Lithium and nephrotoxicity: Unravelling the complex pathophysiological threads of the lightest metal

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ABSTRACT

While lithium remains the most efficacious treatment for bipolar disorder, it can cause significant nephrotoxicity. The molecular mechanisms behind both this process and the development of nephrogenic diabetes insipidus still remain to be fully elucidated but appear to involve alterations in glycogen synthase kinase 3 signalling, G2 cell cycle progression arrest, alterations in inositol and prostaglandin signalling pathways, and dysregulated trafficking and transcription of aquaporin 2 water channels. The end result of this is a

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tubulointerstitial nephropathy with microcyst formation and relative glomerular sparing, both visible on pathology specimens and increasingly noted on non-invasive imaging. This paper will elucidate on the current evidence pertaining to the pathophysiology of lithium induced nephrotoxicity.

KEYWORDS

Chronic kidney disease, fibrosis, lithium, nephrotoxicity, pathophysiology.

INTRODUCTION

Lithium remains the most efficacious therapy for a significant proportion of patients with type 1 bipolar disorder (1, 2). Despite this therapeutic advantages, the use of lithium has been decreasing at least in part because of the perceived risks surrounding its use including the potential for nephrotoxicity with long term use (3). The ability of lithium to cause chronic kidney disease (CKD) or end stage kidney disease (ESKD) is a vexing issue, with contradictory findings reported in the literature. Lithium appears to have the ability to cause at least stage 3 CKD, with a number of studies noting a higher incidence of CKD in those exposed to lithium (4, 5). However, not all papers have replicated this finding, with a recent population based cohort study suggesting that after adjustments for cofounders including sex, age, and baseline eGFR there was no significant difference in the rate of eGFR decline between those on lithium and a comparator group (6). The question of lithium's propensity to cause ESKD is also difficult to answer. The incidence of ESKD attributed to lithium appears to be very low, with ANZDATA from 2000 suggesting that 0.2 to 0.7% of all new ESKD cases for that year were due to lithium as well as a significant lag time of up to 27 years for development (7, 8). The incidence of ESKD may also be decreasing with the use of modern lower serum levels, which may in part account for some of the discrepancies in studies which have used ESKD as an outcome measure (9). Understanding the pathophysiology behind the development of CKD in the form of a progressive tubulointerstitial fibrosis as seen on renal biopsy has been challenging. This paper aims to review and update the pathophysiology of lithium induced nephropathy.

METHODS

A search strategy for this review was developed to identify appropriate studies, sourced from the electronic databases EMBASE, PubMed (NLM) and MEDLINE. All relevant articles published between 1977 and January 2018 were included for analysis. Duplicate studies were removed. The reference lists of articles were examined for additional studies which met the inclusion criteria. Search terms included lithium with the AND operator to combine with nephrotoxicity or nephropathy or chronic kidney disease or nephrogenic diabetes insipidus or renal and pathophysiology.

LITHIUM INDUCED NEPHROPATHY: BIOPSY FINDINGS

The initial biopsy reports pertaining to the potential for lithium induced nephropathy were published in the 1970s. The seminal paper looked at 14 patients managed on chronic lithium and noted focal interstitial fibrosis, tubular atrophy and dilatation of the distal portions of the nephron, with structural lesions being most pronounced in the collecting ducts and distal tubules (10), as well as a multitude of mostly cortical based cysts on gross pathology specimens. Since these initial reports, there have been other studies on histopathological specimens which have looked to clarify the pathology of lithium induced nephropathy. Lithium induced chronic tubulointerstitial nephritis is characterised by tubular atrophy and interstitial fibrosis, with these findings being out of proportion to the extent of vascular or glomerular involvement (11). There is also the striking presence of cortical and medullary microcysts and tubular dilatation, with tubular cystic disease noted in up to 40% of biopsy

specimens. These cystic changes are felt to be relatively specific for lithium induced nephropathy. Whilst other studies have noted similar nonspecific tubulointerstitial changes in patients with affective disorders who have never been treated with lithium, the presence of distal tubular cystic changes appears to separate the two (12). Complicating issues, other agents used in mood disorders such as antipsychotics may also be associated with renal dysfunction, although the data is far more tentative (13). There are no specific findings on immunofluorescence staining, whilst electron microscopy may show variable foot process effacement within the glomeruli (14). Lithium may also have the potential to be directly toxic to podocytes. Both minimal change disease (MCD), which resolves with withdrawal of lithium therapy (15), and focal segmental glomerulosclerosis (FSGS) have been described in those taking lithium. Interestingly, there is a high incidence (37.5%) of greater than 50% foot process effacement on biopsy specimens, suggesting the potential for a primary FSGS process (12).

LITHIUM INDUCED NEPHROPATHY / NEPHROGENIC DIABETUS INSIPIDUS: PATHOPHYSIOLOGY

Lithium is freely filtered across the glomeruli and more than 80% is then reabsorbed within the proximal tubules (16) by the same channel by which the majority of luminal sodium uptake is mediated, the sodium/hydrogen exchanger (NHE3) (17). However, it is at the distal tubules and collecting ducts where lithium appears to exert the majority of its detrimental effects. Within the collecting ducts, lithium is taken up by principal cells through the epithelial sodium channel (ENaC) situated on the apical membrane which have a much greater affinity for lithium when compared to that of sodium (18, 19). Lithium then accumulates within principal cells due to the much lower affinity for the basolateral sodium

efflux pump (the sodium / potassium adenosine triphosphate (ATPase) for lithium when compared to sodium (20). This increased concentration then likely leads to interference with a multitude of downstream signalling pathways which may account for the toxicity seen with chronic lithium exposure.

In terms of nephrogenic diabetes insipidus, such increased concentrations of lithium, possibly through interactions of the inositol and protein kinase C pathways (21) lead to a reduction in cyclic adenosine monophosphate (cAMP) by inhibiting its formation, which subsequently leads to impaired phosphorylation of protein kinase A (PKA). The reduction in phosphorylated PKA causes less phosphorylation of aquaporin 2 (AQP2), the major water channel within the collecting ducts for the reabsorption of water to allow for concentration of urine, by inhibiting its trafficking to the apical membrane (22, 23). AQP2 may also be phosphorylated via mitogen activated protein kinase (MAPK) and perhaps via p38 mediated changes in phosphorylation and ubiquination in order to drive its removal from the apical membrane (24). There additionally appears to be a reduction in the transcription of the gene for AQP2, further inhibiting the uptake of free water by the collecting ducts (25). There are other methods by which lithium is postulated to cause polyuria. In addition to downregulation of AQP2, there is decreased expression of the urea transporters (UT) UT-A1, UT-A3 (22, 26) and UT-B (27, 28) through inhibition of anti-diuretic hormone (ADH) induced phosphorylation of these urea transporters, a process mediated by cAMP (25). Inhibition of glycogen synthase kinase 3 (GSK3), felt to be a central component in the development of lithium induced nephropathy, may also play a role in the development of NDI.

The osmosensitive transcription factor nuclear factor of activated T cells 5 (NFAT5) is a downstream target of GSK3 and regulates the expression of both UT-A1 and potentially AQP2 (29). There also appears to be dysregulation of components of the cyclooxygenase

(COX) and prostaglandin pathways. Prostaglandin E2 (PGE2) production is enhanced in lithium induced NDI due an increase in COX2 activity within medullary interstitial cells (25, 30). Under normal circumstances, PGE2 has an inhibitory effect on ADH through its action on the prostaglandin EP3 receptor which leads to decreased cAMP levels (31) and subsequent PGE2 mediated lysosomal degradation of AQP2 (25). The increase in local PGE2 and COX2 production has been attributed to the inhibition of GSK3 (32). In contract to this effect of GSK3 on COX2 expression, lithium does not appear to change COX1 expression (possibly upregulating it according to some studies (33, 34)) suggesting that COX2 is the primary source of increased PGE2 production (35). Lithium also appears to reduce levels of medullary organic osmolytes including inositol, taurine, betaine and sorbitol which may reduce the medullary osmotic gradient and be yet another mechanism by which lithium impairs the kidneys concentrating ability (36).

In contrast, less is known about how lithium induces chronic tubulointerstitial fibrosis. The development of interstitial fibrosis is also thought to revolve around increased concentrations of lithium within the principal cell. Such increased levels of lithium have been postulated to lead to the inhibition of GSK3, a protein kinase involved in cell differentiation, cell cycle progression and normal epithelial function and survival (17, 37). The inhibition of GSK3 has long been thought a key pathway for the action of lithium in bipolar disorder within the central nervous system (38, 39). Within the kidney GSK3 inhibition appears to be restricted to cells within the distal nephron, consistent with the idea that lithium must be present in a sufficient concentration as can occur with its accumulation within principal cells, in order to induce GSK3 suppression (40). Under normal conditions GSK3 is constitutively active within cells and its lithium induced phosphorylation leads to its suppression and subsequent perturbation of multiple downstream signalling pathways (29) involved in cell cycle progression. GSK3 inhibition leads to the eventual increased nuclear expression of c-Myc,

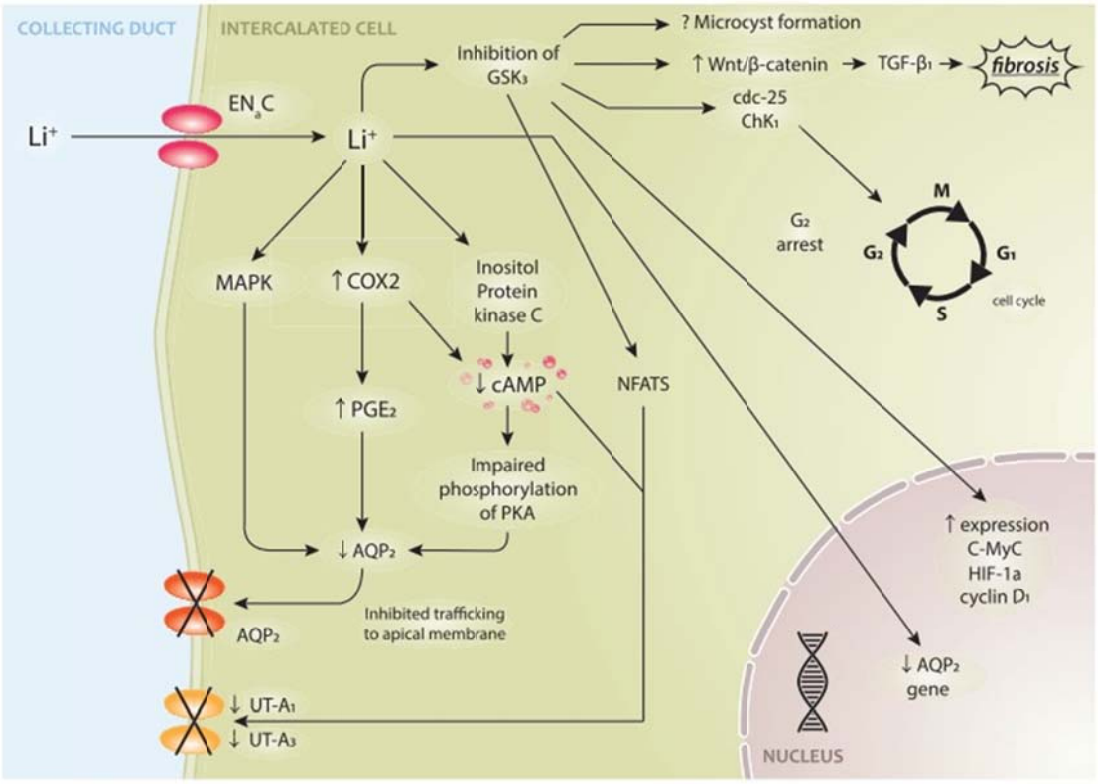
cyclin D1 and hypoxia-inducible factor 1a (HIF-1a), proteins involved in the regulation of cell cycle progression (41). Other cell cycle regulatory processes that may be affected include the overexpression of β-catenin, a component of the Wnt/β-catenin signalling pathway (26). Interestingly, amiloride, used in the treatment of NDI, was recently shown to limit the further progression of fibrosis in a rodent model, a process thought to be mediated by a reduction in ENaC lithium uptake and subsequent effects on GSK3 (18). Lithium is known to induce the proliferation of principal cells, consistent with its effects on proteins involved in cell cycle progression, but interestingly this proliferation of principal cells eventually leads to a change in the cellular organisation of the collecting ducts with a decrease in the ratio of principal to intercalated cells though a decreased number of principal cells (7, 32, 42). The prevailing theory is that lithium, possibly through effects of a cell division cycle 25 (cdc25)-checkpoint kinase 1 (Chk1) mediated pathway, leads to a G2 arrest of principal cells, explaining why their initial proliferation is subsequently followed by a decreased number of principal cells (20, 43).

Microcysts, characteristic of lithium induced nephropathy, have also been shown to be GSK3 positive (33). It is not known if this G2 arrest of principal cells directly leads toward microcyst formation, but it is certainly suggestive given the presence of not only phosphorylated GSK3, but that microcysts in human biopsy specimens have been shown to be AQP2 positive, suggesting that the collecting ducts can be the origin of these microcysts (40). GSK3, in conjunction with the von Hippel-Lindau tumour suppression protein, has also been shown to regulate the microtubules which are involved in the maintenance of cilium within the collecting tubules (7). In other cystic renal diseases cilia dysfunction has been suggested to be involved in cystogenesis although this mechanism of cyst formation has not been definitely proven in lithium induced nephropathy. Microcyst formation appears to precede the subsequent rise in serum creatinine, and microcysts appear to occur in the

majority of patients with lithium induced nephropathy (44). Lithium induced GSK3 inhibition may also be important in the increase in profibrotic factors. GSK3 has previously been shown to phosphorylate β-catenin, a transcription factor involved in epithelial to mesenchymal transition, which has been proposed to be important in fibrogenesis (18). Fibrosis within the kidney is characterised by the development of myofibroblasts from fibroblasts, the deposition of collagens I, III, and fibronectin, inflammatory cell infiltration and podocyte depletion (45).

Transforming growth factor beta 1 (TGF-β1), which has previously been implicated in the development of pro-fibrotic processes, has been shown to be increased in chronic lithium use (46). The prolonged G2 cycle arrest may be one of the driving mechanisms behind the upregulation of TGF-β1, as G2 arrested cells can activate c-Jun NH2 terminal signalling to stimulate the production of profibrotic cytokines such as TGF-β1 (20). Other groups have proposed that lithium may damage both the endoplasmic reticulum and mitochondria of cells, causing an increase in oxidative stress and subsequent tubulointerstitial nephropathy (47, 48) and implicating ischemia in the development of this process (49), although interestingly this theory is not supported by other models which suggest that mitochondrial dysfunction may be involved in the pathogenesis of bipolar disorder itself and that therapy with lithium may improve mitochondrial energy production through stabilisation of its respiratory chain (50). The end result of the fibrotic processes described is a chronic interstitial fibrosis with proximal tubular atrophy, with cystic disease caused by dilated distal tubules and collecting ducts with likely secondary glomerulosclerosis (17, 51). In keeping with this hypothesis, proteinuria, often a central pathogenic process in primary glomerular diseases, is a late event in lithium induced nephropathy and only occurs once extensive tubulointerstitial damage and subsequent glomerular disease begins to develop (52).

FIGURE 1: The effects of lithium on the kidney.



Lithium exerts its deleterious effects on the kidney in a multitude of ways. Through interactions with MAPK, inositol protein kinase C, COX2 and by a direct suppressive effect on the expression of the AQP2 gene lithium decreases the ability of AQP2 to be trafficked and inserted into the apical membrane resulting in a decreased concentrating ability and diabetes insipidus, a process also contributed to by GSK3 and cAMP mediated reduction in the urea transporters UT-A1/3. Whilst these effects appear to be responsible for the ability of lithium to induce diabetes insipidus, it is the inhibition of GSK3 that appears to be the linchpin for the development of chronic lithium nephropathy. Inhibition of GSK3 leads initially an increase in intercalated cells through upregulation of cell cycle related proteins such as C-MyC, cdc-25 and ChK1, but then ultimately to a subsequent G2 cycle arrest with a reduction in the number of intercalated cells. GSK3 inhibition may induce the formation of

microcysts, and ultimately lead to fibrosis and chronic tubulointerstitial changes through the upregulation of TGF-1β.

OTHER RENAL EFFECTS OF LITHIUM

Whilst lithium may cause progressive CKD through a tubulointerstitial nephropathy, it may also have a potential, albeit lesser, ability to cause direct toxicity to podocytes. This was initially suggested by the finding of FSGS in biopsy specimens with > 50% foot process effacement, which is uncommon in secondary FSGS purely mediated by hyperfiltration injury (12), and is further implicated by the rare development of lithium induced MCD. The aetiologic process of lithium related to MCD is suggested by the reversal (in the majority of cases) of the nephrotic syndrome with the cessation of lithium (15). The development of the nephrotic syndrome is typically observed within the first few years of lithium therapy, but may be seen as late as 20 years of treatment (53). The pathophysiology behind this process is incompletely understood, but may involve the potential of lithium as a cationic ion to disrupt the anionic glycosaminoglycans present within podocyte foot processes (15), or by the upregulation of T-cell specific cytokines such as interleukin 1 (IL-1) through lithium's ability to interfere with the phosphoinositol pathway, needed for appropriate T-cell responses (15, 53).

Recently, there have been some studies which suggest that lithium may increase the risk for renal cancers. One paper suggested that the rates of both malignant tumours such as renal cell carcinoma, and benign tumours such as oncocytoma were significantly higher in lithium

treated patients when matched against others with similar age, estimated glomerular filtration rate (eGFR) and sex (54). Another group noted that there was an increased rate of tumours related to cells of the collecting duct in a small sample of lithium treated patients (55). One potential mechanism for this link was suggested to be lithium's ability to interfere with GSK3 (56). The validity of the proposed findings have been questioned, with a nationwide study with more robust power and methodology finding no association between the use of lithium and the rate of renal or other cancers, with the somewhat surprising finding that lithium may even decrease the risk of development of upper respiratory tract cancers (1, 56, 57).

The short term use of lithium may have potential renoprotective effects. In experimental models of acute kidney injury (AKI) induced by various mechanisms, including cisplatin, ischemia-reperfusion and endotoxin, the use of a single dose of lithium after the administration of the initial nephrotoxic insult improved renal function, accelerated the rate at which this occurred, and attenuated tubular damage (58-60). This protective effect of lithium has been attributed to its ability to promote tubular cell proliferation and repair, leading to a more rapid repopulation of tubular cells and thus attenuated response to injury (17). The proposed mechanism again centres around the inhibition of GSK3 by lithium and its subsequent upregulation of proliferative downstream processes, including HIF-1a, c-Myc and cyclin D1 (41).

Table 1: Major intracellular targets of lithium and their effects

CONCLUSIONS

Whilst lithium remains the most efficacious therapy for bipolar disorder there are some significant toxicities which may be associated with its long-term use. The pathophysiology of this process, which appears to centralise around its accumulation within principal cells and subsequent perturbation of multiple cell cycle signalling processes, remains incompletely understood. Nonetheless, such molecular processes are beginning to come to light with the potential to help guide clinical practice in the future.

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Table 1: Major intracellular targets of lithium and their effects

TARGET	EFFECT	DOWNSTREAM EVENTS	DISEASE
INOSITOL / PROTEIN KINASE C	Reduced cAMP	Impaired phosphorylation of protein kinase A Inhibited trafficking of AQP2	NDI
MAPK / P38	Impaired phosphorylation of AQP2	Removal of AQP2 from apical membrane	NDI
CYCLIC AMP	Reduced ADH mediated phosphorylation of urea transporters	Decreased UT-A1, UT-A3, UT-B	NDI
COX2	Increased production of PGE2	Decreased cAMP Increased lysosomal degradation of AQP2	NDI
GSK3	Increased nuclear expression of c-Myc, cyclin D1, HIF-1a Overexpression of β-catenin	Proliferation of intercalated cells Induction of TGF-β1, eventual fibrosis Microtubule regulation in	Nephropathy

	Interaction with VHL	cilia, perhaps microcyst formation	Nephropathy
	Interaction with NFAT5	Regulation of UT-A1, perhaps AQP2 expression	Nephropathy
			NDI
CDC-25 / CHK1	G2 arrest of cell cycle	Initial proliferation of intercalated cells followed by decreased numbers	Nephropathy

ABBREVIATIONS

AKI (acute kidney injury); ATP (adenosine triphosphate); AQP2 (aquaporin 2); cAMP (cyclic adenosine monophosphate); cdc25 (cell division cycle 25); Chk1 (checkpoint kinase 1); CKD (chronic kidney disease); COX (cyclooxygenase); eGFR (estimated glomerular filtration rate); ENaC (epithelial sodium channel); FSGS (focal segmental glomerulosclerosis); ESKD (end stage kidney disease); GSK3 (glycogen synthase kinase 3); HIF-1a (hypoxia inducible factor-1a); IL-1 (interleukin-1); MAPK (mitogen activated protein kinase); MCD (minimal change disease); NDI (nephrogenic diabetes insipidus); NFAT5 (nuclear factor of activated T cells 5); NHE3 (sodium/hydrogen exchanger); PGE2 (prostaglandin E2); PKA (protein kinase A); TGF-1β (transforming growth factor 1β); UT (urea transporter).