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Glycogen synthase kinase-3 regulation of urinary concentrating ability

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Abstract

Purpose of review—Glycogen synthase kinase-3 (GSK3) is an enzyme that is gaining prominence as a critical signaling molecule in the epithelial cells of renal tubules. This review will focus on recent findings exploring the role of GSK3 in renal collecting ducts, especially its role in urine concentration involving vasopressin signaling.

Recent findings—Recent studies using inhibition or tissue-specific gene deletion of GSK3 revealed the mechanism by which GSK3 regulates aquaporin 2 water channels via adenylate cyclase or the prostaglandin-E_2 pathway. In other studies, postnatal treatment with lithium, an inhibitor of GSK3, increased cell proliferation and led to microcyst formation in rat kidneys. These studies suggest that loss of GSK3 activity could interfere with renal water transport at two levels. In the short term, it could disrupt vasopressin signaling in collecting duct cells and in the long term it could alter the structure of the collecting ducts, making them less responsive to the hydro-osmotic effects of vasopressin.

Summary—Ongoing studies reveal the crucial role played by GSK3 in the regulation of vasopressin action in the renal collecting ducts and suggest a possible use of GSK3 inhibitors in disease conditions associated with disrupted vasopressin signaling.

Keywords

aquaporin 2; cyclooxygenase; glycogen synthase kinase-3; nephrogenic diabetes insipidus; prostaglandin; vasopressin

Introduction

Glycogen synthase kinase-3 (GSK3) is a serine/ threonine protein kinase that was discovered in 1980 by Sir Dr Phillip Cohen and named for its ability to phosphorylate and inhibit glycogen synthase, a key regulator of glycogen synthesis [1]. However, studies since then have identified GSK3 as a critical enzyme which coordinates multiple signaling pathways that regulate cellular processes including gene transcription, cytoskeletal organization, cell cycle progression, cell differentiation and normal epithelial function and survival [2,3]. Hence, GSK3 is currently considered a key target for drug discovery in Alzheimer's disease, cancer and diabetes [4▪,5▪,6]. GSK3 is highly conserved throughout evolution in eukaryotes [7] and exists in two isoforms, GSK3α and GSK3β, encoded by distinct genes located on separate chromosomes [8▪]. Since the α and β isoforms share 98%

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sequence homology in their kinase domains [9], no truly isoform-specific inhibitors have been developed yet [8▪,10]. GSK3 is active under resting/unstimulated conditions and is inhibited by rapid and reversible phosphorylation of serine 9 of GSK3β and serine 21 of GSK3α [11–13]. GSK3 is also regulated by protein–protein interaction and intracellular sequestration [14].

There is increasing evidence that GSK3 plays an important role in renal water transport. New evidence emerging from studies using tissue-specific gene knockout or inhibitors of GSK3 in rodent models and cell culture systems suggests that this kinase could play a crucial role in vasopressin-mediated urine concentration by the renal collecting ducts. This review will highlight recent studies that explore two key factors that regulate the collecting duct's response to vasopressin: firstly, the role of GSK3 in prostaglandin (PGE) and adenylate cyclase-mediated effects on aquaporin 2 (AQP2), and secondly, its role in maintenance of epithelial morphology of the renal collecting duct.

Glycogen Synthase Kinase-3 in The Kidneys

Glycogen synthase kinase-3 isoforms are ubiquitously expressed in the body. However, most studies have focused on GSK3β, since global knockout of GSK3β is lethal whereas GSK3α knockout mice survive [15,16]. Both GSK3α and GSK3β are expressed in the kidneys [17], and GSK3β expression can be detected in renal collecting ducts (principal cells as well as intercalated cells) in mice [18], rats and humans [19▪▪]. During postnatal development, GSK3β protein abundance decreases in the renal cortex with time, whereas in the medulla it remains unchanged [19▪▪]. No published reports exist regarding the expression of GSK3α in the kidneys. On the basis of discoveries on the functional role of renal GSK3β as a pro-apoptotic and antiproliferative signaling factor, studies have found that GSK3 inhibition could be protective in acute kidney injury [20–22]. Whereas inhibition of GSK3 could be beneficial in this regard, recent studies also suggest that GSK3 is important for the maintenance of water homeostasis by the kidneys.

Glycogen Synthase Kinase-3 in Water Transport: Role in Vasopressin Signaling

Regulation of water balance by the kidney is one of its fundamental homeostatic functions and is tightly controlled by vasopressin. In response to an antidiuretic stimulus, the pituitary gland secretes vasopressin, which binds to its type 2 receptor (V2R) in renal collecting ducts, activating adenylate cyclase and increasing intracellular cyclic adenosine monophosphate (cAMP) levels. cAMP activates protein kinase A or exchange protein directly activated by cAMP (EPAC), which in turn potentiates transcription [23–25], as well as trafficking to the apical plasma membrane [26] of the AQP2 water channels. Following an osmotic gradient, water enters the principal cells through AQP2 and exits through the AQP3 or AQP4 water channels on the basolateral membrane, resulting in the formation of concentrated urine.

Studies over the past 6 years have explored the role of GSK3 in the maintenance of water homeostasis by the kidneys [18,19▪▪,27,28▪▪,29,30]. Initial speculations on a possible role of GSK3 in renal water transport were based on the observation that lithium (Li^+), which is commonly used for treatment of bipolar disorders, inhibits GSK3 in the clinical therapeutic range and can cause renal toxicity [31]. Li^+ has been used therapeutically for more than 150 years and remains an important treatment for bipolar disorders [32,33]. Patients on long-term Li^+ treatment often have an irreversible and clinically important reduction in maximal urinary concentrating ability, which may lead to nephrogenic diabetes insipidus (NDI), with detectable impairment in renal concentrating ability reported in up to 40% patients [34].

This important renal side effect of Li^+ therapy was known long before the discovery of GSK3.

Lithium is a reversible inhibitor of GSK3 with an IC_{50} value of approximately 1mM [35], acting as a direct competitive inhibitor of Mg^{2+}[36] or indirectly by increasing the inhibitory phosphorylation of GSK3α and GSK3β [13,37]. In the kidney, Li^+ inhibits GSK3β, as demonstrated by a decrease in renal GSK3β kinase activity [18], as well as an increase in serine-9 phosphorylated GSK3β in mice and cultured renal cells [18,19▪▪,27,28▪▪,29,30,38]. Li^+-induced reduction in urinary concentrating capacity and polyuria can be detected as early as 8 weeks in humans [39] and within 5–7 days in rodents [29,30,40,41]. It is accompanied by a drastic down-regulation of AQP2 expression along the entire collecting duct [42–44]. In LiCl-treated mice, the time course of GSK3 inhibition coincides with decreases in AQP2 expression [29], as well as increases in polyuria [29,30], suggesting that loss of GSK3 activity could be a crucial factor in the impaired urine-concentrating ability in these mice. Though Li^+ is a highly specific inhibitor of GSK3, it is not selective and is known to activate multiple pathways including protein kinase B/phosphoinositide 3-kinase, protein phosphate 2A as well as mitogen-activated protein kinases [29,35]. Nevertheless, studies in cultured renal cortical collecting duct cells have demonstrated that LiCl or GSK3-selective small molecule inhibitors could reduce AQP2 expression induced by desmopressin (dDAVP), a synthetic analog of vasopressin [27]. Hence, many of the effects of Li^+ treatment could overlap with those expected from GSK3 inhibition.

Further evidence for a direct role of GSK3β in urine concentration was provided by studies with renal collecting duct-specific GSK3β knockout mice [18]. These mice were not overtly polyuric under basal conditions. However, their ability to concentrate urine in response to water deprivation or dDAVP treatment was diminished, accompanied by significant reduction in AQP2 mRNA, protein levels as well as its trafficking to the apical membrane [18]. This suggests that GSK3β gene deletion reduces the collecting duct's response to the hydro-osmotic effects of vasopressin.

In humans, Li^+-induced polyuria is not sensitive to vasopressin, whereas in rats, polyuria and down-regulation of AQP2 expression can be partially reversed by water deprivation, dDAVP treatment or by stopping LiCl treatment [44]. Evidence obtained from cell culture studies and rodent models suggests that GSK3 could affect vasopressin signaling, indirectly via the cyclooxygenase (COX) pathway, or directly at the level of adenylate cyclase activity.

Glycogen Synthase Kinase-3 and The Cyclooxygenase– Prostaglandin Pathway

Cyclooxygenases are rate-limiting enzymes in the production of PGEs, a group of fatty acid derivatives of which PGE_1 and PGE_2 are known to reduce vasopressin-stimulated water reabsorption in renal collecting ducts [45–47]. COX1, the constitutively expressed isoform, is particularly abundant in collecting ducts [48,49], whereas COX2, the inducible isoform, is restricted to the macula-densa and renal medullary interstitial cells (RMICs) [50,51].

COX2 is negatively regulated by GSK3. In cultured RMICs, treatment with GSK3-selective small molecule inhibitors like SB216763 or LiCl increased COX2 expression [38]. Similarly in LiCl-treated mice, inhibition of renal GSK3 is associated with an increase in COX2 and urinary PGE_2, as well as an onset of NDI within 3–5 days of treatment [30]. Administration of a COX2 inhibitor to LICl-treated mice reduced PGE_2 levels as well as NDI [30]. Any contribution of renal COX1 to the increased PGE_2 in LiCl-treated mice could be ruled out since COX1 levels did not change in these mice and LiCl treatment caused polyuria in COX1 knockout mice. Furthermore, LiCl treatment for 5 days was seen to increase COX2 in

vasopressin-deficient Brattleboro rats, suggesting that the increase in COX2 was independent of vasopressin [30]. These studies suggest that Li^+ inhibits GSK3 leading to up-regulation of COX2 and PGE_2 in RMICs. The increased PGE_2 produced could act in a paracrine manner on the adjoining collecting duct cells, antagonizing vasopressin-mediated cAMP generation, thus leading to polyuria (Fig. 1).

In a recent study, Kortenoeven et al. [28▪▪] investigated this hypothesis further using a mouse cortical collecting duct cell line (mpkCCD), in which LiCl treatment was demonstrated to inhibit GSK3, increase COX2 abundance and decrease AQP2 expression. Inhibition of COX2 alone or COX1 and COX2 in these cells increased AQP2 abundance. This study supports the observation in mice that GSK3 could regulate urine concentration via the COX pathway. Interestingly, Li^+ did not significantly increase PGE_2 production in mpkCCD cells or increase levels of the PGE receptors (EP1 and EP3) known to antagonize vasopressin action in collecting ducts [28▪▪]. However, addition of PGE_2 to the medium reduced AQP2 abundance mainly by mediating AQP2 protein degradation [28▪▪]. The authors suggested that LiCl treatment reduces AQP2 expression by two mechanisms: by up-regulation of the COX2–PGE_2 pathway, which leads to degradation of AQP2, which supports the hypothesis of Li^+-induced up-regulation of COX2 in the RMICs [38] that naturally express this protein and the possible paracrine action of PGE_2 on the collecting duct in the kidney [30], or by reducing AQP2 gene transcription in a PGE-independent fashion. This could be via inhibition of adenylate cyclase activity as described in the next section.

In a contrasting study, chronic treatment with LiCl for 4 weeks induced NDI in rats, but was accompanied by reduced COX1 and COX2 in the inner medulla [52]. Whereas GSK3 activity was not examined in these rats, these differences in COX expression could possibly be attributed to the different rodent models (rats vs. mice) and more importantly to the difference in length of LiCl treatment.

Glycogen Synthase Kinase-3 and Adenylate Cyclase Activity

Adenylate cyclase is a critical component of vasopressin signaling. Previous studies carried out in isolated collecting ducts or kidneys from LiCl-treated rats attributed the decrease in AQP2 expression to reduced vasopressin-dependent adenylate cyclase activity and cAMP generation [53–57]. However, in a contrasting study, Li^+ did not affect vasopressin-induced cAMP generation in dDAVP-treated mpkCCD cells or Brattleboro rats, though Li^+ reduced dDAVP-induced cAMP in normal rats [58].

A direct evidence for a role of GSK3β in the regulation of adenylate cyclase activity was provided by studies with renal collecting duct-specific GSK3β knockout mice [18]. The maximal urinary concentrating ability in these mice in response to water deprivation or dDAVP treatment was significantly compromised when compared to wild-type mice. Consistent with this, total AQP2 mRNA and protein levels, as well as its apical membrane localization, were reduced in the knockout mice. Furthermore, adenylate cyclase activity as well as intracellular cAMP levels in the renal papilla of the knockout mice was reduced in response to dDAVP or forskolin (a ligand of adenylate cyclase). This was the first demonstration that GSK3β regulates adenylate cyclase activity, and that its inactivation leads to reduced cAMP, AQP2 abundance and trafficking, and reduced responsiveness to the antidiuretic actions of vasopressin [18].

Glycogen Synthase Kinase-3 and Collecting Duct Morphology

Glycogen synthase kinase-3 isoforms play a pivotal role in cell cycle progression in embryonic stem cells and other cultured cell types, with GSK3 inhibition being pro-

proliferation and anti-differentiation (reviewed by Force and Woodgett [3,59]). The relative importance of GSK3α and GSK3β in proliferation is not clear. Targeted global knockout of GSK3β in mice resulted in hyperproliferation of cardiomyocytes during embryonic development, partly due to the failure of the cardiomyocytes to adequately differentiate [16]. Mice with global knockout of GSK3α appeared to be normal in this respect [17].

Though a direct link between GSK3 and renal cell proliferation has not been established, studies based on LiCl treatment suggest that inhibition of GSK3 in the renal collecting duct could increase cell proliferation, possibly cause de-differentiation and hence reduce the principal cell's response to vasopressin. In a recent rat study, dams with litters were fed LiCl on postnatal days 7–28 [19▪▪]. The kidneys from LiCl-treated pups developed microcysts and showed an increased rate of tubular cell proliferation. Similar microcysts were observed in the cortical tubules of kidneys from long-term Li^+-treated human patients. The authors attributed the high rate of collecting duct cell proliferation to GSK3β inhibition. Though a direct link between GSK3β inhibition and increased cell proliferation was not demonstrated, the presence of high levels of the inhibited, phosphorylated GSK3β in the epithelia lining the microcysts suggest that inhibition of GSK3β could have contributed to the increased rate of proliferation. Past studies have demonstrated that short-term (3–10 days) or chronic (4 weeks) treatment with LiCl in rats can lead to an increased rate of proliferation, as well as a change in the fraction of intercalated compared to principal cells of the collecting duct [41,42]. Proteomic analysis of renal collecting ducts from LiCl-treated rats demonstrated inhibition of GSK3β as well as increases in several pro-proliferative signaling factors and pathways [29]. It could be hypothesized that GSK3 activity is essential for collecting duct cells to be maintained in their differentiated form and that GSK3 inactivity could lead to proliferation and de-differentiation and hence less AQP2 expression.

Conclusion

Studies so far suggest that GSK3β could play an important role in urine concentration by renal collecting ducts. In contrast, the role of GSK3α in the kidney and especially in renal water transport has not been explored. It is difficult to examine the role of GSK3 in the renal collecting ducts using LiCl in animals, since the effects of Li^+ are systemic rather than tissue-specific, and over time Li^+ accumulates in the tubules leading to secondary and tertiary effects, which might involve multiple signaling pathways. Furthermore, prolonged treatment with Li^+ is known to cause natriuresis and metabolic acidosis, though the connection with GSK3 is not clear in this respect. A better understanding of the role of GSK3 in the renal response to vasopressin could provide a scientific basis for the possible use of GSK3 inhibitors for the treatment of diseases associated with dysregulated vasopressin signaling like congestive heart failure, cirrhosis or polycystic kidney disease.

Acknowledgments

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 564).

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KEY POINTS

- Glycogen synthase kinase-3 (GSK3) inhibition by LiCl increases cyclooxygenase 2 expression and reduces aquaporin 2 AQP2 expression.
- GSK3 gene knockout in the collecting ducts disrupts the collecting duct's response to vasopressin by reducing adenylate cyclase activity, cAMP generation and reduced AQP2 expression and trafficking.
- GSK3 inhibition by chronic LiCl treatment could lead to hyperproliferation of collecting duct epithelial cells.

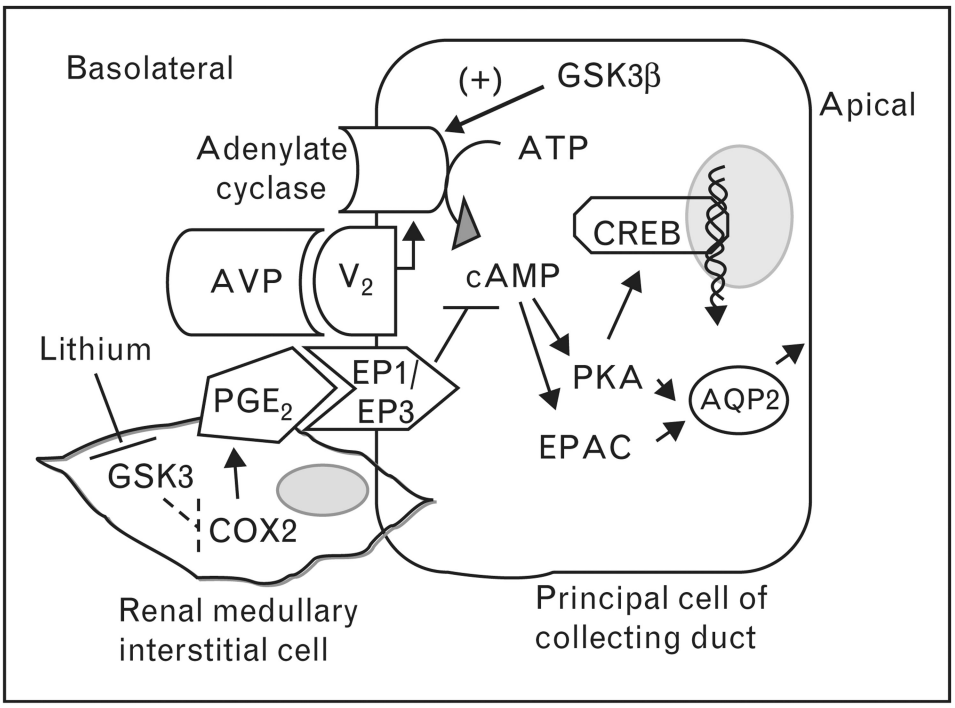

Figure 1.

GSK3-mediated regulation of vasopressin signaling in the collecting duct: inhibition of GSK3 by Li^+ increases COX2 expression and PGE_2 production in the renal medullary interstitial cells. PGE_2 binds to EP1/EP3 receptors, antagonizing the AVP (vasopressin)-mediated cAMP generation. GSK3 also positively regulates adenylate cyclase activity, cAMP generation and AQP2 expression and trafficking in response to AVP. COX, cyclooxygenase; GSK3, glycogen synthase kinase-3; PGE, prostaglandin.