Review

Two Liters a Day Keep the Doctor Away? Considerations on the Pathophysiology of Suboptimal Fluid Intake in the Common Population

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Copeptin • Glucocorticoids • Vasopressin • Metabolic syndrome • Cancer • Chronic kidney disease

Abstract

Suboptimal fluid intake may require enhanced release of antidiuretic hormone (ADH) or vasopressin for the maintenance of adequate hydration. Enhanced copeptin levels (reflecting enhanced vasopressin levels) in 25% of the common population are associated with enhanced risk of metabolic syndrome with abdominal obesity, type 2 diabetes, hypertension, coronary artery disease, heart failure, vascular dementia, cognitive impairment, microalbuminuria, chronic kidney disease, inflammatory bowel disease, cancer, and premature mortality. Vasopressin stimulates the release of glucocorticoids which in turn up-regulate the serum- and glucocorticoid-inducible kinase 1 (SGK1). Moreover, dehydration upregulates the transcription factor NFAT5, which in turn stimulates SGK1 expression. SGK1 is activated by insulin, growth factors and oxidative stress via phosphatidylinositol-3-kinase, 3-phosphoinositide-dependent kinase PDK1 and mTOR. SGK1 is a powerful stimulator of Na⁺/K⁺-ATPase, carriers (e.g. the Na⁺,K⁺,2Cl⁻ cotransporter NKCC, the NaCl cotransporter NCC, the Na⁺/H⁺ exchanger NHE3, and the Na⁺ coupled glucose transporter SGLT1), and ion channels (e.g. the epithelial Na⁺ channel ENaC, the Ca²⁺ release activated Ca²⁺ channel Orai1 with its stimulator STIM1, and diverse K⁺ channels). SGK1 further participates in the regulation of the transcription factors nuclear factor kappa-B NFκB, p53, cAMP responsive element binding protein (CREB), activator protein-1, and forkhead transcription factor FKHR-L1 (FOXO3a). Enhanced SGK1 activity fosters the development of hypertension, obesity, diabetes, thrombosis, stroke, inflammation including inflammatory bowel disease and autoimmune disease, cardiac fibrosis, proteinuria, renal failure as well as tumor growth. The present brief review makes the case that suboptimal fluid intake in the common population may enhance vasopressin and glucocorticoid levels thus up-regulating SGK1 expression and favouring the development of SGK1 related pathologies.

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Introduction

Fine tuning of water balance is an obvious prerequisite for maintenance of cell and blood volume constancy [1]. Decrease of cell volume or of atrial distension triggers thirst and release of vasopressin, a hormone rapidly curtailing renal water excretion [1]. Vasopressin further stimulates vascular smooth muscle contraction thus preventing blood pressure drop during volume depletion [2]. Vasopressin usually prevents significant alterations of cell and blood volume at low water intake [1]. Thus, low water intake had not been considered a major health hazard. Recent observations, however, provided evidence that enhanced vasopressin plasma levels are associated with a large number of clinical disorders. Suboptimal fluid intake leading to enhanced vasopressin release may affect a large portion of the common population, as some 9% of the world wide adult population drink less than half and as many as 40% of adults between 50 and 100% of the fluid intake recommended by the European Food Safety Agency [3].

The present brief review discusses the possibility that those clinical disorders could result from a stimulating effect of vasopressin on adrenocorticotrophic hormone with subsequent increase of glucocorticoid release [4, 5] and up-regulation of the serum and glucocorticoid inducible kinase SGK1 [6, 7].

Impact of drinking behaviour on the vasopressin-cortisol-SGK1 axis

Total water intake (sum of water from food moisture and fluids) varies considerably in the common population [8, 9]. The impact of low daily water intake on long term health has, in the past, attracted little attention [10]. A recent study revealed, however, that plasma vasopressin (ADH) levels were significantly enhanced in low drinkers (≤ 1.2 litres/d of total fluid intake, i.e. sum of drinking water and any other fluids) as compared to high drinkers (2–4 litres/d) [8, 11]. Vasopressin is a known powerful stimulator of glucocorticoid release [4, 5] and low drinkers had indeed significantly higher plasma cortisol levels [8]. The pleiotropic effects of glucocorticoids include upregulation of the serum- and glucocorticoid-inducible kinase 1 (SGK1) [6, 7, 12], an ubiquitously expressed kinase up-regulated during dehydration [13, 14]. Moreover, water deprivation may up-regulate the transcription factor NFAT5 [15], which in turn stimulates the expression of SGK1 [16]. Whatever underlying mechanism, severe water deprivation is followed by marked increase of SGK1 expression at least in the brain [13, 14]. To the best of our knowledge, data showing up-regulation of SGK1 expression following suboptimal fluid intake in humans are lacking. It is conceivable, however, that the enhanced vasopressin levels in low drinkers are associated with a subtle but relevant increase of SGK1 expression resulting in the respective influence on SGK1 sensitive functions (Figure 1).

Association of vasopressin (copeptin) levels with risk and outcome of diseases

Increased plasma vasopressin levels are reflected by a similar increase of the surrogate marker copeptin, a protein released in parallel to vasopressin but more stable than vasopressin and thus reflecting the integrated hydration status more reliably [17]. Individuals with copeptin levels in the top 25% of the general population were shown to have markedly increased risk of developing type 2 diabetes independently of known diabetes risk factors [18], a finding subsequently replicated in different populations [19, 20]. Along those lines, genetic variance of the vasopressin receptor AVPR1B is associated with overweight and diabetes [17, 21]. Rats with high vasopressin levels had higher fasting glucose levels than rats with low vasopressin levels [22]. In obese rats, high vasopressin levels lead to hyperinsulinaemia, glucose intolerance, and insulin insensitivity, whereas an arginine vasopressin receptor

Fig. 1. Putative mechanisms linking suboptimal water intake and SGK1 dependent pathophysiology (ADH = antidiuretic hormone = vasopressin; ACTH = adrenocorticotrophic hormone; SGK1 = serum & glucocorticoid inducible kinase 1; CKD = chronic kidney disease; CHD = Chronic heart disease; IBD = inflammatory bowel disease).

1A (V1aR) antagonist reduced glucose intolerance [22]. Obese rats with low vasopressin were protected against liver steatosis, hepatic triacylglycerol and cholesterol accumulation and expression of hepatic lipogenic genes [22]. Elevated copeptin is not only associated with increased risk of type 2 diabetes but with the entire cluster of metabolic syndrome [23, 24] especially with abdominal obesity [23, 25, 26]. Copeptin predicts not only diabetes but its main complications such as coronary artery disease and individuals with high levels of copeptin actually die earlier than people with normal values of copeptin [24, 27].

Interestingly, high copeptin is also associated with a broad range of other diseases such as heart failure [28], vascular dementia [27], cognitive impairment [29], microalbuminuria [25], chronic kidney disease [17, 30], inflammatory bowel disease [31], cancer [32], and premature mortality [24].

SGK1-sensitive cellular functions

SGK1 is a powerful stimulator of Na^+/K^+ -ATPase, of diverse carriers (e.g. $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter NKCC, NaCl cotransporter NCC, Na^+/H^+ exchanger NHE3, and Na^+ coupled glucose transporter SGLT1), and ion channels (e.g. epithelial Na^+ channel ENaC, the Ca^{2+} release activated Ca^{2+} channel Orai1 with its stimulator STIM1, the neuronal kainate receptor, and diverse K^+ channels) [33-35]. SGK1 further participates in the regulation of the transcription factors nuclear factor kappa-B NF κ B, p53, cAMP responsive element binding protein (CREB), activator protein-1 (AP-1), and forkhead transcription factor FKHR-L1 (FOXO3a) [33]. SGK1 participates in the orchestration of a wide variety of complex cellular functions including

organization of the cytoskeleton [36], cell volume regulation [37], cell survival and cell proliferation [7, 38, 39], cell migration [40, 41], degranulation [36, 42], hormone release [37, 43], renal tubular Na^+ reabsorption [37, 43-46], renal tubular K^+ transport [47], gastric acid secretion [7, 37], as well as intestinal Na^+ and nutrient transport [43]. SGK1 may affect neuronal excitability [48], but the potential pathophysiological role of SGK1 in the brain remained hitherto elusive.

Impact of SGK1 on renal transport and hypertension

SGK1 stimulates the $\text{Na}^+, \text{K}^+, 2\text{Cl}^-$ cotransporter NKCC [43], the NaCl cotransporter NCC [7, 37, 45, 49, 50], the Na^+/H^+ exchanger NHE3 [37, 51-55] and the epithelial Na^+ channel ENaC [7] and thus augments renal tubular salt reabsorption [7, 37, 44, 46, 56]. Moreover, SGK1 stimulates salt appetite and thus salt intake [7, 43, 57]. Increased SGK1 activity thus predisposes to extracellular volume expansion and hypertension [50, 56, 58-61]. Along those lines, several SGK1 gene variants are associated with increased blood pressure [60] including combined polymorphisms in intron 6 [I6CC] and exon 8 [E8CC/CT] [37, 43, 62]. The [I6CC/E8CC/CT] gene polymorphism is more common in Africans (10%) than in Caucasians (3-5%) [37, 43]. Blood pressure is normal in gene targeted mice lacking SGK1 (*sgk1*^{-/-}) at regular diet [43], but, in contrast to blood pressure of wild-type littermates, does not increase following induction of hyperinsulinism with high-fructose diet or high-fat diet [43, 63]. Apparently, hyperinsulinism leads to hypertension through SGK1-sensitive mechanisms such as stimulation of renal tubular salt reabsorption [37, 43]. Along those lines, SGK1 contributes to glucocorticoid-induced hypertension [37]. Furthermore, maternal SGK1 may be critically important for fetal programming of hypertension. SGK1 is expressed in the endometrium [64] and maternal SGK1 is required for the hypertension in the offspring following protein restriction during pregnancy [65].

Impact of SGK1 on intestinal transport and obesity

SGK1 stimulates the intestinal Na^+ coupled glucose transporter SGLT1 [37, 66]. Enhanced activity of the carrier fosters the development of obesity, an effect presumably due to acceleration of postprandial increase of plasma glucose concentration, which is followed by excessive insulin release and subsequent fat deposition [37, 43]. SGK1 up-regulates SGLT1 and may thus support the development of obesity [37, 43]. SGK1 further supports adipocyte differentiation and adipogenesis [67]. Along those lines, the I6CC/E8CC/CT SGK1 gene variant is associated with increased body weight and enhanced risk to develop diabetes [37]. In diabetic individuals hyperglycemia may in turn stimulate intestinal SGK1 expression [37, 43] with subsequent up-regulation of intestinal SGLT1 activity thus supporting further weight gain.

SGK1 sensitive Ca^{2+} channel activity and platelet function

By stimulating the transcription factor nuclear factor kappa B (NF κ B), SGK1 up-regulates the expression of the Ca^{2+} channel Orai1 and of its stimulator, the Ca^{2+} sensing protein STIM1, which accomplish the store operated Ca^{2+} entry (SOCE) [7, 37, 68-70]. Upon store depletion SOCE leads to an increase of cytosolic Ca^{2+} concentration, a key event in the stimulation of blood platelets. SGK1-sensitive upregulation of the platelet Ca^{2+} channel Orai1/STIM1 enhances the sensitivity of blood platelets to stimulators leading to enhanced degranulation and aggregation [68]. Moreover, SGK1 stimulates coagulation by stimulating tissue factor expression [37]. Up-regulation of SGK1 thus predisposes to thrombosis [68] and stroke [59, 71].

Role of SGK1 in tumor growth

Strong SGK1 expression was observed in diverse tumors [39] including non-small cell lung cancer [72], colon cancer [39], prostate cancer [73], ovarian tumors [7], myeloma [74], and medulloblastoma [7]. Intriguing evidence suggests that SGK1 may confer survival of tumor cells [7, 43, 75, 76], such as interleukin 6 (IL6)-induced survival of cholangiocarcinoma cells [39, 43], interleukin 2 (IL2)-dependent survival of kidney cancer cells [7], angiotensin II-induced survival of fibrosarcoma-derived cells [77], and androgen receptor-dependent survival of prostate cancer cells [7]. SGK1 silencing overcomes resistance of breast cancer cells to chemotherapy [39, 43, 78], and pharmacological SGK1 inhibition blunts androgen-induced growth of prostate cancer cells [37]. SGK1 further attenuates the proapoptotic effect of membrane androgen receptors (mAR) [7] in colon carcinoma cells [40, 79]. SGK1 knockout counteracts the development of spontaneous tumors in APC deficient mice [37] and chemically induced colonic tumours in wild-type mice [7]. Parallel inhibition of SGK1 may enhance the efficacy of treatment with cytotoxic drugs or radiation [80].

SGK1 influences cell proliferation and cell death by up-regulating channels and transporters, such as the store operated Ca^{2+} entry (SOCE) accomplished by Orai1/STIM1 [7, 68, 69, 80-82]. SOCE maintains oscillations of cytosolic Ca^{2+} activity, which are required for depolymerization of the actin filament network, a prerequisite for cell proliferation [39, 43]. Ca^{2+} entry is driven by the cell membrane potential, which is generated by SGK1 sensitive K^{+} channels [39, 43].

SGK1 is further in part effective by inactivation of the proapoptotic forkhead transcription factor Foxo3a/ FKRHL1 [7], inhibition of glycogen synthase kinase GSK-3 with subsequent up-regulation of oncogenic β -catenin [43, 75], activation of IKK β , with subsequent phosphorylation and degradation of the inhibitory protein I κ B and translocation of NF κ B into the nucleus [39], activation of the ubiquitin ligase MDM2 with subsequent MDM2-dependent ubiquitination and proteosomal degradation of proapoptotic transcription factor p53 [7], interference with SEK1 binding to JNK1 and MEKK1 [39, 43], as well as up-regulation of Ran binding protein (RanBP), which in turn modifies the microtubule network and decreases taxol sensitivity of cancer cells [83].

SGK1 stimulates cellular glucose uptake, a prerequisite of the excessive glycolytic flux due to aerobic glycolysis in tumor cells [43]. SGK1 further stimulates the $\text{Na}^{+}/\text{H}^{+}$ ion exchanger [70], which generates an alkaline cytosolic pH thus enhancing glycolytic flux [7]. SGK1 is up-regulated by ischemia, which renders tumor cells particularly dependent on glycolysis [37, 39, 43, 84].

Low SGK1 abundance has been found in some types of prostate cancer, ovarian tumors, hepatocellular carcinoma and adenomatous polyposis coli (APC) [7, 39, 43]. A positive correlation was observed between SGK1 abundance and patient survival in adrenocortical carcinoma [85, 86]. Possibly, tumor cells with high activity of related kinases such as PKB/ Akt isoforms or SGK3 downregulate SGK1 and do not require SGK1 for growth and survival.

SGK1 sensitive inflammation and fibrosis

SGK1 contributes to the orchestration of inflammation [33] including inflammatory bowel disease [87, 88]. The kinase is required for inactivation of the transcription factor Foxo1, which stimulates expression of the IL23 receptor [89] and is thus required for the stimulating effect of interleukin 23 (IL-23) on the generation of interleukin (IL)-17-producing CD4 $^{+}$ helper T cells (T_{H17} cells) [90]. T_{H17} cells upregulate the pro-inflammatory cytokines GM-CSF, TNF- α and IL-2 and play a pivotal role in autoimmune disease [90]. Up-regulation of SGK1 thus presumably predisposes to a particularly severe form of experimental autoimmune encephalomyelitis with enhanced infiltration of T_{H17} cells into the central nervous system [90].

Table 1. Comparison of clinical conditions correlated with enhanced copeptin levels and the respective disorders shown or expected following SGK1 excess. Among the clinical conditions associated with high copeptin levels only cognitive impairment [27, 29] may be related to mechanisms other than increased SGK1 expression. The other clinical disorders are presumably at least in part due to enhanced SGK1 expression and activity. This does, however, not rule out the involvement of further mechanisms and additional experimental effort is needed to define the pathophysiological role of SGK1 in individuals with suboptimal fluid intake.

Enhanced Copeptin levels are associated with	References	Enhanced SGK1 activity may contribute to	References
Hypertension	[23, 24]	Hypertension	[37, 43, 50, 56, 58-63]
Obesity	[23-26]	Obesity	[37, 43]
Type 2 diabetes	[18-20]	Type 2 diabetes	[37]
Coronary artery disease	[24, 27]	Atherosclerosis, stroke	[59, 68, 71, 107-109]
vascular dementia	[28]	Cardiac remodeling/fibrosis	[7, 103-106, 110]
Heart failure	[25]	Proteinuria	[101, 111]
Microalbuminuria	[17, 30]	Renal fibrosis	[101]
Chronic kidney disease	[31]	Inflammatory bowel disease	[87, 88]
Inflammatory bowel disease	[32]	Cancer	[7, 37, 39, 40, 43, 72-80]
Cancer			

SGK1 further participates in the orchestration of tissue fibrosis. Excessive SGK1 expression was observed in lung fibrosis, diabetic nephropathy, glomerulonephritis, experimental nephrotic syndrome, obstructive nephropathy, liver cirrhosis, fibrosing pancreatitis, peritoneal fibrosis, Crohn's disease and coeliac disease [7, 43, 91, 92]. SGK1 expression is up-regulated by TGF β [43], a key stimulator of fibrosis [88, 93-98]. TGF β is in part effective through transcription factors Smad2/3 [7], which are degraded by the ubiquitin ligase Nedd4L [7]. SGK1 inactivates Nedd4L and thus augments the effects of TGF β [7]. SGK1 activates NF κ B [43], a transcription factor fostering inflammation and fibrosis [7, 99, 100]. NF κ B regulated proteins include connective tissue growth factor (CTGF), which contributes to cardiac fibrosis [43], renal proteinuria and failure [101], as well as skin aging [102] following mineralocorticoid excess. SGK1 is further involved in angiotensin II-induced cardiac CTGF formation and fibrosis [103, 104], in cardiac remodelling following increased afterload [7, 105, 106] and in augmentation of fibronectin formation at excessive extracellular glucose concentrations [7].

Conclusions

Compelling evidence suggests that suboptimal fluid intake is followed by pathophysiologically relevant release of vasopressin, which in turn may foster the development of several clinical disorders including metabolic syndrome, abdominal obesity, type 2 diabetes, hypertension, coronary artery disease, heart failure, vascular dementia, cognitive impairment, microalbuminuria, chronic kidney disease, inflammatory bowel disease, cancer, and premature mortality (table 1). At least in theory, vasopressin could be effective by stimulating the release of adrenocorticotrophic hormone with subsequent glucocorticoid release and enhanced expression of serum and glucocorticoid inducible kinase SGK1. Alternatively, dehydration could stimulate SGK1 through upregulation of the transcription factor NFAT5/TonEBP. Similar to suboptimal water intake SGK1 has been shown to participate in the pathophysiology of hypertension, obesity, diabetes, thrombosis, stroke, cardiac failure, proteinuria, renal failure, inflammatory bowel disease, and tumor growth (table 1). Additional experimental effort is needed to explore whether SGK1 contributes to cognitive impairment during suboptimal water intake, and whether suboptimal water intake is associated with further SGK1 sensitive pathologies such as autoimmune disease, allergy and excessive gastric acid secretion. Moreover, more rigorous experimental evidence

is required defining the potential contribution of SGK1 to the pathophysiology following suboptimal water intake. Whatever mechanisms involved, optimal water intake may prevent, delay or attenuate those severe potentially life threatening clinical disorders.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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