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Metabolic and Kidney Diseases in the Setting of Climate Change, Water Shortage, and Survival Factors

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ABSTRACT

Climate change (global warming) is leading to an increase in heat extremes and coupled with increasing water shortage, provides a perfect storm for a new era of environmental crises and potentially, new diseases. We use a comparative physiologic approach to show that one of the primary mechanisms by which animals protect themselves against water shortage is to increase fat mass as a means for providing metabolic water. Strong evidence suggests that certain hormones (vasopressin), foods (fructose), and metabolic products (uric acid) function as survival signals to help reduce water loss and store fat (which also provides a source of metabolic water). These mechanisms are intricately linked with each other and stimulated by dehydration and hyperosmolarity. Although these mechanisms were protective in the setting of low sugar and low salt intake in our past, today, the combination of diets high in fructose and salty foods, increasing temperatures, and decreasing available water places these survival signals in overdrive and may be accelerating the obesity and diabetes epidemics. The recent discovery of multiple epidemics of CKD occurring in agricultural workers in hot and humid environments may represent harbingers of the detrimental consequences of the combination of climate change and overactivation of survival pathways.

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The 21st century is bringing new challenges with population expansion, a decrease in natural resources, and climate change. Mean temperatures increased by 0.8°C since 1880, with two thirds of the change occurring since 1975, and they are projected to increase by 3°C to 4°C by the end of the 21st century.[1,2] Temperature extremes have also increased by 75% because of climate change.[3] Continued population growth and to a lesser extent, climate change have also resulted in decreasing water resources.[4,5] Today, one half of the world population suffer moderate water shortage (*i.e.*, 1.0–1.7 m^3 water per person per year), and 10% have extreme water shortage (defined as <0.5 m^3 per person per year), with the primary areas affected being Africa, southern and eastern Asia, and the Middle East.[4]

Increasing water shortage coupled with climate change increases the risk for dehydration-associated diseases. For example, there is increasing evidence that climate change may have a role in epidemics of CKD that are occurring among workers in hot environments.[6] While this latter paper focuses on the sites of these epidemics and their relationship to local temperatures and changing climate, space constraints prevented it from being able to address a more central question on the biology of water conservation and how it relates to disease. Here we review how various species protect themselves from dehydration, and we identify nutrient, hormonal and metabolic pathways triggered by hyperosmolarity that link water conservation with survival. We also discuss how these pathways may predict diseases that will dominate the next millennium. Importantly, climate change, heat stress, and water shortage not only will affect kidney disease, but risk for metabolic diseases including obesity and diabetes.

HOW ANIMALS SURVIVE WATER SHORTAGE

The transition of vertebrates from sea based to land was associated with many adaptations, but some of the most important were mechanisms to conserve water, including

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ways to store water, minimize water loss, and generate water.[7]

Water Storage

Some terrestrial animals store water in their bladders. The water-holding frog (*Cyclorana platycephala*) of the Sandy Desert of Australia, for example, stores so much water that it may double its weight.[8] These frogs were a favorite source of water for the Tiwi people during hot summers. Some frogs live 5 years without drinking water, which is because they utilize water stored in their bladders and also generate water during the metabolism of fat.[7,8] The giant tortoise of the Galapagos Islands stores water in their urinary bladder. After rain, the tortoise voids their bladder urine (which contains urea and other waste products) and drinks copiously to refill their bladder with fresh water. When needed, the turtle reabsorbs the water through the bladder wall, while at the same time, excreting some of its wastes into it, and over time, the osmolarity of the bladder urine increases.[9]

Reduced Urinary Water Losses

Homer Smith[6] proposed that the evolution from aquatic to terrestrial environments required efficient ways to excrete nitrogen to help minimize loss of water.[10] Most aquatic animals excrete ammonia, the simplest nitrogen product, as their means for eliminating nitrogen waste products (ammoniotely). In contrast, ammonia is not an appropriate compound for nitrogen excretion by terrestrial animals, because its renal excretion requires 400 ml water per 1 gram ammonia and blood levels >0.05 mM are neurotoxic.[10] Rather, urea excretion is common among land amphibians and mammals, because it is concentrated easily and with low toxicity. Most effective is excretion of uric acid (uricotely), which requires only 1/50 the amount of water as that for the excretion of ammonia. Excretion of uric acid is the principal mechanism for nitrogen excretion in birds, reptiles, and some amphibians.[10] Here, the uric acid is precipitated in the cloaca, where the last water is absorbed, and then, the urate pellet is excreted.

Although ureotelic animals have obligate water loss to help excrete metabolic wastes, urinary loss is minimized by urinary concentration, a process largely driven by vasopressin (or vasotocin in lower vertebrates). Vasopressin reduces water excretion by allowing water reabsorption in the collecting ducts, but it also increases sodium and urea reabsorption. The reduction in urea excretion by vasopressin improves urinary concentration by increasing urea accumulation in the renal medulla, which aids water reabsorption.

Reducing Nonrenal Water Loss

Water loss also occurs through the skin and lungs, where it helps regulate body temperature when animals are exposed to heat. A lack of sweating can result in a marked rise in body temperature and circulatory collapse (heat shock). In contrast, excessive sweating without rehydration may result in hypernatremia and volume depletion.

Desert rodents minimize water loss by hiding during the day in burrows, where temperatures are lower and humidity is high. Lungfish coat themselves with slime to minimize water loss as they burrow and estivate in the mud. Estivating frogs (*C. platycephala*) form cocoons from sloughed epithelial layers of skin.[11] Tree frogs decrease water loss by secreting an impermeable waxy material onto their skin.[11] Lemurs estivate in tree hollows to avoid sun exposure and reduce their metabolism and water needs. The dromedary camel conserves water by minimizing sweating because of a reduction in sweat glands. The camel also does not pant and has adaptations in its nose that minimize respiratory losses of water.[12,13] The consequence is significant diurnal variation in body temperature (as much as 6°C), with temperatures occasionally reaching 40°C on hot days.[12] To prevent dehydration, camels ingest large volumes (up to 57 L) of water at one sitting. Despite these preventive measures, camels can become severely dehydrated.[14]

Metabolic Water

Water is also generated during fat and glycogen metabolism. Fat is anhydrous and contains only 10% water by weight,[15] but when fat is oxidized, water and carbon dioxide are released. For every gram of fat metabolized, 1.12 ml water is generated.[16] Liver or muscle glycogen also generates 0.6 ml water per gram of glycogen metabolized.[17] Because glycogen is water soluble, it also releases potassium and water during metabolism, accounting for an additional 3 ml water per gram of glycogen metabolized.[18,19] The marked diuresis after initiation of a low-carbohydrate diet is partially because of water released during glycogen metabolism.[19] Although glycogen metabolism produces metabolic water, most organisms store more fat than glycogen. Thus, fat is the major source of metabolic water for most animals.

Metabolic water is used by many animals to survive periods of water shortage. Marine whales obtain much of their water from the burning of fat.[20] Although capable of ingesting seawater and excreting a urine more concentrated than seawater, whales rarely use this method for obtaining water.[20] Lungfish obtain water from fat metabolism while they estivate in the mud for 1–2 years. Desert rodents, such as the sand rat (*Psammomys obesus*), have high body fat, which they use to generate water during times of need. Larger desert animals, such as the camel and oryx, also use metabolic water, and in the oryx, this may account for 24% of its overall water needs.[21]

Some obligatory water loss by the lung occurs during fat metabolism because of the need to excrete carbon dioxide that may counter the gain of water provided during fat metabolism.[22] However, animals like camels have developed techniques to reduce water loss from their airways and skin.[12,13]

SURVIVAL MECHANISMS ASSOCIATED WITH DEHYDRATION

Because fat and glycogen act as storage for water, it is not surprising that survival mechanisms associated with starvation and water shortage have overlapping metabolic pathways. Here, we discuss some of these mechanisms.

Vasopressin: The Survival Hormone

Vasopressin is an old hormone, with its predecessor, vasotocin, appearing 700 million years ago.[23] Although vasopressin reduces urinary water losses in response to a loss of intracellular or extracellular fluid, it has other actions that may aid water conservation.[24] For example, vasopressin may also reduce nonrenal water loss[25,26] by acting *via* V2 receptors in the lungs.[27] Vasopressin also reduces fever because of antipyretic effects that reduce water loss.[24] In frogs, vasotocin reduces water loss through the skin and stimulates water reabsorption from the bladder when frogs are exposed to dehydrating stimuli.[11,23] In humans, however, the reduction of sweating in dehydrated individuals occurs *via* a vasopressin-independent mechanism.[28,29]

Vasopressin has other survival functions (Figure 1). Acute infusion of vasopressin increases serum glucose in humans,[30] likely by stimulating glycogenolysis and gluconeogenesis.[31–34] Vasopressin stimulates glucagon release from islet cells.[34] Vasopressin stimulates sodium reabsorption in the cortical and outer medullary collecting ducts.[24] Vasopressin also stimulates protein synthesis, cell proliferation, and cell hypertrophy *in vitro*.[35]

Vasopressin also may stimulate fat accumulation. Vasopressin blocks fat oxidation[31,32] and enhances fat accumulation by blocking lipolysis in fasting animals.[32,35,36] In fasting animals, vasopressin reduces ketosis but increases glucose levels.[32] Vasopressin enhances insulin resistance and fatty liver accumulation in the obese Zucker rat.[37]

Vasopressin secretion is associated with stress responses that improve chances for survival. For example, vasopressin acutely increases BP and induces vascular constriction *via* the V1a receptor.[35] Vasopressin stimulates adrenocorticotrophic hormone release from the anterior pituitary *via* the V1b receptor[38,39] and catecholamine release from the adrenal medulla, where both V1a and V1b receptors are expressed.[40] Vasopressin activates the renin-angiotensin system[35] and stimulates aldosterone release.[35] These stress responses are associated with vasopressin–mediated behavioral changes that include aggression, anxiety, impulsivity, and memory.[36,41,42]

Fructose: The Survival Nutrient

The effect of vasopressin to stimulate fat accumulation (by blocking fat oxidation), increase blood glucose (*via* gluconeogenesis), increase BP, and stimulate stress responses is reminiscent of the effects of fructose.[43] It is of interest that fructose, but not glucose, stimulates vasopressin release in humans.[44,45] We recently showed that orally administered fructose augments circulating vasopressin levels (as determined by measuring copeptin, a validated biomarker for vasopressin[46]) and urinary concentration in dehydrated rats.[47] Fructose also stimulates urinary sodium reabsorption[48] and reduces urea excretion[49] similar to vasopressin.

Dehydration also results in endogenous fructose production because of activation of the aldose reductase-sorbitol dehydrogenase (polyol) pathway.[50] We found that acutely dehydrated mice show a blunted vasopressin response if endogenous fructose metabolism is abolished (by using fructokinase knockout mice) (C. Roncal-Jimenez *et al.*, unpublished data). These studies emphasize a strong relationship between fructose and vasopressin.

We speculate that fructose may be a primary nutrient for survival, especially under conditions of reduced food or water availability. Indeed, the administration of fructose to fasting humans increases glucose levels (likely from the metabolism of fructose itself) and reduces

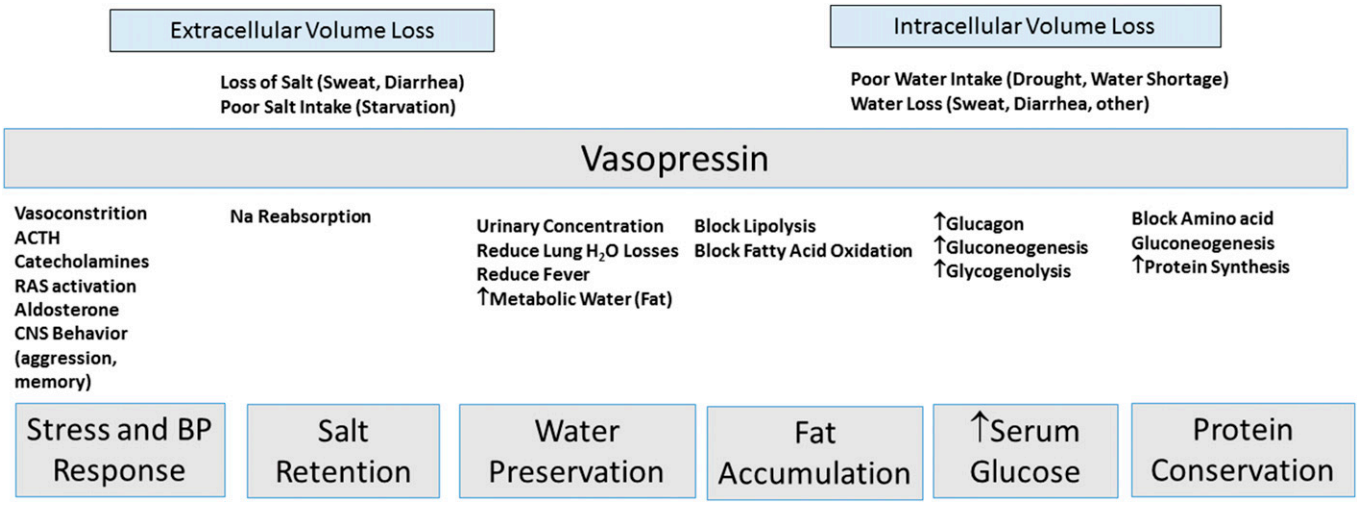

Figure 1. Vasopressin, the ultimate survival hormone. Vasopressin may have originated as a survival hormone for situations where the organism suffered from either extracellular volume or intracellular volume loss. The effects of vasopressin include actions much greater than simply preventing the loss of water but also, include generating a stress response, increasing BP, stimulating protein synthesis, stimulating fat accumulation, and maintaining elevated serum glucose (insulin resistance) to provide energy to the brain. ACTH, adrenocorticotrophic hormone; CNS, central nervous system; RAS, renin angiotensin system.

ketosis, amino acid–induced gluconeogenesis, urinary nitrogen (ammonia and urea) excretion, and sodium excretion.[49] These are the same effects observed when vasopressin is given to starving animals.[32] Thus, fructose and vasopressin may act similarly to preserve water, salt, and fat while maintaining glucose levels as a source of energy for brain function. Viewed this way, the action of vasopressin to stimulate fat accumulation provides a mechanism for not only storing water but also, providing energy during times of food or water deprivation.

Uric Acid: The Metabolic Danger Signal

As discussed earlier, birds and reptiles excrete uric acid as their primary means for excreting nitrogen to minimize water loss.[10] Despite uric acid being a potent extracellular antioxidant,[51] the uric acid generated during fructose metabolism stimulates hepatic fat accumulation (by blocking fat oxidation) and gluconeogenesis, increases BP, and stimulates impulsivity in laboratory animals.[52–56] In rodents, uric acid potentiates the effect of fructose to stimulate hepatic fat accumulation and gluconeogenesis.[57,58] These data suggest that uric acid may also be a metabolic survival factor, which is consistent with observations that serum uric acid increases with both dehydration and starvation.[59]

Interestingly, the rise of uric acid that occurs with protein degradation and amino acid–induced gluconeogenesis is reversed with fructose in fasting humans.[49] Likewise, although vasopressin reduces uric acid excretion in healthy subjects,[60] in the syndrome of inappropriate antidiuretic hormone, serum uric acid is low, and urinary uric acid excretion is high.[61,62] Thus, whether uric acid has a role in water handling remains unclear and deserves additional studies.

DEHYDRATION IN HUMANS

Dehydration in the Hot Environment

Humans have obligate daily water losses from the lungs (250 ml/d) and urine (350–500 ml/d). In hot conditions, water losses from sweat may increase to 3–4 L/h and 8 L over a 24-hour period.[15] Subjects working in hot tropical environments acclimate by producing a higher sweat rate that is lower in sodium, thereby resulting in less increase in core temperature, and also, they have higher plasma volume, less oxygen utilization, and less lactate accumulation.[63] However, this adaptation may result in greater water loss and increased risk for hyperosmolarity.[63] To help counter water loss from sweat, subjects living in the tropics tend to have slightly higher core temperatures during the day, with a greater fall at night, showing a similar trend as that observed in camels.[64]

Dehydration develops easily in the hot environment. An increase in serum osmolarity of 10 mosM/kg occurs within 40 minutes of exercise in the heat[65] or with water deprivation for 24 hours.[66,67] The Tsimane Indians of the Amazon show evidence of dehydration in 40% of subjects, especially on days with high temperatures and strenuous physical activity, despite mean water intake of 6 L daily.[68] Chronic recurrent dehydration is also common in sugar cane workers in Central America who work under hot and humid conditions.[69–71] After dehydration occurs, mental and physical performance worsen,[65,72,73] total sweat volume decreases,[74] and relative water content of sweat decreases (reflected by higher sodium concentration).[63] Energy intake also decreases, which results in a reduction in obligate osmoles required for excretion.[67] Ultimately, confusion, seizures, and coma may develop.

Diseases Favored by Water Shortage and Climate Change

Heat Stroke and Acute Mortality

Heat waves increase the risk for heat stroke and heat-associated mortality.[75–77] In 2015, >1400 deaths occurred from heat stroke in Andhra Pradesh, India.[78] In a case-control study performed in Arizona, the risk for heat-associated death was 3.5-fold among agricultural workers and 2.3-fold in construction workers, and it was disproportionately higher in Native American and Hispanic American men.[77]

Kidney Stones

The risk of kidney stones is increased in subjects with low urine output because of the effect of urinary concentration to increase concentrations of poorly soluble constituents, like calcium oxalate and uric acid. There is a relationship between mean daily temperature and risk for kidney stones, especially when temperatures exceed 30°C.[79]

CKD

Heat stress doubles the risk for developing CKD among those working in hot environments.[80] Recently, epidemics of CKD have been reported in India, Sri Lanka, Mexico, and Central America.[81–86] The CKD observed in these areas is not because of the classic causes of CKD, such as diabetes or hypertension, but rather, seems to be a type of chronic tubulointerstitial disease.[87,88] Although the roles of toxins and infections have not been completely ruled out, common risk factors for each of the epidemics are hot temperatures and recurrent dehydration that can be linked with climate change.[89]

Although acute dehydration is known to cause a transient reduction in kidney function without permanent renal damage, chronic recurrent heat–induced dehydration causes CKD in mice.[50] The mechanism for CKD may involve hyperosmolarity-induced alteration of fructose and vasopressin metabolism (Figure 2). The rise in serum osmolarity stimulates vasopressin and increases intrarenal fructose generation *via* activation of the aldose reductase pathway.[50] The metabolism of fructose within the proximal tubule results in local oxidative stress, inflammation, and uric acid generation, which induce local injury.[90] Experimental studies also document a role for vasopressin in CKD.[91] An increase in serum and urinary uric acid also occurs with heat and exercise, which increases the risk for urinary urate crystal formation.[89,92]

The possibility that dehydration may be a risk factor for CKD should also be considered. Low urine output[93,94] and high urine osmolarity[95] predict risk for the progression of CKD. Low intake of plain water increases the risk for CKD,

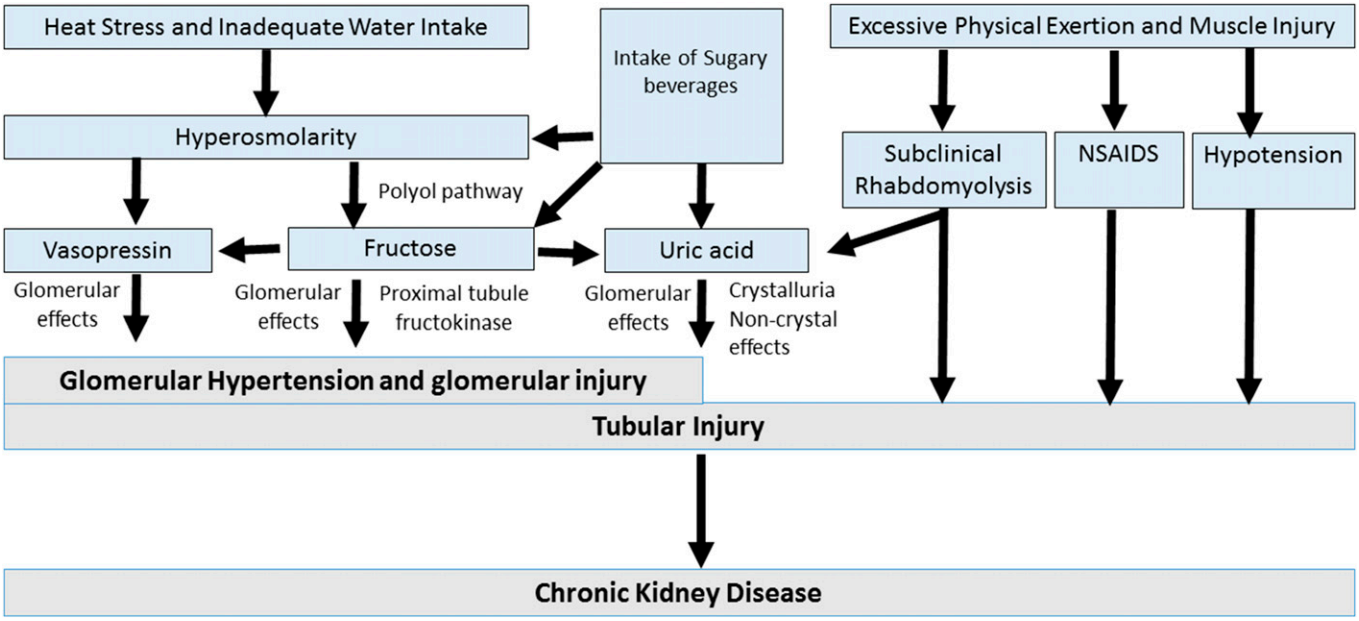

Figure 2. Potential mechanisms involved in heat stress–associated CKD. CKD occurring in response to recurrent dehydration may involve a variety of mechanisms. Central to the loss of water is the development of hyperosmolarity, which stimulates the release of vasopressin, and the generation of fructose in the kidney from activation of the polyol (aldose reductase-sorbitol dehydrogenase) pathway.[50] Vasopressin acts to increase glomerular hydrostatic pressure and increases the risk for progression of kidney disease.[91,123,124] Endogenous fructose production is also metabolized by fructokinase in the proximal tubule, resulting in tubular injury and the release of oxidants, uric acid, and chemokines.[90] Fructose may also increase vasopressin levels,[125] and likewise, rehydration with sugar beverages may provide additional fructose, with an amplification of the vasopressin and uric acid levels.[47] Furthermore, other factors that may be involved include low–grade muscle injury associated with excessive physical exertion leading to subclinical rhabdomyolysis,[126] an increased risk for nonsteroidal anti–inflammatory drug (NSAID) use, and rarely, hypotension from volume depletion. Volume depletion may also be associated with activation of the renin-angiotensin system and development of hypokalemia, which may also play a role in kidney disease.

whereas intake of other beverages does not show the same effect.[94] Likewise, high vasopressin levels (indicated by high plasma copeptin levels) are associated with increased risk for microalbuminuria.[96,97] Currently, there is a randomized trial to determine if supplementation with water to increase urinary output to >3 L/d slows the progression of CKD.[98]

Obesity, Metabolic Syndrome, and Hypertension

As mentioned, fructose and vasopressin show similar effects to increase fat stores and conserve water (Figure 3). This suggests that transient elevations in serum osmolarity because of either a relative water deficit or a high-sodium diet might be associated with increased risk for obesity and metabolic syndrome. Evidence supporting hyperosmolarity as a risk factor for obesity and metabolic syndrome is increasing. First, obese subjects have elevated plasma sodium and plasma osmolarity.[99] Second, plasma hypertonicity predicts the development of diabetes in subjects >70 years old.[100] Third, subjects with metabolic syndrome and insulin resistance have elevated plasma copeptin levels.[101–104] Fourth, elevated levels of plasma copeptin predict development of diabetes[96,105] and obesity.[96]

Although inadequate hydration and hot temperatures facilitate hyperosmolarity, it could also be enhanced by a high intake of salt with a less than adequate intake of water. In this regard, low water intake predicts development of insulin resistance,[106] whereas increasing water intake is associated with weight loss, at least in overweight subjects.[107] High salt intake is also associated with obesity, metabolic syndrome, and diabetes[108–112] and predicts these conditions independent of energy intake or intake of sugary beverages.[112–114] Thus, the development of obesity is not simply because of greater intake of soft drinks consequent to salt-induced thirst, which has been suggested.[115] Furthermore, subjects given a high-salt diet show reduced insulin sensitivity within 5 days.[116] Conversely, hyperinsulinemia promotes distal tubular sodium retention.[117]

Hyperosmolarity likely increases the risk for obesity and metabolic syndrome by stimulating vasopressin (Figure 3). Indeed, water loading reduced fat content of the liver of obese Zucker rats coupled with a reduction in vasopressin levels.[37] However, hyperosmolarity is likely acting *via* another pathway as well. We recently found that mice fed a high-salt diet for 5 months develop leptin resistance, obesity, and metabolic syndrome (M.A. Lanaspa *et al.*, unpublished

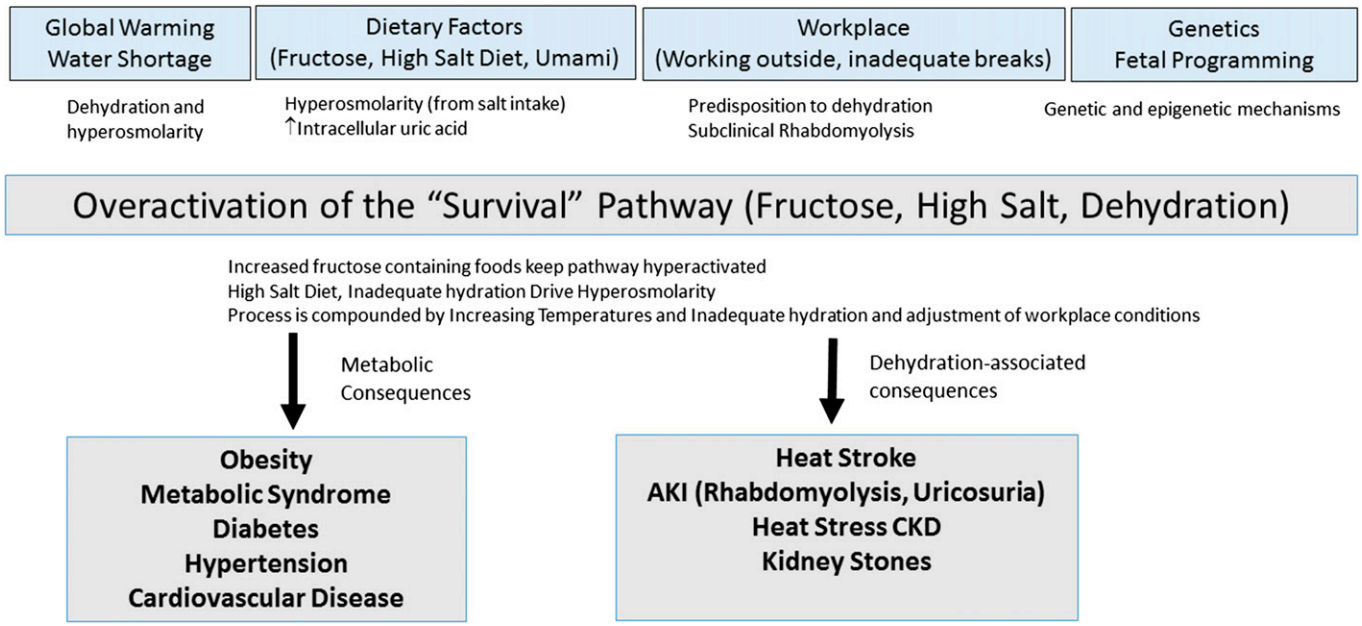

Figure 3. Modern diseases engaged by water shortage and global climate change. Although the vasopressin system was developed as a survival mechanism when the host lost either intracellular or extracellular volume, in modern society, it may, instead, be associated with the development of diseases. Climate change and water shortage triggered with diets high in fructose (sugar), salt, and umami foods may lead to overactivation of this pathway. The metabolic effects of high osmolarity may include the syndrome of obesity, metabolic syndrome, and diabetes. In contrast, recurrent dehydration and highly concentrated and acidic urine may increase the risk for crystallization of uric acid and chronic kidney damage.

data). The mechanism was shown to be caused by hyperosmolarity-mediated upregulation of aldose reductase in the liver, which resulted in endogenous fructose generation *via* the polyol pathway. Importantly, mice unable to metabolize fructose because of genetic deletion of fructokinase were protected from developing metabolic syndrome and fatty liver, despite ingesting equal amounts of salt.

Hypertonicity also regulates BP and the immune system.[118–120] Specifically, a high-salt diet activates a transcription factor, NF of activated T cells 5, that stimulates macrophages to sequester salt in the skin, thereby modulating BP. Salt-induced hypertonicity also activates T helper 17 lymphocytes involved in host defense.[121]

SUMMARY

In summary, climate change and low water intake are increasing our risk for dehydration–associated kidney diseases, including kidney stones, heat stroke, and CKD. Hyperosmolarity, especially in a sedentary environment, may also increase the risk for obesity and diabetes. We speculate that hyperosmolarity triggers factors originally designed to aid survival by increasing fat stores and conserving water, such as vasopressin, endogenously produced fructose, and uric acid. Overactivation of these pathways may act in synergy with Western diets high in fructose-containing sugars, salt, and purine-rich foods to accelerate the obesity and diabetes epidemics (Figure 2).[43,50,91,122] Similarly, recurrent dehydration and heat stress may also be playing a role in causing CKD *via* similar pathways.[89]

More studies are needed to investigate the effect of climate change and water shortage on kidney disease and diabetes and especially, the role of vasopressin, fructose, and uric acid. Intervention studies to improve worksite conditions and hydration among agricultural workers in tropical communities and other at–risk groups are recommended. Recognizing the importance of the kidney in climate change–associated disease will prepare nephrologists to face an increase in heat stress–associated kidney diseases predicted to occur in the next decades.

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DISCLOSURES

R.J.J. has several patents and patent applications related to lowering uric acid or blocking fructose metabolism in the treatment of metabolic diseases. R.J.J. and M.A.L. are members of a startup

company, Colorado Research Partners LLC (Aurora, CO), that is trying to develop inhibitors of fructose metabolism. R.J.J. also has some shares with XORT Therapeutics (Calgary, AB, Canada), which is a startup company developing novel xanthine oxidase inhibitors. R.J.J. is on the Scientific Board of Amway as well.

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