nagoya, Japan|Clinical Trial Site, Osaka, Japan|Clinical Trial Site, Sapporo, Japan|Clinical Trial Site, Shinjuku-ku, Japan|Clinical Trial Site, Tokyo, Japan|Clinical Trial Site, Daegu, Korea, Republic of|Clinical Trial Site, Gwangju, Korea, Republic of|Clinical Trial Site, Seoul, Korea, Republic of|Clinical Trial Site, Amsterdam, Netherlands|Clinical Trial Site, Nijmegen, Netherlands|Clinical Trial Site, Barcelona, Spain|Clinical Trial Site, Granada, Spain|Clinical Trial Site, Madrid, Spain|Clinical Trial Site, Kaohsiung, Taiwan|Clinical Trial Site, Taichung, Taiwan|Clinical Trial Site, Taipei, Taiwan|Clinical Trial Site, Liverpool, United Kingdom|Clinical Trial Site, London, United Kingdom|Clinical Trial Site, Newcastle, United Kingdom|Clinical Trial Site, Nottingham, United Kingdom|Clinical Trial Site, Oxford, United Kingdom|Clinical Trial Site, Salford, United Kingdom

Abbrevation: GPCR, G protein-coupled receptor; AKI, acute kidney injury; COVID-19, Corona Virus Disease 2019; PEG1,Prostaglandin E1

mean postoperative creatinine levels. However, differences in other endpoints, such as the incidence of hepatic artery thrombosis, postoperative bleeding, in-hospital mortality, and post-transplant hospital stay, were not statistically significant between the two groups [118]. Currently, three clinical trials exploring the therapeutic efficacy and safety of the analog alprostadil (liposomes as drug carrier) in contrast-induced AKI and pediatric AKI are underway (Table 5).

Abnormal purine metabolism plays a crucial role in the development of AKI. Extracellular ATP (eATP) is metabolized by CD39 to AMP/ADP, which is further degraded by CD73 to adenosine. Platelet P2Y12 receptor antagonists, such as clopidogrel and prasugrel, are commonly used in clinical practice to prevent and treat thrombotic events associated with cardiovascular disease. In patients with renal insufficiency and acute coronary syndromes, P2Y12 inhibitors have been shown to significantly reduce patient mortality [HR 0.82, 95% CI 0.54–0.96; $P=0.006$] and the risk of re-infarction (HR 0.53, 95% CI 0.30–0.95; $P=0.033$) [119]. However, clinical studies targeting renal purinoceptors are limited. Purine metabolism intermediates, which act as GPCR ligands, have also garnered much attention in clinical research. Two clinical trials are currently underway to explore the efficacy and safety of recombinant human CD39 protein in post-operative cardiac AKI and septic AKI. However, these studies are still in their early stages.

The pathogenic role of complement C5 in acute kidney injury has been demonstrated at animal and clinical levels. Ravulizumab, a novel long-lasting C5 inhibitor, received FDA approval as the drug of choice for treating acute episodes of atypical hemolytic uremic syndrome (aHUS), characterized by the main clinical features of microangiopathic hemolytic anemia, acute kidney injury, and thrombocytopenia triad [120]. Another RCT showed that patients with severe COVID-19 often had AKI, and Ravulizumab treatment was effective in improving the overactivation of the complement cascade in patients with AKI, with a significant decrease in blood free C5 levels and a significant recovery of eGFR at 30 days of follow-up ($P=0.009$). However, unfortunately, compared with the control group, patients in the Ravulizumab group had increased exposure to hemodialysis at day 30 (9% vs. 18%) [121]. Two additional clinical trials investigating the efficacy and safety of Ravulizumab in patients with AKI are ongoing (Table 5), and more research evidence is needed on the protective role of Ravulizumab in AKI, including AKI to CKD transition.

Conclusion and perspectives

AKI is a serious public health problem with high morbidity and mortality, and an in-depth understanding of the characteristics and pathogenesis of disease is an effective strategy to prevent and treat this disease. As mentioned above, GPCRs play an important role in both the repair after mild AKI injury and the progression of CKD after severe AKI injury. Moreover, there are many newly discovered promising GPCRs, such as cannabinoid receptors, fatty acid receptors, and lysophospholipid receptors, hold great potential for therapeutic intervention. Of note, the specificity of the tissue localization of target GPCRs in vivo needs to be taken into consideration in future clinical translation.

Although previous studies on GPCRs in AKI have mainly focused on post-injury hemodynamic changes, apoptosis, and inflammation, recent advances in technology, such as single-cell sequencing, ATAC analysis, and metabolomics, have led to the discovery of new pathogenic mechanisms, including immunometabolic reprogramming and iron death, which suggest that GPCRs may have additional roles and mechanisms in AKI. Moreover, the development of ultra-low temperature electron microscopy (cryo-EM) in crystallology has highlighted the advantages of GPCR signaling properties, such as biased signaling, in drug development, which could lead to improvements in existing drugs and reduction of side effects. Furthermore, these advancements provide new opportunities to identify and explore new therapeutic targets for the development of more effective drugs to improve the prognosis of AKI patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12964-024-01802-8.

Supplementary Material 1: **Supplementary Table 1** Basic information of GPCRs. The explanation of class, activation mode and G signaling can be found in Figs. 1, 2 and 3.

Supplementary Material 2: **Supplementary table 2** Expression of GPCRs in human kidney. The expression of GPCRs mentioned above is extracted from the Higgins Normal Tissue Panel dataset from Nephroseq database providing the gene expression by log2 median-centered ratio for human normal kidney tissue (https://www.nephroseq.org/). It contains 34 normal kidney samples from various kidney structures were analyzed on cDNA microarray.

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Author contributions

Liangjing Lv wrote the main manuscript text and prepared Figs. 1, 2 and 3. Yong Liu, Jiachuan Xiong, Shaobo Wang, Yan Li, Bo Zhang and Yinghui Huang analysed and interpretated the data. Jinghong Zhao designed and revised the study. All authors reviewed the manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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