Lithium in Kidney Diseases: Big Roles for the Smallest Metal

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Lithium, the lightest metal, with an atomic number of 3, was formally introduced into medicine in 1949, when John Cade discovered the therapeutic effects of lithium carbonate on bipolar disorder. Since then, lithium has become one of the most effective and widely prescribed drugs for mood stabilization in the treatment of psychiatric disorders.1 Recent studies in both experimental and clinical settings have further revealed the potential of lithium as a neurotrophic and neuroprotective agent for the treatment of acute brain injury (e.g., stroke or ischemia), as well as chronic neurodegenerative diseases, such as Alzheimer’s, Parkinson’s, and Huntington’s diseases. Multiple signaling pathways and molecular and cellular targets have been identified to account for lithium’s neurologic effects.2 In addition, lithium has been shown to modulate several aspects of hematopoiesis, such as enhancing the production and release of G-CSF, improving the quantity and quality of neutrophil, increasing monocyte differentiation and activity, and assisting in hematopoietic stem cell mobilization in bone marrow transplantation.3

The clearance of lithium depends exclusively on renal excretion, and, as people age, the ability of lithium clearance decreases. Interestingly, after glomerular filtration, 80% of the filtered lithium is reabsorbed via renal tubules. Because of its unique interactions with kidney cells, lithium has been an important and versatile tool for understanding renal physiology and pathophysiology.4 In medicine, despite its usefulness in psychiatric and neurologic disorders, lithium is known to have adverse effects in kidneys, which, not surprisingly, depend on the dose and duration of use, patient age and health status, and the presence of concurrent medications.5 The notable adverse effects of lithium include acute lithium toxicity, CKD, and nephrogenic diabetes insipidus (NDI), which are especially common in persons with long-term use and in elderly patients.5 In stark contrast, if used briefly and at low doses, lithium can be renoprotective. In this regard, recent studies have shown the protective effects of lithium in experimental models of AKI induced by renal ischemia-reperfusion,6,7 nephrotoxin,8 and endotoxin.9 In this issue of JASN, Bao et al. report that a single dose of lithium given after AKI promotes the recovery and repair of kidneys, whereas de Groot and colleagues show that lithium induces G2 cell cycle arrest in the principal cells of the collecting ducts, which may contribute to the development of NDI.10,11

Bao et al. revealed the beneficial effect of lithium in kidney recovery after AKI using both cisplatin nephrotoxic and ischemic models.10 Cisplatin induced AKI in mice, as indicated by elevated serum creatinine and tubular cell death in the forms of necrosis and apoptosis. The injury was nevertheless reversible and serum creatinine began to gradually decrease after day 3 of treatment, although it was still significantly higher than that in control mice by day 7. Remarkably, a single dose of lithium given at day 3 markedly improved the recovery of renal function. Consistently, cisplatin-induced tubular damage was also attenuated by postinjury treatment of lithium. At the molecular level, lithium was shown to promote the expression of genes involved in cell proliferation, including cyclin D1, c-Myc, and HIF-1α. On the basis of these observations, the authors concluded that delayed treatment with a single dose of lithium accelerates recovery of renal function, promotes proliferation of renal tubular cells, and improves kidney repair in cisplatin-induced AKI.10 It is noteworthy that lithium was given during the recovery phase of AKI in this study, and, therefore, the observed effect is distinct from those shown for lithium given before or during AKI.6–9

To further understand how lithium promotes renal recovery after AKI, Bao et al. went on to examine glycogen synthase kinase-3β (GSK3β), a direct and relatively specific target of lithium.10 Not surprisingly, cisplatin led to activation of GSK3β both in kidneys and in cultured renal tubular cells, which was inhibited by postinjury lithium treatment. Inhibition of GSK3β by lithium induced nuclear expression of cyclin D1, c-Myc, and HIF-1α and enhanced proliferation of cultured renal tubular cells after cisplatin injury. These effects of lithium on cell proliferation were recapitulated by overexpression of a kinase-dead mutant of GSK3β in the tubular cells after cisplatin injury. In contrast, a constitutively active mutant of GSK3β further inhibited cell proliferation after injury and abrogated the proliferative effects.
of lithium. These findings led to the conclusion that GSK3β inhibition is necessary and sufficient for lithium-induced gene expression and associated cell proliferation.10 Although the evidence in cultured tubular cells is compelling, whether lithium’s effect on kidney recovery in vivo is and only is through GSK3β inhibition remains to be substantiated. For example, if lithium promotes kidney repair merely or largely by inhibiting GSK3β, then the beneficial effect of lithium would be lost in renal tubule-specific GSK3β knockout mice. Is this true? Pertaining to this question, a recent study demonstrated that GSK3β ablation from proximal tubules protects against AKI induced by mercuric chloride and, importantly, accelerates kidney repair and regeneration in this injury model.12

How does GSK3β regulate cell proliferation? By immunofluorescence staining and coimmunoprecipitation, Bao et al. suggested the interaction of GSK3β with cyclin D1, c-Myc, and HIF-1α.10 It was further speculated that these pro-proliferative proteins may be substrates of GSK3β; in other words, they contain serine/threonine residues that may be phosphorylated by GSK3β, resulting in their downregulation or degradation. However, this study has yet to provide direct evidence to support this scenario using experimental models of AKI.10

In addition to cisplatin nephrotoxicity, Bao et al. also examined lithium in ischemic AKI, in which mice were subjected to 22 minutes of bilateral renal ischemia followed by reperfusion for up to 48 hours. Lithium was given 8 hours after ischemia.10 With regard to the effects of lithium on kidney recovery in this model, one limitation is that the dissection of injury and recovery/repair phases is not clear. After 24-hour reperfusion, serum creatinine was significantly increased and the high level of serum creatinine was maintained at 48 hours, suggesting that kidney injury, and not repair or recovery, still predominated.10 Therefore, the protective effects of lithium on renal function and tubular damage could be the result of suppressing cell death, as suggested by other studies,6–9 and not the result of promoting cell proliferation and regeneration. The effect of lithium on renal recovery in ischemic AKI should be better observed within a reperfusion period >48 hours to ensure that the recovery does occur. Furthermore, in this study direct evidence of cell proliferation in kidneys is lacking, although it is shown that lithium enhanced the expressions of cyclin D1, c-Myc, and HIF-1α in injured mice.10

In this regard, staining of cell proliferation and regeneration markers such as PCNA, Ki-67, and BrdU would be helpful.

Despite the limitations, this study, by demonstrating the effect of lithium on tubular regeneration and repair in AKI, has significantly extended our knowledge of this drug and may broaden its potential therapeutic applications in kidney diseases. Moreover, an interesting finding of this study is that in cultured human colon cancer cells, lithium suppressed cell growth and sensitized the cells to cisplatin-induced apoptosis.10 This observation, in agreement with recent findings in endometrial cancer and pancreatic ductal adenocarcinoma,13,14 suggests that lithium may reduce the adverse effects of cisplatin in kidneys and enhance the anticancer efficacy during chemotherapy, an inference that requires further in vivo work using tumor-bearing animal models to establish.15

The study by de Groot et al. examined the effects of long-term (up to 13 days) lithium use on renal principal cells and its contribution to NDI,11 an important renal adverse effect of lithium that is characterized by polyuria and polydipsia due to renal resistance to arginine vasopressin (AVP) and consequent failure of urine concentration.5 AVP, a hormone released from the pituitary in response to hypovolemia or hypernatremia, plays a central role in concentration of urine by the kidney. In renal principal cells, AVP regulates the expression of aquaporin-2 (AQP-2) water channel and its apical membrane insertion, leading to water reabsorption in the collecting duct and concentrated urine.16 Two major effects of lithium on collecting duct—downregulating AQP-2 expression and reducing the number of renal principal cells—have been suggested to contribute to NDI.4 Consistent with previous reports,17 de Groot et al. showed that lithium induced downregulation of AQP-2 both in cultured murine principal collecting-duct cells and in kidneys.11 Of note, lithium initiated the proliferation of murine principal collecting–duct cells and especially increased the number of the cells in S and G2 phase of the cell cycle. However, sustained cell cycle progression caused by lithium affected G2/M transition and led to G2 cell cycle arrest. Inhibition of checkpoint kinase 1 attenuated lithium-induced accumulation of cells in G2 phase, suggesting a role for checkpoint kinase 1 in mediating G2 arrest in lithium-treated principal cells.11

These in vitro findings were further confirmed by in vivo experiments. Mice treated with lithium developed NDI, as indicated by increased urine volume and decreased urine osmolality. Lithium induced cell proliferation mostly in collecting ducts, as shown by an increased number of cells positive for PCNA. Costaining of the PCNA-positive cells with respective markers of principal and intercalated cells revealed that most proliferative cells were principal cells, especially during the 4–7 days of lithium treatment. Remarkably, 30%–40% of PCNA-positive principal cells were also positive for pHistone-H3 nuclear foci following 7–13 days of lithium treatment, suggesting that the PCNA positive cells were not necessarily proliferating; rather they got stuck in G2 phase. Thus, sustained lithium exposure may induce a G2 arrest in principal cells in vivo.11 This observation may provide a logical explanation for the paradox that lithium initiates principal cell proliferation but eventually results in a reduced number of principal cells. Further studies are needed to understand the consequences of such a persistent G2 cell cycle arrest, such as its contribution to renal fibrosis and CKD that may also be induced after long-term lithium treatment.5

In conclusion, lithium may play distinct roles in renal pathology. On one hand, short-term treatment with low doses of lithium has therapeutic potential for the treatment of kidney diseases, such as AKI; on the other hand, long-term use of lithium at relatively high dosages may impair the kidney function of concentrating urine, leading to NDI. The two
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DISCLOSURES

None.

REFERENCES


Arrestin(g) Podocyte Injury with Endothelin Antagonism

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Proteinuria is a major pathologic feature of a wide variety of progressive CKD. Even if it is accompanied by a normal GFR, proteinuria indicates significant kidney dysfunction and its presence has been incorporated into definitions for CKD.1 Because proteinuria is an independent risk factor for CKD, it is imperative to determine the mechanisms leading to its development. Current antiproteinuric therapy relies mainly on renin-angiotensin inhibition, but this is only partially successful and novel treatments are urgently needed.2

In this issue of JASN, Buellì et al. examine how endothelin-1 (ET-1) mediates podocyte injury/dysfunction.3 The endothelins are a family of vasoactive peptides with a variety of roles in human disease, with ET-1 being the most relevant in kidney pathology. ET-1 binds to two receptors, endothelin A and endothelin B receptors (ETAR and ETBR, respectively). In general, ETAR is responsible for vasoconstrictive and pathologic actions of ET-1, whereas ETBR governs protective vasodilatory functions. Therefore, selective blockade of ETAR with pharmacologic agents such as sitaxsentan and atrasentan has been explored as a renoprotective therapy, and positive results in reducing proteinuria were demonstrated in a variety of kidney diseases, including diabetic nephropathy.4

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