

REVIEW ARTICLE

Kidney Biomimicry—A Rediscovered Scientific Field That Could Provide Hope to Patients with Kidney Disease

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Most studies on kidney disease have relied on classic experimental studies in mice and rats or clinical studies in humans. From such studies much understanding of the physiology and pathophysiology of kidney disease has been obtained. However, breakthroughs in the prevention and treatment of kidney diseases have been relatively few, and new approaches to fight kidney disease are needed. Here we discuss *kidney biomimicry* as a new approach to understand kidney disease. Examples are given of how various animals have developed ways to prevent or respond to kidney failure, how to protect themselves from hypoxia or oxidative stress and from the scourge of hyperglycemia. We suggest that investigation of evolutionary biology and comparative physiology might provide new insights for the prevention and treatment of kidney disease. © 2013 IMSS. Published by Elsevier Inc.

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The prevalence of chronic kidney disease (CKD) has reached epidemic proportions. Given that >10% of the worldwide general population shows signs of kidney dysfunction (reduced renal function and/or albuminuria), CKD has emerged as a global health problem that requires better understanding and exploration of the underlying causes as well as new preventive therapeutic opportunities (1). Subjects with CKD have an unusually high mortality rate primarily due to cardiovascular disease (CVD) and infectious complications, and the unstandardized CV mortality risk of patients starting dialysis is 15-fold higher than age- and sex-matched non-CKD counterparts (2). For many years nephrologists have searched for specific pharmaceutical and/or nutritional interventions that may slow the slippery-slope descent in renal function towards end-stage renal disease (ESRD) and the commensurate development of the highly atherogenic uremic phenotype (3). Unfortunately, there is probably no other patient group in which there have been so many negative randomized controlled trials using drugs and interventions (4), and the patient with ESRD continues to have

one of the highest morbidity and mortality rates for any disease (1). Sir Winston Churchill once wrote “*Success is nothing more than going from failure to failure with undiminished enthusiasm*” and it is in his spirit of continued hope, energy and enthusiasm that nephrologists must continue to search for novel approaches that can lead to new treatments of renal disease and its devastating complications.

Biomimicry—Nature Knows Best

The science of biomimicry (i.e., comparative physiology) may, in our opinion, be a golden opportunity for nephrologists to learn about possible novel treatment strategies of human renal disease. In her famous book, Janine Benyus (5) stated that biomimicry is “*the science that studies nature’s models and then imitates or takes inspiration from these designs and processes to solve human problems.*” One of the earliest examples of biomimicry was the study of birds to enable the creation of flying machines. Although Leonardo da Vinci (1452–1519) was never successful in creating a machine that actually flew, he made numerous notes and sketches based on his observation of birds that flew. The Wright Brothers, who in 1903 succeeded in flying the first aircraft, also derived inspiration from their

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observations of birds. As discussed by Zhang (6), biomimicry has inspired countless novel cutting edge designs in biomedical research such as spider silk-made artificial skin. The termite's ability to maintain constant temperature and humidity in their termite mounds in Africa (despite markedly varying outside temperatures) and its influence on human building design is yet another example on how inspirations from nature can help human development (7).

Evolution provides the natural experimental system in which success in adaptation represents the ultimate triumph in survival in slowly changing environments. One of the key aspects of survival in changing environments is a means for regulating the intracellular and extracellular body fluid composition and to find ways to either adapt to, or eliminate, waste products generated during metabolism. Fluid and electrolyte metabolism as well as assessment and management of renal function lies in the home of the nephrologist. We would like to suggest that studies of "kidney biomimicry" in other species may be illuminating and provide new insights into how to approach human kidney disease. In this article we will discuss some amazing examples from nature on how certain animals manage to protect their kidney function in extreme conditions such as the enormous water and sucrose intake in hummingbirds, low oxygenation and extensive renal vasoconstriction during deep sea diving in seals, extreme oxidative stress in naked mole rats and constant azotemia in vampire bats. Bears (*Ursidae*), metabolic magicians that have developed amazing mechanisms to avoid azotemia despite reduced renal function during hibernation (Figure 1), will also be discussed (8).

Prevention of Kidney Injury—Protection from Ischemia

One of the most common consultations that nephrologists receive is for acute kidney injury secondary to ischemia such as following an episode of hypotension or major surgery. Prolonged ischemia of donor kidneys is also associated with delayed graft function and acute kidney injury (9). The pathogenesis of the acute renal injury is complex but is thought to relate to oxidative stress and inflammation that develop during the reperfusion period (ischemia-reperfusion syndrome) (10). Interestingly, some animals have developed ingenious ways to protect themselves from this type of kidney damage.

Diving Seals—How They Cope with Ischemia during Deep Sea Diving?

Seals (*Phocidae*) have developed an extraordinary ability to survive prolonged asphyxia during underwater dive. Elephant seals can descend up to amazing 2 km during diving for periods that can extend to up to 100 min per dive

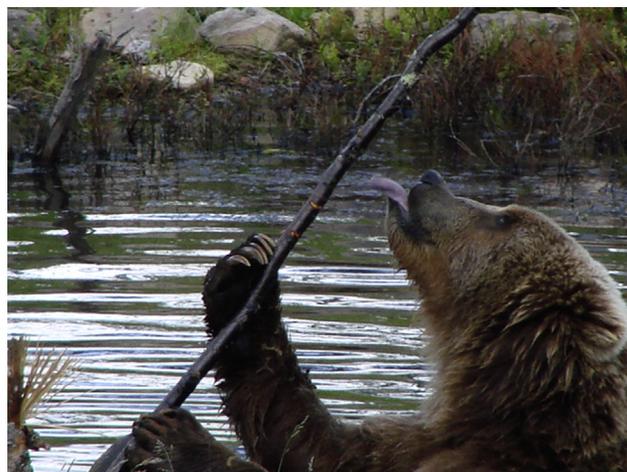


Figure 1. Brown bear (*Ursus arctos*) from central Sweden. Hibernating bears represent an amazing example of how creatures can adapt to extreme living conditions. During 4–6 months of hibernation in their winter den, the inactive bears do not eat, drink, defecate or urinate. Despite markedly reduced renal function during hibernation, serum urea levels decrease and bears do not lose any bone mass and only little muscle mass. Determining how hibernating bears manage to keep their muscle mass and reuse urea despite prolonged inactivity and reduced renal function could help us to find novel treatment strategies for patients with end stage renal disease and catabolic disorders associated with prolonged bed rest. Photograph taken by Peter Stenvinkel.

(11). The diving lifestyle of seals requires extreme cardiovascular adjustments to maintain sufficient oxygenated blood to the heart and brain. To help reduce oxygen demands, seals will reduce their heart rate and cardiac output and reduce their blood supply via vasoconstriction of several organs, including the kidneys. Bron et al. (12) obtained angiograms in harbor seals and demonstrated that the constriction of small arterial branches is so intense that blood flow is essentially lost in muscle, skin, kidney, liver and spleen during diving. Kidneys are subjected to prolonged vasoconstriction during diving with cessation of renal function, which is followed by reperfusion after each diving episode (13). Inulin clearance has been measured and decreases >90% during dives that lasted longer than the seal's aerobic dive limit (14). Halasz et al. (15) studied isolated perfused kidneys from both dogs and seals subjected to 60 min of ischemia at 35°C. In contrast to the massive urine flow during recovery in the seal kidneys, kidneys from dogs did not produce urine at all. Thus, the seal kidney is unusually tolerant to ischemia and ischemic acute kidney injury.

It is likely that several mechanisms are operative to help protect the seal kidney from ischemic injury. First, the kidneys of seals may be better adapted to anaerobic metabolism, as levels of glycolytic enzymes are generally higher in the seal kidney compared to adult dogs (16). Seals also show an increased ability for aerobic, fat-based metabolism during hypoxia associated with routine diving (17).

One of the products of fat metabolism is β -hydroxybutyrate, which may help protect against ischemic injury by providing an energy fuel that replaces glucose (18). Ischemia-reperfusion is also associated with increased production of reactive oxygen species (ROS) (19). Not surprisingly, seals have developed an outstanding antioxidant defense against ischemia-reperfusion injury, and their kidneys have higher levels of glutathione disulfide reductase, glucose-6-phosphate dehydrogenase and total glutathione levels compared to pig kidneys (20). This antioxidant system may be stimulated by prolonged (1–3 months) fasting (21), a phenomenon that is not observed in rats as oxidative stress tends to increase with food deprivation in this species (22). Although the exact mechanism(s) leading to the upregulation of antioxidant defenses during prolonged fasting in seals is unknown, prolonged fasting has been shown to activate glutathione biosynthesis (23), hypoxia inducible factors (24) and (via Nox4) the redox-sensitive transcription factor Nrf2 in elephant seals (25). One might posit that the upregulation of antioxidant systems with fasting is an adaptive response that provides protection during the diving for food. Recently, fasting has been found to stimulate Nrf2 activity *in vivo* via SIRT-1-dependent mechanisms in both mouse and humans (26), and the induction of Nrf2 protects mice from fasting-induced oxidative stress to the mitochondria (22). Thus, further studies of the mechanisms regulating the antioxidant systems with fasting and diving in the seal could potentially provide insights as to how to prevent ischemic renal injury in humans.

Other Examples of Animals Protected from Ischemic Renal Injury

Numerous other animals have also developed mechanisms to protect their kidney function. One of the most striking examples is the wood frog (*Rana sylvatica*) that freezes during the winter with blood flow maintained due to the accumulation of glucose and urea that acts like an antifreeze. These frogs also upregulate antioxidant systems in their tissues to protect against ischemia-reperfusion injury (27). Another example is the hibernating ground squirrel (*Ictidomys tridecemlineatus*), which is known to reduce its body temperature to 2–10°C during torpor in association with a reduction in heart rate to 3–5 beats/min. Hibernating squirrels can remain at this temperature for 10–14 days at a time following by intermittent warming (24–48 h) before going back into their torpid state. Interestingly, recent studies by Jani et al. (28) have shown that the squirrel kidneys are protected from cold ischemic injury regardless of whether they are obtained during the summer or during hibernation. Unlike the mouse, the kidneys from hibernating squirrels were protected from cold ischemia-induced apoptosis (28). Understanding how animals such as the ground squirrel, seal and wood frog protect

themselves from ischemic injury could be of great value to the prevention and treatment of acute kidney injuries in humans.

Decreased Renal Function Associates with Azotemia

A hallmark of renal dysfunction is the retention of urea (or carbamide), which is the main nitrogen-containing substance in the urine of mammals. Nephrologists are generally aware that urea levels can be reduced relative to the level of GFR in the setting of reduced production (such as from protein restricted diet, protein-energy wasting or liver disease) or increased relative to the GFR in catabolic states, gastrointestinal bleeding or with volume depletion. However, imagine an animal that reduces its urea levels as GFR falls and the potential benefit of harnessing this amazing technique in ESRD patients.

Hibernating Bear—Renal Failure without Azotemia

Many bears will hibernate for 4–6 months each winter during which time they will be anuric. GFR decreases to <25% of normal, but minimal urine is produced due to the reabsorption of fluid from the bladder, which becomes “leaky” during this time. Serum creatinine rises during hibernation, consistent with the reduction in GFR and anuria, but interestingly, levels of urea do not increase, but rather fall. In a recent study performed in 16 free-ranging bears from central Sweden, we found that whereas serum creatinine doubled, serum urea halved during winter hibernation (29).

The fall in serum urea reflects several processes including decreased production due to the fasting. However, the most important feature is the recycling of urea back into proteins. Mammals normally cannot metabolize urea, but ureases are present in gut bacteria. The current primary hypothesis is that urea is recycled due to its secretion into the intestinal lumen, its breakdown by urease-expressing bacteria, and its reconstitution into protein. A consequence of urea recycling is the preservation of protein stores, which has been documented using ¹⁴C-phenylalanine as a tracer (30). For example, bears only lose about 10–15% of their muscle protein content during hibernation (31), resulting in minimal skeletal muscle atrophy (32). In our recent study, serum levels of total, essential, non-essential and branched chain amino acids did not change during hibernation. However, changes in individual amino acids ornithine, citrulline and arginine indicated an active, although reduced urea cycle and nitrogen recycling to proteins (29).

The unique ability of bears to recycle urea during hibernation is not observed in other hibernating animals such as hedgehogs (33) and ground squirrels (34). In bears this mechanism is likely turned on at a time-point before hibernation by yet undefined trigger(s) that could include

changes in the bear diet, temperature or hours of daylight. Nelson et al. (35) reported that urea levels start to decrease in autumn prior to entering hibernation, suggesting that changes in the bear diet may contribute to this metabolic switch. The typical diet of bears during late summer and autumn includes enormous amounts of berries from the *Vaccinium* family such as lingonberries, huckleberries and bilberries (36). As berries contain little proteins, the need to synthesize and excrete urea diminishes. Moreover, as berries contain resveratrol (sirtuins) (37), which recently were reported to regulate the urea cycle via deacetylation of the carbamoyl phosphate synthetase (have a pivotal role in ammonia detoxification), it should be tested if dietary shifts from summer to autumn in bears affect sirtuin activity. Fruits also contain fructose that generates uric acid during its metabolism, and uric acid has also been found to inhibit enzymes involved in urea synthesis (38). The bear bladder also becomes leaky during hibernation, allowing reabsorption of urea (39). It is assumed that gut bacteria break down urea that is then used to generate glutamine and reutilized for amino acid and protein synthesis. If we can determine what triggers the changes in urinary bladder urea transport during hibernation and the composition of the intestinal microbiota in hibernation compared to the active summer state, nephrologists might better understand how bears can prevent azotemia despite reduced renal function.

Adaptation to Azotemia

Urea, while representing a key nitrogenous end product in mammals, can also have an important role in urinary concentration and in the recycling of protein. Although it has been believed that moderately high urea concentrations in the human uremic milieu are largely nontoxic, studies suggest that urea retention may affect intestinal barrier function (40) and insulin resistance (41). Although urea is often considered toxic at high concentrations, there are animals that live normally with high urea concentrations in their blood. The classic example are sharks (*Selachimorpha*) and rays (*Elasmobranchs*) that can have serum urea levels >2000 mg/dL (range 300–500 mM), which they use to counter the high osmolarity of sea water. However, there are mammals that also live normally under azotemic conditions.

Vampire Bat—An Animal That Has Adapted to Constant Azotemia

Although many animals naturally ingest a high-protein diet, the rapid ingestion of blood in vampire bats (*Desmodus rotundus*) is exceptional. Following their massive ingestion of blood, which results in a 30–40% increase in the body weight, the full bat may not be able to take off and fly.

Thus, an almost instant massive increase urine flow (4 ml/kg/min) must ensue, which will attain a peak about 25–30 min after feeding (42). About 45 years ago McFarland and Wimsatt (43) found that blood urea concentrations chronically ranged between 27 and 57 mmol/L (depending on the time point after feeding) in a colony of vampire bats fed bovine blood once a day. They calculated that during ingestion the average blood intake was 11.6 g (about 2.2 g of protein or 0.35 g of nitrogen), which would correspond to a daily protein intake of about 6 kg (!) in a 70-kg man. This massive protein intake causes a chronic azotemic environment in the vampire bat and, as discussed by Singer (44), it creates a mismatch between the metabolic demand and GFR. Singer (44) calculated that whereas most mammals that ingest a high protein intake have a GFR-to-urinary nitrogen ratio ranging between 5 and 25, the ratio of the vampire bat is only about 0.8. To be able to conserve proteins, most protein-eating animals have adapted some degree (20–55%) of intestinal urea hydrolysis by gut microflora (44). As vampire bats ingest enormous amounts of protein via blood, they have a very low rate of intestinal urea hydrolysis (45). The shrew is another example of small mouse-sized animal that, like vampire bats, ingest massive amounts of proteins daily (about 70% of their body weight) and thus have constant azotemia (44).

In many species including humans (46), salmon (47) and rats (48), a high protein intake can cause glomerulosclerosis and kidney failure, likely via a mechanism involving hyperfiltration and increased glomerular pressure. However, there is no mention of kidney pathology in a histological study of vampire bats (49). It is therefore of interest not only to know why and how the vampire bat handles chronic azotemia but also why it can maintain normal renal function despite chronic hyperfiltration.

Diabetes without the Complications

Diabetes mellitus remains the worldwide most common cause of CKD (50), and long standing diabetes mellitus can lead to a number of diabetic complications. So why can some animals live most of their whole lives in a chronically hyperglycemic state without complications?

Hummingbirds—The Diabetic Nectarvore That Masters GFR Adjustment

Few birds have a more impressive metabolism than the hummingbird (*Sepehanoides*). With a heart rate of 1200 beats per minute, a respiratory rate of 250 breaths per minute, and wings that flap 50 beats per second, they have one of the highest metabolic rates of any vertebrate (51), amounting to 100 times that of an elephant. Their diet consists almost exclusively of nectar (a 20–30% sucrose

solution), which has minimal amino acids, and as such they must occasionally feed on insects to provide their low nitrogen needs (49).

During the day the hummingbird will ingest 4–5 times of its body mass in nectar, excreting the water and converting the sugar into fat, resulting in a creamy white fatty liver within hours (52). Due to the high intake of sucrose, the blood glucose levels of hummingbirds are markedly elevated, with fasting levels of 17 mM (300 mg/dl) and after feeding on nectar as high as 42 mM (740 mg/dL) (53). Although the levels of glycated hemoglobin is the highest ever-reported in birds, it is lower than HbA1c levels observed in diabetic humans (53). The reason for this is not entirely clear but as the life span of red blood cells is about six times shorter in birds than in humans (54), red blood cell survival may contribute. How hummingbirds can tolerate prolonged hyperglycemia without developing long-term complications of diabetes in kidney, eyes and vasculature definitely warrants further studies.

Prevention of Oxidative Stress and Aging

In 1956 Harman published the hypothesis that aging was the consequence of prolonged oxidative stress (55). Chronic kidney disease in humans is also a type of premature aging, not only with regard to atherosclerotic disease but also with regard to other common features of the uremic senescent phenotype such as osteoporosis, protein energy wasting, hypogonadism, infertility, cognitive dysfunction and frailty (56). Indeed, the toxic and inflamed uremic milieu affect many factors known to accelerate the aging process including klotho deficiency, oxidative stress, telomere shortening, exhaustion of stem cells and DNA damage (56). Increased oxidative stress is a common feature of the uremic phenotype (19,57). Today there is no doubt that aging is associated with increased oxidative stress. In this regard, there is probably no animal more interesting than the naked mole rat.

Naked Mole Rat—Has This Ugly Rodent Found the Fountain of Youth?

Naked mole rat (*Heterocephalus glaber*) is a mouse-sized rodent that lives up to eight times longer than similar sized mice (4 vs. 30 years) and maintains good health for most of its life (58,59). Buffenstein (60) estimated that their increased age and healthy life span would be equivalent to an 80-year-old human with the biological age of 30 years. In addition to delayed aging, the naked mole rat is very resistant to both experimentally induced tumorigenesis and spontaneous cancer (61,62) as well as pain (63). These blind and eusocial animals are native to parts of East Africa and live in colonies of up to 300 animals with a single



Figure 2. Naked mole rat (*Heterocephalus glaber*) is an ugly-looking, blind, long-living and cancer-resistant rodent native to parts of East Africa that lives in burrows. Revealing the secrets of the remarkable ability of the naked mole rat to resist extreme high levels of oxidative stress could provide nephrologists with clues on how to extend life span of prematurely aged patients, such as those with end stage renal disease.

breeding female in complicated burrow systems about 1.5 meters below the soil surface (Figure 2). They are well adapted to their underground existence in total darkness, which makes them extremely resistant to low oxygen and the high oxidative damage to which they are subjected (64).

The natural variation in maximum lifespan of different species may be due to either differences in ROS generation, antioxidant defenses and/or levels of accrued oxidative damage to, lipids and proteins. As naked mole rats tolerate high level of oxidative stress they must have adapted mechanism during evolution to circumvent the effects of high oxidative stress into potentially lethal or devastating diseases (65). It was recently reported that although naked mole rats have similar levels of amyloid beta as a mouse model of Alzheimer disease they showed no sign of extracellular plaques (66). Moreover, it is of major interest that elevated protein carbonylation and oxidative stress does not affect protein function and structure in this remarkable long-living species (67). The deciphering of mechanism(s) by which the naked mole rat protect itself from the detrimental effects of oxidative stress could help scientists to find key contributors in the aging process. Naked mole rats have significantly higher levels of the tumor suppressor protein p53 and the transcription factor Nrf2; they increase even further in response to toxins (59). In theory, enhanced cell signaling via Nrf2, which inhibits NF- κ B activation and regulates hundreds of genes that regulate genes encoding antioxidant and detoxifying molecules (68) may sustain a healthy long life. As CKD patients have decreased expression of Nrf2 (69) the consequent downregulation of antioxidant enzymes may explain why inflammation (70) and oxidative stress (19) are such common phenomena in the uremic phenotype. Thus, targeting Nrf2 would be a logical treatment strategy in CKD patients (68). The recent unforeseen side effects of the Nrf2-agonist bardoxolone in the treatment of CKD patients with type 2 diabetes (71) may have discouraged nephrologists to target this transcription factor. However, as

theoretical considerations support the use of Nrf2-targeted therapies in the prematurely aged and inflamed uremic phenotype (68), we hope the unfortunate development with bardoxolone will not decrease enthusiasm for finding therapeutic interventions targeting Nrf2 in CKD. As several recent studies have shown that nutritional compounds such as allicin, resveratrol, polyphenols, curcumin and catechins can modulate the activation of Nrf2-Keap1 system (72), further studies should be conducted to evaluate the effects of a “healthy diet” on inflammation and oxidative stress biomarkers in CKD patients. It has been demonstrated that in high fat diet-fed mice, curcumin attenuates the Nrf2 signaling defect, muscular oxidative stress and glucose intolerance (26). Finally, as it recently was discovered that higher skin concentrations of extremely high-molecular mass hyaluronan in the naked mole rat mediated their remarkable cancer resistance (73), further studies should be conducted to evaluate if targeting this pathway may prevent human cancer and extend life.

In summary, nephrologists can learn much by involvement in studies of comparative physiology of different mammals such as hibernating bears, vampire bats, hummingbirds, naked mole rat and seals. Such an engagement could help to increase our understanding of how to protect kidney functions during extreme living conditions. In specific, further studies on the interaction between azotemia and the intestinal microbiota, urea transport mechanisms in the urinary bladder and how intermittent fasting affect the expression of the transcription factor Nrf2 and its relation to oxidative stress parameters in different mammals would be of interest to pursue.

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