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Lithium in the Kidney: Friend and Foe?

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ABSTRACT

Trace amounts of lithium are essential for our physical and mental health, and administration of lithium has improved the quality of life of millions of patients with bipolar disorder for >60 years. However, in a substantial number of patients with bipolar disorder, long–term lithium therapy comes at the cost of severe renal side effects, including nephrogenic diabetes insipidus and rarely, ESRD. Although the mechanisms underlying the lithium–induced renal pathologies are becoming clearer, several recent animal studies revealed that short-term administration of lower amounts of lithium prevents different forms of experimental AKI. In this review, we discuss the knowledge of the pathologic and therapeutic effects of lithium in the kidney. Furthermore, we discuss the underlying mechanisms of these seemingly paradoxical effects of lithium, in which fine-tuned regulation of glycogen synthase kinase type 3, a prime target for lithium, seems to be key. The new discoveries regarding the protective effect of lithium against AKI in rodents call for follow-up studies in humans and suggest that long-term therapy with low lithium concentrations could be beneficial in CKD.

J Am Soc Nephrol 27: 1587–1595, 2016. doi: 10.1681/ASN.2015080907

The alkali metal lithium is naturally present in the soil, and the uptake of trace amounts of lithium by the drinking water or diet is essential for our mental and physical health.[1] Animals fed with a lithium-deficient diet exhibited higher mortality rates, chronic inflammation, and abnormalities in reproduction and behavior.[1] In agreement, humans living in areas with relatively high natural lithium levels in their drinking water display reduced all–cause mortality rates and less harmful behavioral problems, like homicide and suicide.[2,3] Other than the necessity of trace amounts of lithium, the benefits of lithium in the treatment of bipolar disorder have been known for >60 years, and despite large efforts of pharmaceutical companies to develop alternatives, lithium is even today the most effective medication for this disease.[4]

However, an important drawback of lithium medication is the development of severe renal side effects (Table 1).[5] On the short term (months to years), lithium causes nephrogenic diabetes insipidus (NDI), a urinary concentrating defect, in approximately 20% of patients, resulting in polyuria, dehydration, thirst, and compensatory polydipsia. Dependent on dose and duration of treatment, long–term (decades) lithium therapy increases the chance to develop ESRD 6- to 8-fold.[5–7] Recently, two studies also reported an increased incidence of solid renal tumors in chronic lithium users compared with the general population.[8,9] However, because of several limitations of these studies as outlined by Licht *et al.*[10] and contradictory findings in the study from Pottegård *et al.*,[11] which included many more patients, we will not regard renal tumor development as a side effect of lithium treatment at this point.[10,11]

In contrast to these adverse effects of lithium treatment, accumulating evidence suggests that the administration of low lithium amounts (<0.6 mM in blood) improves kidney function in different animal nephropathy models. Single-bolus injections or short-term treatment (<1 week) of lithium reduced adriamycin-, LPS-, cisplatin-, gentamicin-, and ischemia-induced AKI,[12–18] whereas prolonged treatment (≥1 month) alleviated kidney damage because of ischemia-reperfusion, hypertension, and the autoimmune disease lupus erythematosus.[19–21] To understand these opposing findings, we will first present an overview of renal lithium handling and then, discuss the molecular pathways underlying the toxic and potential therapeutic effects of lithium in the kidney.

RENAL LITHIUM HANDLING

Lithium has a similar charge and size as sodium, and various reports from approximately 1970 to approximately 1985 showed that their renal filtration and reabsorption are similar. Lithium is, thus, freely filtered in the glomerulus and largely reabsorbed in the proximal tubule, which reabsorbs 70% of filtered sodium. Consequently, lithium was proposed as a quantitative marker for sodium reabsorption in the

Published online ahead of print. Publication date available at www.jasn.org.

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Table 1. Toxic effects of lithium on the kidney and proposed mechanisms

Effect[a]	Segment	Proposed Mechanism	References
NDI	Distal tubule and collecting duct	Reduced water uptake because of downregulation of AQP2 and loss of principal cells	38,40–42,80,117
Cellular remodeling (increase of intercalated versus principal cells)	Distal tubule and collecting duct	Not known; possibly a consequence of lithium–induced G2 arrest of collecting duct principal cells and/or lithium–induced metabolic acidosis	42,80,117
Interstitial fibrosis	Throughout all of the kidney	Not known; possibly a result from prolonged activation of the Wnt signaling pathway	69,71,75,118–120
Tubular atrophy	Proximal tubule[b]	Not known but often linked with interstitial fibrosis in various renal diseases (interstitial fibrosis tubular atrophy)	69,71,74,75,118
Tubular dilation	Collecting duct[b]	Not known; likely a result from increased cell proliferation	75,83,86,120,121
Microcysts	Distal tubule and collecting duct	Not known; likely caused by increased cell proliferation	75,77,83,118,120
Glomerulosclerosis	Glomerulus	Not known; possibly a consequence of progressive renal damage	75,118

[a]The toxic lithium effects are arranged in chronological order of appearance.
[b]Described for these segments, but studies did not exclude occurrence in other segments.

proximal tubule.[22,23] Later, however, micropuncture studies showed that the actual delivery of lithium at the end of the proximal convoluted tubules exceeds that of sodium by approximately 14%, showing that lithium is reabsorbed to a lower extent than sodium.[24] Proximal sodium reabsorption takes place through transcellular and paracellular pathways, accounting for approximately one third and approximately two thirds of proximal sodium reabsorption, respectively. Although lithium is also reabsorbed through both pathways (Figure 1), the contribution of the transcellular pathway is much less, probably explaining its lower total proximal reabsorption.[25–27] The lithium-transporting proteins in the proximal epithelium have not been identified, but ion flux studies give us some insight. The Na^+/H^+ exchanger (NHE3), responsible for most of the luminal Na^+ uptake, is thought to mediate lithium uptake at the apical side of the cell, because its close family member, NHE1, transports lithium very well.[28–30] However, this remains to be investigated. Basolateral lithium efflux is likely not mediated by the Na^+/K^+-ATPase because of its low affinity for lithium but by NHE1, which depending on the electrochemical gradient, can transport lithium in both directions.[29,31,32] Because NHE1 is expressed in the basolateral membrane of epithelial cells of all nephron segment, except the macula densa and collecting duct intercalated cells, basolateral lithium transport is attributed to NHE1 in all lithium-transporting segments.[31,33]

Another 3%–10% of filtered lithium is reabsorbed in the thick ascending limb of Henle (Figure 1).[24] This transport is mainly mediated by the paracellular pathway and driven by the transepithelial voltage difference created by potassium efflux by renal outer medullary K^+ 2 and activity of the $Na^+/K^+/2Cl^-$ cotransporter 2.[28,34,35] Finally, lithium is reabsorbed in late distal tubules and collecting duct, where no paracellular transport takes place because of the impermeability of tight junctions to cations (Figure 1).[24,36] Here, lithium is taken up from the prourine by the principal cells of the collecting duct through the epithelial sodium channel (ENaC).[37]

TOXIC EFFECTS OF LITHIUM TREATMENT

NDI

NDI is characterized by the inability of the kidney to concentrate prourine.[38–40] Urine concentration is mediated by the principal cells of the collecting duct that express aquaporin-2 (AQP2) water channels at their apical membrane and thereby, allow transcellular water reabsorption. Lithium treatment causes dysregulation of AQP2 expression and trafficking on the short term and loss of principal cells on the long term.[41,42] Lithium–induced AQP2 downregulation is a consequence of ENaC-mediated influx of lithium into principal cells, which is shown by ENaC inhibition studies on cultured collecting duct cells.[37] In agreement, ENaC inhibition attenuated and ENaC ablation prevented the development of lithium-induced NDI.[43,44] Within the cell, lithium inhibits glycogen synthase kinase type 3 (GSK3), a serine/threonine protein kinase that regulates many processes, including cell cycle progression, cell differentiation, and normal epithelial function and survival.[45–49] GSK3 consists of two isoforms (α and β), which are inhibited directly by lithium but also, indirectly, by the increased phosphorylation of serines 9 and 21 on GSK3β and -α, respectively.[50] Different studies showed that GSK3 plays an important role in urine concentration and lithium-induced NDI, because the use of GSK3 inhibitors other than lithium also reduced AQP2 abundance in collecting duct cell cultures.[37] Furthermore, ablation of GSK3α or -β in mice caused polyuria

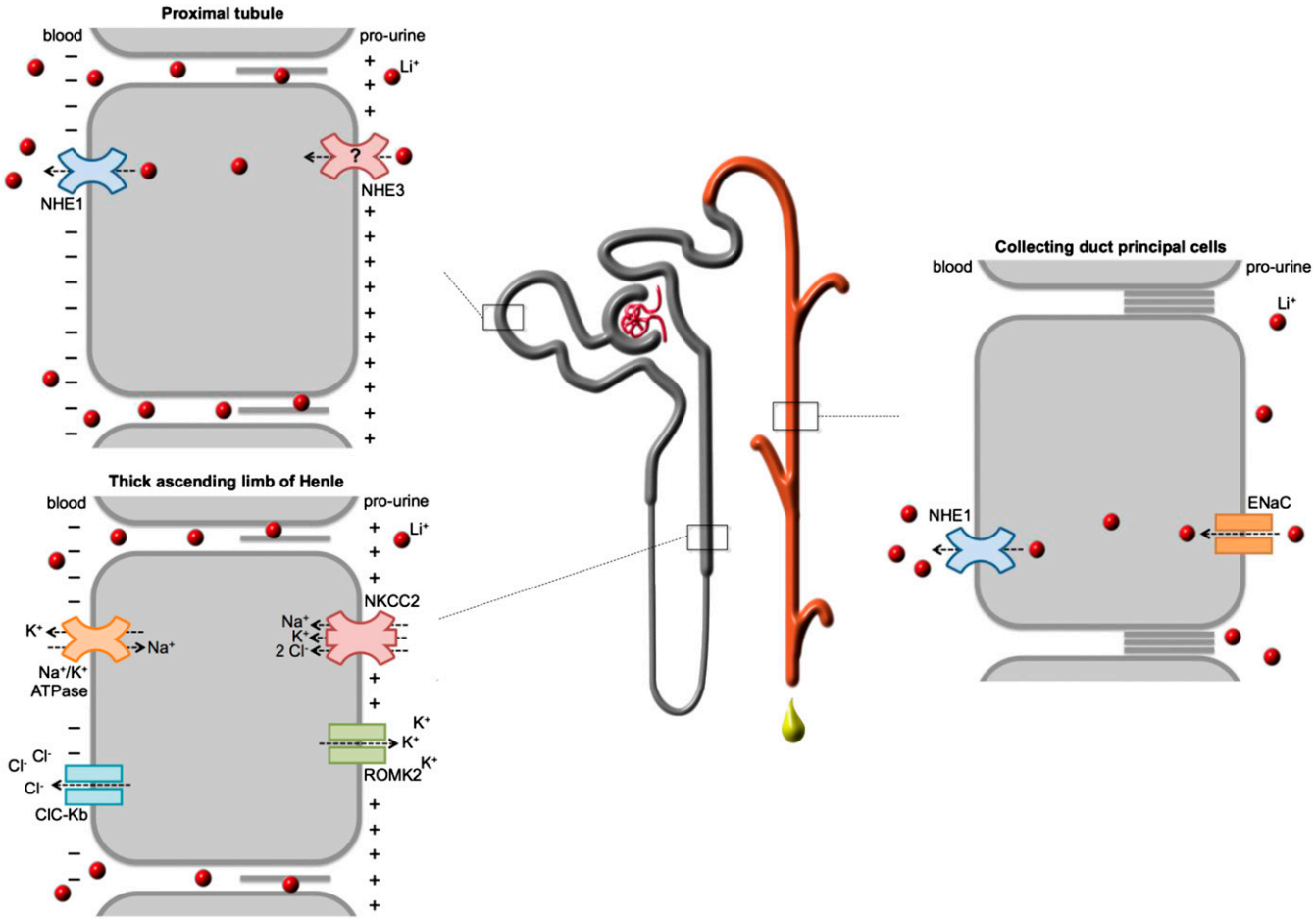

Figure 1. Lithium is reabsorbed in different segments of the renal tubule and in the collecting duct. Lithium is freely filtered in the glomerulus and subsequently reabsorbed by different nephron segments. In the proximal tubules, lithium is, to a minor extent, reabsorbed through the transcellular pathway, which likely involves NHE3 at the apical plasma membrane and NHE1 at the basolateral plasma membrane. In the distal tubules and collecting duct, transcellular lithium uptake from the prourine occurs through the ENaC, whereas NHE1 likely mediates the cellular efflux to the interstitium. In both the proximal tubule and thick ascending limb of Henle (TAL), lithium is reabsorbed in a paracellular fashion, which is driven by the generated transcellular luminal–positive electrical gradient. In the TAL, this gradient is accomplished by luminal K^+ efflux by renal outer medullary K^+ 2 (ROMK2); K^+, Na^+, and Cl^- influx b $Na^+/K^+/2Cl^-$ cotransporter 2 (NKCC2); and basolateral extrusion by the Na^+/K^+-ATPase and ClC-Kb chloride channels (as indicated).

and a reduced AQP2 abundance, whereas subsequent lithium treatment in the GSK3α knockout mice only slightly reduced their urine concentrating ability.[51,52] How the inhibition of GSK3 by lithium ultimately leads to NDI has not been identified but may involve β-catenin, which is increased in expression in lithium-induced NDI and targeted for degradation by GSK3.[48,53–55] Although basal β-catenin activity is necessary for AQP2 expression in collecting duct cell cultures, overactivation of the canonical Wnt-β-catenin pathway might contribute to lithium-induced NDI, because it induces transcription of proliferative genes, which is also observed in principal cells of lithium-treated rodents.[56,57] Loss of polarization, which occurs with proliferation, reduces AQP2 expression *in vitro*.[58] This, however, may not hold, because treatment of lithium NDI mice with the mammalian target of rapamycin 1 inhibitor rapamycin blocked their principal cell proliferation but not NDI.[59] It, thus, remains to be established whether β-catenin has a role in lithium-induced NDI.

In lithium-induced NDI, urinary PGE2 levels are increased and contribute significantly to the disorder, because inhibition of cyclooxygenase-2 in rodents and patients strongly attenuated their lithium-induced polyuria.[60–62] PGE2 activates the EP3 receptor in principal cells, leading to a reduced cAMP signaling, AQP2 expression, and plasma membrane targeting.[48,63] Importantly, renal PGE2 production is stimulated by flow-stimulated release of ATP and its degradation products by activation of their P2Y receptors.[64] Indeed, blocking the $P2Y_{12}$ receptor attenuated lithium-induced NDI and reduced urinary PGE2 levels.[65] A different mechanism was obtained with $P2Y_2$ knockout mice.[66] These mice were also protected from the development of lithium-induced polyuria, but

because these mice exhibited increased urinary PGE2 levels, this protection was attributed to the observed reduced EP3 receptor abundance. Thus, blocking PGE2 production or modulating EP3 receptor abundance seems effective to attenuate lithium NDI.

ESRD

The most severe clinical side effect of lithium is the development of ESRD. Its prevalence in lithium-using patients was reported as approximately 1.5%, which is six to eight times higher than in the general population.[7,67] The duration of lithium treatment is an important factor, because the vast majority of patients with ESRD were treated for >15 years with lithium.[7,67] Although a report in 2014 suggested that the less–controlled treatment regime for lithium in the 1960s and 1970s strongly contributed to the development of ESRD, a later report showed that 5% of patients who started lithium treatment after 1980 and continued for 10–29 years also displayed evidence of ESRD.[6,68] Whether this treatment regime reduces the occurrence of lithium-induced ESRD compared with the practices in the 1960s and 1970s remains to be addressed.

Kidney damage in humans and rodents chronically treated with lithium is mostly characterized by proximal tubular atrophy and chronic interstitial fibrosis (Table 1).[69–72] Some lithium–treated patients also display glomerulosclerosis, but animal studies revealed that this pathology occurs after the onset of interstitial fibrosis and tubular atrophy.[7,69,72–75] Although this suggests that glomerulosclerosis results from damage at other renal segments, it probably constitutes an essential step in the final progression to ESRD.[76] Other than these pathologic features, histology on biopsies or magnetic resonance imaging scans revealed that a number of lithium-treated patients also displays renal microcysts.[75,77] The development of these cysts is likely a direct consequence of lithium uptake by principal cells, because these cysts mainly originate from the distal tubule and collecting duct.[75] Renal cyst formation often results from disturbances in the function of the primary cilium.[78] Because cilium function is dependent on GSK3 activity, the high levels of inactive GSK3, as observed in renal tubules and cysts from lithium-treated animals, might be the primary cause for renal cyst formation.[54,78]

It seems evident that the early development of lithium–induced proximal tubular atrophy and interstitial fibrosis is an essential step toward ESRD. How lithium treatment causes these pathologies is still poorly understood. It is not known whether ESRD results from the influx of lithium into principal cells or other renal cells. We recently found that lithium caused a G2 arrest of principal cells, whereas others found a direct link between G2–arrested renal cells and the elevated production of TGF-β1, which plays a crucial role in the development of renal fibrosis.[76,79,80] In agreement with these findings, the expression of TGF-β1 is enhanced in collecting ducts of lithium-treated rats.[69] Elevated β-catenin levels in principal cells might also contribute to the fibrosis, because Dickkopf-1, an antagonist of canonical Wnt signaling, and ICG-001, which disrupts β-catenin–mediated gene transcription, strongly reduced interstitial fibrosis in mouse nephropathy models.[81,82]

As pointed out, lithium can easily enter proximal tubule cells, and a recent study showed that, several days after a single lithium dose, which was below or similar to therapeutic amounts given to patients with bipolar disorder, the proximal tubule exhibited an enhanced expression of different proproliferative proteins.[18] Importantly, the development of NDI can further aggravate the potential direct pathologic effect of lithium on proximal tubules, because polyuric rats were shown to have an enhanced capacity of transcellular proximal sodium transport and a corresponding increase in NHE3 abundance, likely as a consequence of the hypovolemia-induced activation of the renin-angiotensin system.[30,83,84] Considering NHE3 as the main lithium entry site of proximal tubule cells, this likely also elevates the proximal uptake of lithium. Thus, chronic exposure to therapeutic lithium amounts, certainly combined with NDI, will increase lithium fluxes in proximal tubular epithelia, which may directly cause or contribute to the proximal tubular atrophy and interstitial fibrosis. It is clear that, to develop medication to prevent or attenuate lithium–induced ESRD development, a better understanding of the etiology is needed.

POTENTIAL BENEFICIAL EFFECTS OF LITHIUM

Lithium Reduces Kidney Damage in Various Nephropathy Models

Although chronic intake of high lithium amounts causes renal damage, accumulating evidence from animal studies indicates that administration of low lithium amounts is beneficial in preventing kidney disease caused by nephrotoxic compounds, inflammation, or oxidative stress. In mice, the administration of a single lithium dose 3 days after the induction of AKI by cisplatin largely prevented acute tubular necrosis and reduced serum creatinine levels.[18] The protective effect of lithium was ascribed to its stimulatory effect on tubular cell proliferation and repair, allowing the kidney to repopulate the damaged proximal epithelium.[18] Similarly, a 6-hour pretreatment with lithium prevented adriamycin–induced podocyte injury, which was shown by a reduced albuminuria and reduced expression of podocytopathic mediators B7–1 and MCP-1.[17] A single lithium bolus 1 hour before or simultaneously with LPS injection strongly reduced inflammation and apoptosis of renal cells in mice.[12,17] Importantly, a single dose of 40 mg lithium chloride per 1 kg body wt was effective in all above–mentioned experiments. Although serum lithium levels were not determined in these experiments, the used dose is well below the dose of single lithium chloride injections (200–300 mg/kg body wt) administered to mice to reach the therapeutic range of serum lithium levels in humans.[85] Also, long–term lithium treatment of mice with lupus erythematosus, an autoimmune disease, attenuated the

progression of tubulointerstitial damage and ESRD.[19] Serum lithium levels were not determined, but the mice were injected daily with 4 mg lithium chloride (approximately 120 mg/kg body wt), which likely resulted in lithium levels within the therapeutic range (0.6–1.0 mM).[86] It remains to be determined why this dose improved the kidney function of lupus mice, whereas it causes renal disease in other animals and humans.[86]

Finally, rats that were injected 30 minutes before ischemia-reperfusion with lithium displayed reduced levels of renal oxidative stress, because they exhibited a diminished mitochondrial membrane depolarization and reactive oxygen species (ROS) production.[13] In addition, a 30-day pretreatment of rats with lithium reduced renal damage induced by ischemia-reperfusion, which was shown by the reduction in BUN and serum creatinine and the improved preservation of the tubular structure.[20] Remarkably, lithium treatment of mice 8 hours after the onset of ischemia-reperfusion was also effective in reducing kidney injury, because these mice exhibited less necrosis and a faster recovery of serum creatinine levels.[18] In these experiments, the applied lithium doses were below clinical levels, because they were maximally 50 mg lithium chloride per 1 kg body wt; the 30-day treatment lead to the low serum level of 0.4 mM.

Molecular Mechanisms of the Renoprotective Effects of Lithium

Although lithium also targets inositol monophosphatase and inositol polyphosphate phosphatase,[50] there is no evidence that these targets confer renoprotection. Instead, several GSK3–specific inhibitors other than lithium, like TDZD-8 or BIO, mimicked the protective effects of lithium.[12,15,16,18,87–89] Consistently, mice carrying an inactive GSK3β mutant were protected from mercuric chloride–induced nephrotoxic injury.[90] Therefore, we will focus on GSK3 as the target of lithium contributing to renoprotection with lithium (Figure 2).

GSK3 Inhibition Allows Cell Repair by Activating Proproliferative Pathways

During AKI, the tubular epithelium is damaged and requires repair to prevent chronic damage. Proximal tubule–specific GSK3β knockout or lithium–induced GSK3 inhibition in mice with AKI increased the ability of damaged tubules to undergo repair by enhancing their capacity to proliferate.[18,90] This increased capacity might be caused by an enhanced β-catenin–mediated transcription of proliferative genes (canonical Wnt signaling), because this pathway was also activated in cultured mouse proximal tubular cells treated with lithium and the GSK3 inhibitor BIO.[89] Although canonical Wnt signaling is essential for self-repair during AKI,[91] it is less evident whether pharmacologic repair by lithium also requires canonical Wnt signaling. In fact, the lower lithium amounts used in the AKI mice barely affected canonical Wnt signaling, whereas the expression of proliferative proteins, such as cyclinD1, c-Myc, and HIF-1α, were increased.[18] Xu *et al.*[53] suggested that a moderate GSK3 inhibition might activate the repair machinery by preventing GSK3-mediated degradation of these proliferative proteins in a Wnt-independent manner (Figure 2, left panel). Because prolonged canonical Wnt signaling induces kidney damage,[81,82] activation of the repair machinery without activating Wnt signaling by moderate GSK3 inhibition might be an exciting potential novel therapeutic strategy in treating kidney disease. Additional research is required to confirm the existence of a Wnt-independent regulation of this repair machinery by GSK3.

GSK3 Inhibition Reduces Inflammatory Responses by Regulating NF-κB

In different forms of human kidney disease, renal NF-κB–mediated transcription is associated with proteinuria and other forms of kidney injury.[92] When activated, the NF-κB family members p50, p52, RelA, RelB, and c-Rel form homodimers/heterodimers/trimers, which mediate proinflammatory gene transcription.[92] Renal GSK3β deficiency or GSK3 inhibition prevented tubular and glomerular damage induced by proinflammatory NF-κB signaling.[17,93] NF-κB function is regulated by both GSK3α and GSK3β.[94,95] During kidney injury, active GSK3 promotes the nuclear translocation of NF-κB by phosphorylating RelA at serine 467.[17,92] Additionally, GSK3 activates p50 by phosphorylation and induces the nuclear translocation of the NF-κB family members by blocking Inhibitor-κB,[95,96]

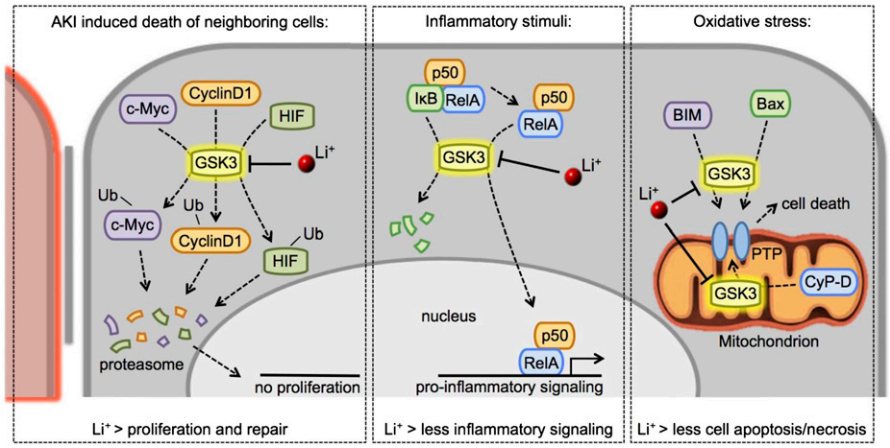

Figure 2. Lithium-induced GSK3 inhibition confers renoprotection via different mechanisms. Upon AKI–induced cell death, an inflammatory response, or increased oxidative stress of proximal tubule cells, activated GSK3 prevents tubular repair and induces proinflammatory gene transcription and apoptosis/necrosis. By inhibiting GSK3, lithium intervenes and reduces activation of these nephrotoxic pathways. Details are in the text. PTP, permeability transition pore.

thereby enhancing the inflammatory response (Figure 2, center panel). Direct inhibition of NF-κB in different nephropathy models mostly prevented the proinflammatory signaling[92] and reduced damage to both tubular as well as glomerular cells.[17,93,97] Importantly, specific NF-κB inhibition was not merely beneficial, because it also induced apoptosis of renal cells.[17] Recent studies showed that the adverse effect of NF-κB inhibition might be overcome by regulating GSK3 activity, because GSK3 inhibition prevented nuclear translocation of NF-κB but did not induce cell apoptosis.[17] Finally, the anti-inflammatory effect of GSK3 inhibition on the kidney might be partially mediated by the modification of systemic inflammatory responses, because GSK3 also plays an important in this process (an overview is in ref. 98).

GSK3 Inhibition Protects against Oxidative Stress by Regulating Mitochondrial Permeability

Progression of renal injury is associated with graded increases in oxidative stress.[99] ROS mediate or accelerate renal injury by triggering inflammatory responses or promoting cell apoptosis, necrosis, senescence, and fibrosis.[99,100] Different GSK3 inhibitors, including lithium, prevent ROS-induced apoptosis of mesangial cells and renal proximal epithelial cells.[87,101–103] Although the molecular mechanism by which GSK3 inhibition prevents renal oxidative damage has not been investigated, studies on extrarenal tissues show that ROS–induced GSK3 activation induces the opening of the mitochondrial permeability transition pore, eventually resulting in cell death.[104,105] Active GSK3α/β induces permeability transition pore opening by activating Bax and BIM in the cytosol and cyclophilin-D in the mitochondrion (Figure 2, right panel).[106] Other than reducing the sensitivity to ROS, lithium and other GSK3 inhibitors also increase the activity of antioxidant proteins, including Bcl-2, in both animal models and humans.[107–111] Although the involved mechanisms are poorly studied, they might involve GSK3-mediated degradation of the transcription factor Nrf2, which upregulates the expression of different antioxidant proteins, like Bcl-2, and recently emerged as an important player in protection against AKI.[112–116]

CONCLUDING REMARKS

Although the damaging renal side effects in patients with bipolar disorder treated with lithium are well known, exciting recent data reveal that usage of the same drug on the short term and at a low dose may form a novel and cheap therapy in the prevention of AKI. It will be highly interesting to discover from future studies if this also holds true for humans and whether long-term treatment of low lithium amounts is also beneficial in preventing CKDs.

ACKNOWLEDGMENTS

This project received support from Radboud University Medical Center Grant 2012.IGMD (to P.M.T.D.), a grant from the Society of Experimental Laboratory Medicine (to P.M.T.D.), a Niels Stensen Fellowship (to T.d.G.), and Marie Curie Fellowship PIOF-GA-2012-332395 (to T.d.G.).

DISCLOSURES

None.

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