Vampire bat, shrew, and bear: comparative physiology and chronic renal failure

MICHAEL A. SINGER
Department of Medicine, Queen’s University, Kingston, Ontario, Canada K7L 3N6
Received 28 November 2001; accepted in final form 7 February 2002

Singer, Michael A. Vampire bat, shrew, and bear: comparative physiology and chronic renal failure. Am J Physiol Regulatory Integrative Comp Physiol 282: R1583–R1592, 2002; 10.1152/ajpregu.00711.2001.—In the typical mammal, energy flux, protein metabolism, and renal excretory processes constitute a set of closely linked and quantitatively matched functions. However, this matching has limits, and these limits become apparent when animals adapt to unusual circumstances. The vampire bat and shrew have an extremely high protein intake, and the glomerular filtration rate (GFR) is not commensurate with the large urea load to be excreted. The vampire bat is chronically azotemic (blood urea concentration 27–57 mmol/l); yet there is no information as to how this animal has adapted to such an azotemic internal environment. A high protein intake should also lead to chronic glomerular hyperfiltration; yet neither animal appears to develop progressive renal failure. The American black bear, on the other hand, has adapted to a prolonged period without intake or urine output. Despite continued amino acid catabolism with urea production, this mammal is able to completely salvage and reutilize urea nitrogen for protein synthesis, although the signals that initiate this metabolic adaptation are not known. The vampire bat, shrew, and bear are natural models adapted to circumstances analogous to chronic renal failure. Unraveling these adaptations could lead to new interventions for the prevention/treatment of chronic renal failure.

How have these animals adapted to such unusual circumstances, and can we learn new approaches for the prevention/treatment of chronic renal failure from such natural models?

First, the general design features of mammals with respect to nitrogen metabolism and excretory functions of the kidney are briefly described. With these general characteristics as a reference state, what is known about the adaptation of several small mammals to an extremely high protein intake and about the bear’s adaptation to months without intake and excretion is reviewed.

Although our understanding of these adaptations is limited, the existing data do suggest areas of inquiry that could result in new management strategies for chronic renal failure.

Design principles and quantitative functional interactions can be studied by the use of allometric scaling analysis (12). This technique deals with the effects of changes in body size (or scale) on biological functions and structures. Many morphological and physiological variables scale, relative to body size, according to allometric equations of the following general form: $y = ax^b$, where $y$ is a biological variable, $a$ is a proportionality coefficient, $x$ is body mass, and $b$ is the scaling exponent (59).

We would expect biological functions that are closely linked to scale to body mass in a similar fashion, i.e., to have similar scaling exponents. Furthermore, the ratio of biological functions with the same exponent would give a value that is independent of body size and, hence, a design feature of mammals in general (60, 68). It should be stressed, however, that these ratios do not necessarily allow any conclusions about cause and effect.

It is also obvious that design rules that apply to mammals varying in size from mouse to elephant will suppress individual species differences.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Perhaps the best-studied biological variable is resting metabolic rate (RMR), which has a scaling exponent of 0.75 (64, 76). About 20% of RMR can be accounted for by the energy expenditure for whole body protein turnover (73, 74), with muscle the principal tissue (73). In mammals studied at energy equilibrium, whole body protein turnover, which reflects the balance between synthetic and degradative processes, scales to body size, with an exponent of 0.74 (53). In addition, the turnover of tRNA and rRNA has been found to scale to body size, with exponents of 0.78 and 0.69, respectively (61).

Jackson and co-workers (17, 29, 33, 34) investigated urea production in normal adult men and women of different body composition consuming their habitual diets. Daily urea production per kilogram of body weight was relatively independent of daily protein intake over the range 0.5–1.4 g/kg body wt. However, there was a close relationship between urea production and RMR (33). In addition, with the use of these same data (17, 29, 33, 34), total daily urea production can be fitted to body mass by the following allometric equation: urea production (g N/day) = 0.52W^{0.76}, where W is body mass in kilograms. Although these data are for humans only and the weight range studied is limited, urea production over protein intakes of 0.5–1.4 g·kg^{-1}·day^{-1} scales to body size with an exponent similar to that of RMR. Finally, urinary nitrogen excretion (8) and glomerular filtration rate (GFR) (64) also scale to body size, with exponents of 0.72 and 0.77, respectively. The allometric equations for all these biological functions are given in Table 1. In summary, the scaling data describe close links between energy flux (RMR), protein and RNA turnover, urea production, and kidney excretory processes.

In addition, because the coupling between RMR and GFR is also observed in birds, reptiles, and fish (12, 65), this particular design feature has been well conserved from an evolutionary perspective.

**NITROGEN METABOLISM**

For most amino acids, the initial catabolic step involves removal of the amino group by transdeamination with generation of ammonia. The carbon skeleton is further processed, and because the majority of amino acids are gluconeogenic, the end result is conversion to glucose. The subsequent fate of the ammonia depends on the type of animal. Mammals detoxify ammonia at a considerable energetic cost through the synthesis of urea, which is subsequently excreted.

A simplified model of nitrogen metabolism is illustrated in Fig. 1. The metabolic nitrogen pool consists mainly of free amino acids and ammonia. Amino acids enter the pool from ingested protein or from degradation of body protein. Catabolism of amino acids gives rise to urea. A portion of the urea appearing in the urea pool is excreted in the urine, and a portion is transferred to the (large) bowel, where it is hydrolyzed by bacterial urease. A part of this nitrogen (as ammonia) is resynthesized back into urea, whereas the remainder is available for other synthetic processes. The rate of urea production is equal to the rate of urea excretion by the kidney plus the rate of urea hydrolysis in the bowel.

The intestinal hydrolysis of urea by microflora appears to be a general mammalian feature (14, 24, 70, 79), and in fact the functional interactions between intestine, kidney, and urinary bladder are emerging as a sophisticated system for regulating nitrogen excretion/conservation. Specific urea transporters have been identified in the colon and kidney collecting duct (3, 54, 62, 66, 80). Urea transport processes (passive and active) can be induced in the collecting duct of rats fed a low-protein diet (32, 58, 66). Urea reabsorption from the mammalian urinary bladder has been observed in ground squirrels (24) and the bear (47).

The adaptive importance of renal urea transporters for purposes other than water conservation/osmoregulation is underscored by the observation that a similar transporter may exist in the freshwater trout (40). This fish demonstrates net tubular urea reabsorption against an apparent concentration gradient. Because, in freshwater fish, urea does not play any significant role in osmoregulation, the purpose of this reabsorptive process is unclear. Could the function of urea reabsorption in teleost fish be for nitrogen conservation?

![Fig. 1. Nitrogen metabolism (modified from Ref. 34).](http://ajpregu.physiology.org/DownloadedFrom/10220033.5)
A specific urea transport protein has also been described in mammalian liver (36), and it is believed that at least one function for this transporter is facilitation of the movement of urea, after its synthesis, out of hepatocytes and into the extracellular space. Menyhart and Grof (43) demonstrated that urea, even at concentrations as low as 8.3 mmol/l, produced significant inhibition of argininosuccinate lyase, one of the urea-ornithine cycle enzymes. Although ammonia is generated intramitochondrially in the liver, the final steps in urea synthesis, including the reaction catalyzed by argininosuccinate lyase, occur within the cytosol (15). Given the observation by Menyhart and Grof, the hepatic urea transporter could actually function as a regulator of ureagenesis by controlling the cytosolic concentration of urea. Klein et al. (36) also reported that the hepatic urea transport protein was significantly increased in abundance in rats made uremic by five-sixths nephrectomy. The physiological interpretation of this observation is not entirely clear. Klim et al. (37) described increased urea production from alanine or glutamine in isolated hepatocytes from uremic rats, whereas Cano et al. (16) reported decreased ureagenesis from these same substrates in isolated rat hepatocytes from their uremic animals (compared with controls in both cases). Even though the experimental designs differed, it is difficult to resolve the discrepancy between these results. If hepatic urea production is increased in chronic uremia, then upregulation of the urea transporter would be an appropriate adaptive response.

In humans, over the range of protein intakes in which daily urea production per kilogram of body weight is constant, there is an inverse relationship between intake and rate of urea hydrolysis (per kg body wt) and a positive relationship between intake and urea excretion per kilogram of body weight (17, 33).

Only limited urea kinetic studies have been done in other mammals (except the bear; see American black bear), but the results are consistent with the observations in humans. For example, in muskrats (14), the rate of urea hydrolysis was 67% higher in fall and winter, when forage protein levels are lowest, than in spring and summer. Herbivores such as the 13-lined ground squirrel and the Wyoming ground squirrel (24) have much higher levels of urea hydrolysis than the carnivorous badger (24) and the American marten (26). There is also good evidence in humans that a significant fraction of nitrogen released by intestinal hydrolysis can be used for synthetic processes other than the resynthesis of urea (21, 34, 38, 42, 50). That is to say, intestinal hydrolysis is not simply a “futile” process for cycling urea but should be considered a nitrogen salvage system contributing to “effective nitrogen intake” (33). The overall excretion/conservation of nitrogen involves the coordination of multiple processes such as GFR, urea reabsorption in the kidney collecting duct and urinary bladder, and transport of urea into the bowel.

In summary, mammals possess a set of biochemical/physiological processes that link energy flux, protein metabolism, and renal excretory functions. A component of the linkage involves urea transporters in the colon, kidney, liver, and probably urinary bladder, which regulate nitrogen excretion/conservation in response to changes in dietary protein intake.

The signals by which these interdependent processes communicate are unknown. There is circumstantial evidence (65) that ammonia might be a signal molecule mediating adjustments in GFR in response to changes in amino acid oxidation (i.e., urea production).

An additional constraint that relates to the capacity of structural elements in a set of physiological/biochemical processes needs to be introduced. A scaling analysis of oxygen supply during maximum performance in mammals has led to the principle of symmorphosis (30, 60). Symmorphosis postulates that the structural design of components comprising a system is matched quantitatively to functional demand (30). Applying this principle to the mammalian metabolic/renal set of functions, one would expect the magnitude of GFR (the scaling exponent of which is composed of the exponents for two structural parameters: glomerular number and capillary surface area) (64) to be appropriate for metabolic needs and not to contain a large excess capacity. This expectation will be addressed in ANIMALS WITH A HIGH PROTEIN INTAKE, in which we examine the features of animals adapted to a high protein intake.

ANIMALS WITH A HIGH PROTEIN INTAKE

Can we establish a measure of how much GFR is appropriate for metabolic needs? Because metabolic demand relates to the rate of amino acid catabolism, whole body protein turnover or rate of urea production would be the best measure. Unfortunately, comparative animal data available for these functions are very limited. There are considerable data on urinary nitrogen excretion that could be used as an index of amino acid deamination/oxidation, because in mammals, urea nitrogen comprises the bulk of urinary nonprotein nitrogen (2). However, because a variable fraction of urea is transported into the bowel, where it is hydrolyzed, urinary nitrogen excretion will underestimate the extent of amino acid deamination. From a renal perspective, the net rate of urea (nitrogen) excretion will be a function of the rate of filtration less the rate of reabsorption in the collecting duct (32, 58, 66) and, possibly, the bladder (24, 47). Collecting duct urea reabsorption is increased in animals fed a low-protein diet (32, 58, 66). Because filtration is clearly the predominant process in the excretion of urea, and with the above qualifications in mind, the GFR-to-urinary nitrogen excretion ratio will be used as a crude global measure of the match between glomerular function and metabolic demand. For mammals, in general, what would be the expected value for this ratio; i.e., how much GFR does the “typical” mammal have for each gram of nitrogen excreted per day? There are several approaches to this question.
From the allometric equations in Table 1, for a mammal on a practically nitrogen-free but energy-complete diet, the value would be 32.7 (4.78/0.146) ml·min GFR⁻¹·g N excreted⁻¹·day⁻¹. However, this value would probably be close to the upper limit in mammals. If, instead, we use the allometric equations for urea production and GFR (Table 1) and assume that 70% of urea nitrogen is excreted in the urine [30% of urea being hydrolyzed in the bowel (17)], then the ratio would be 13.1 (4.78/0.36) ml·min GFR⁻¹·g N excreted⁻¹·day⁻¹. Finally, blood urea levels have been measured in many mammals (human, cow, dog, goat, guinea pig, horse, rabbit, rat, sheep, pig, and elephant) spanning a large size range and average 2–10 mmol/l (63, 67). This range of blood urea concentrations is probably related to the protein content of the diet. With the use of a GFR predicted by the allometric equation (Table 1) and the assumption that all urinary nitrogen is in the form of urea and urea clearance is ~50% of GFR (51), in a mammal of given weight, e.g., 70 kg, a blood urea concentration of 2 mmol/l would correspond to a ratio of 25 ml·min GFR⁻¹·g N excreted⁻¹·day⁻¹ and a blood urea concentration of 10 mmol/l would correspond to a ratio of 5 ml·min GFR⁻¹·g N excreted⁻¹·day⁻¹.

Thus the design feature of a typical mammal eating its usual diet would include a GFR of 5–25 ml·min⁻¹·g N excreted⁻¹·day⁻¹ and a blood urea concentration of 2–10 mmol/l. If an animal increases its protein intake, the amount of urea nitrogen to be excreted would increase. The GFR-to-urinary nitrogen excretion ratio would fall unless GFR increased commensurate with the augmented nitrogen load. A fall in the ratio would be reflected by a rise in the blood urea concentration. Data in the literature indicate that the metabolic demands imposed by an increase in protein intake are not matched by an increase in GFR.

As reviewed by Brenner et al. (7), acute or chronic increases in protein intake can increase GFR 40–150% above baseline values. For example, GFR was ~70% higher in rats maintained on a 35% protein chow than in rats fed a 6% protein chow. Harbor seals can have a threefold increase in GFR several hours after a fish meal (28). However, GFR is not able to increase commensurate with metabolic demand. In dogs fed a meat meal (10 g/kg), GFR increased on average by 39% acutely, but plasma urea concentration increased an average of 67% acutely, indicating that the change in GFR was not sufficient to maintain a constant plasma urea level (48). The same observation has been made in adult men who were studied not acutely but over 2-wk periods after a change in protein intake (13). Urea clearance increased by 87% above baseline when protein intake was increased from the lowest level (zero) to the highest level (44 g/day). However, plasma urea concentration also rose by 165% above baseline, indicating that the change in GFR was not commensurate with the increase in urea synthesis. All these observations indicate a limited capacity of GFR to respond to increases in metabolic demand created by increases in protein intake and are consistent with the principle of symmorphosis. Because protein intake (and, hence, required nitrogen excretion rate) can be increased more than GFR, what is the lower limit of the ratio (GFR/urinary nitrogen excretion) that is tolerated in nature? In other words, from an evolution/natural selection perspective, how much mismatch between metabolic demand and glomerular function is allowed when this mismatch is created by a primary increase in metabolic demand?

There are several small mammals that naturally ingest a high-protein diet. The limited data available for these mammals in terms of nitrogen excretion and GFR are sufficient to allow us to estimate GFR-to-urinary nitrogen excretion ratios.

Marten and white-tailed prairie dog. Harlow and Buskirk (26) measured nitrogen metabolism in martens and white-tailed prairie dogs before and during a fast. Before fasting, the martens and prairie dogs were maintained on ad libitum food and water. Mean body mass was 1.2 and 1.15 kg for the prairie dog and marten, respectively. GFR, measured as creatinine clearance, was 5.06 and 2.46 ml/min in the marten and prairie dog, respectively. Harlow and Buskirk measured daily urine urea excretion, and the values before fasting were 65 and 15 mmol/day for the marten and prairie dog, respectively. If we assume that urinary nitrogen is entirely accounted for by urea nitrogen, the GFR-to-urinary nitrogen excretion ratios are 2.78 (5.06/1.82) and 5.86 (2.46/0.42) ml·min⁻¹·g N⁻¹·day⁻¹ for the marten and prairie dog, respectively. These ratios are associated with blood urea concentrations before fasting of 16.2 and 12.1 mmol/l in the marten and prairie dog, respectively. Both of these animals do not hydrolize urea within the intestine (24, 26), but detailed urea kinetic measurements have not been made. About 5% of injected labeled urea is hydrolized in both animals.

Vampire bats. Vampire bats are nocturnal and forage once nightly, during which time the vampire bat engorges itself with blood until it is satiated. McFarland and Wimsatt (41) studied selected aspects of renal function in a colony of vampire bats fed bovine blood once a day. The rapid ingestion of blood results in a 30–40% increase in body weight, which can hinder the bat’s flying ability. The vampire bat shows almost instantaneous micturition with feeding and can achieve peak urine flow rates of 4.0 ml·kg⁻¹·min⁻¹ within 30 min after starting a feed. This osmotic diuresis is probably due to the rapid absorption of plasma fluids during feeding (with extracellular volume expansion) and is followed by a phase of water conservation. This phase is necessitated by the high insensible water loss and the fact that vampires do not utilize free water, even if it is available in their roosts. For example, 7 h after a meal, urine osmolality can reach 4,600 mosM, with urine urea concentrations of ~3,000–3,500 mmol/l.

Average blood intake was 11.6 g in this colony of bats (26 g mean body wt). Solids comprised 2.5 g of the blood meal, and protein represented 86% of these solids. Hence, these bats consumed 2.2 g of protein, which
would contain 0.35 g of nitrogen. [Protein is ~16% nitrogen (23).] If it is assumed that the bats are in nitrogen balance, then average daily nitrogen excretion would be 0.35 g.

Unfortunately, McFarland and Wimsatt (41) did not measure GFR. The GFR predicted for a 26-g mammal by the allometric equation (Table 1) is 0.29 ml/min. An indirect check on whether this value is reasonable can be done as follows.

Because the scaling exponent for GFR is a combination of the exponents for two structural parameters [glomerular number and glomerular capillary surface area (64)], an indirect answer would involve comparing actual bat kidney weight with that predicted by the mammalian allometric equation.

Horst (31) found that vampire bats with a mean body weight of 30 g had an average kidney weight of 197 mg. With the use of Stahl's mammalian allometric equation for kidney weight (69) (Table 1), a 30-g mammal would have a single-kidney weight of 185 mg. Because the vampire bat does not have a kidney much larger than that of a similar-sized mammal, its glomerular number and glomerular capillary surface area would probably be as predicted allometrically. Thus it is probably reasonable to assume that the bat's GFR is no higher than that given by the mammalian allometric equation. The bats studied by McFarland and Wimsatt (41) would have a GFR-to-urinary nitrogen excretion ratio of 0.83 (0.29/0.35) ml·min⁻¹·g N excreted⁻¹·day⁻¹.

In these bats, blood urea concentrations ranged from 27 to 57 mmol/l, depending on whether feeding had occurred 24 h or 30 min before the measurement (41). Clearly, this ratio (0.83) is insufficient to maintain blood urea concentrations within the normal mammalian range (2–10 mmol/l).

Harlow and Braun (25) measured intestinal urea hydrolysis in the vampire bat and observed an extremely low rate. This observation is consistent with the postulate that high rates of urea hydrolysis function to conserve nitrogen in mammals exposed to a low protein intake (25); hence, a high rate would be unnecessary in the vampire bat, considering its enormous protein intake.

In summary, the vampire bat has a nitrogen excretion rate ~33 times larger than it would have on a nitrogen-free diet with apparently little comparable adjustment in its GFR above that for mammals of similar size.

**Shrew**. Shrews are small highly active mouselike mammals. Measurement of RMR in these animals is difficult because of their activity and excitability, and values have been obtained that are about two to three times that predicted by the mammalian allometric equation (10, 19, 39). Shrews have voracious appetites and consume ~70% of their body weight in food daily (18). The shrew feeds on a wide variety of common insects. The prey of the shrew is ~30% solid (39), and ≥50% of this solid portion is protein (10). Buckner (10) measured urinary nitrogen excretion rates in four species of shrew. The results for daily nitrogen excretion were 0.075 g for *Suncus cinereus* (3.6 g body wt), 0.140 g for *Suncus arcticus* (5.4 g body wt), 0.086 g for *Microsorex hoyi* (3.5 g body wt), and 0.130 g for *Blarina brevicauda* (20.1 g body wt).

If it assumed that protein is 16% nitrogen (23) and that these animals are in balance, these excretion rates are equivalent to protein intakes of 2,800–11,340 g in a 70-kg animal. Unfortunately, no measurements of GFR are available for the shrew. However, kidney weight is available for several different shrews, and as an indirect answer (as used for the vampire bat), we can compare actual kidney weight with that predicted by the mammalian allometric equation.

The Etruscan shrew (2.45 g body wt) and the musk shrew (8.95 g body wt) have kidney weights (both kidneys) of 0.047 and 0.14 g, respectively (5). The allometric equation (Table 1) predicts combined kidney weights of 0.044 and 0.13 g for a 2.45- and 8.95-g mammal, respectively, values very close to those of the shrew. Again, as reasoned for the vampire bat, because the shrew kidney is not much larger than the kidney of a similar-sized mammal, its glomerular number and glomerular capillary surface area would probably be as predicted allometrically. The shrew's GFR is probably close to that predicted by the allometric equation.

For the four species studied by Buckner (10), the calculated ratios using a GFR as predicted by the allometric equation would be 0.84, 0.61, 0.71, and 1.82 for *S. cinereus*, *S. arcticus*, *M. hoyi*, and *B. brevicauda*, respectively.

No measurements of plasma urea concentrations are available for the shrew, but because the vampire bat with a comparable GFR-to-urinary nitrogen excretion ratio cannot maintain a blood urea concentration <27 mmol/l, the prediction would be that the shrew would have a similar blood urea concentration. No measurements of rates of urea hydrolysis in this mammal are available.

Table 2 summarizes the results for these small mammals as well as data for a typical mammal. Although the ratio range for mammals in general is quite broad (i.e., 5–25), the values for the vampire bat and shrew clearly fall well below this range. For these mammals, a huge protein intake has increased urea excretion. In the vampire bat, intestinal hydrolysis is suppressed, and since there has not been a commensurate upward adjustment in GFR, blood urea concentrations have also significantly increased. Because the blood urea concentration is inversely related to the GFR-to-urinary nitrogen excretion ratio, it is not unreasonable to speculate that the vampire and the shrew may be approaching the lower limit of this ratio. The vampire bat with a ratio of ~0.8 has blood urea levels chronically between 27 and 57 mmol/l. The shrew with a ratio of 0.6 most likely has an even higher concentration.

These observations raise a number of questions with respect to current concepts of chronic renal failure.

First, by definition, the vampire bat and, most likely, the shrew suffer from azotemia. In these two mammals, the mismatch between metabolic demand and GFR is due to a large increase in the former. In patients with chronic renal failure, the mismatch be-
However, despite continual amino acid oxidation/with a high protein intake as a percentage of production.

The observations in the shrew and vampire bat challenge this concept. These two mammals should have chronic hyperfiltration due to their high protein intake; yet there is no evidence that either develops progressive renal failure. Vampire bats are known to live up to 19.5 yr (75), and histological studies of the kidney make no mention of glomerular sclerosis (57). How then do these mammals avoid renal failure, given their exposure to a potent and persistent hyperfiltration stimulus? This ability is even more incredible, given that there are natural examples in which hyperfiltration does lead to kidney damage. The spawning Pacific salmon develops an extreme protein catabolic state attributed to hypercorticoidism (55, 78), and this state is associated with progressive glomerular sclerosis (56). Uncovering how the vampire bat and shrew have adapted to a chronic hyperfiltration stimulus could conceivably lead to the development of interventions for the prevention of chronic renal failure.

American black bear. Unlike the vampire bat and shrew, which have adapted to a protein-rich diet, the American black bear has adapted to diametrically different conditions, which could be considered analogous to chronic renal failure. This mammal survives winter for up to 5 mo at near-normal body temperature without eating, drinking, urinating, or defecating (1). During this dormant period, RMR decreases by ~50% (44) and GFR by ~70% (9) compared with the active state. However, despite continual amino acid oxidation/deamination with urea production and complete reabsorption of urine by the bladder, the plasma urea concentration actually falls and lean body mass is maintained (4, 9, 47).

The key to the bear’s adaptation to a prolonged fast is its ability to completely recycle urea nitrogen and utilize the nitrogen for protein synthesis. The blood urea (in mg/dl)-to-creatinine (in mg/dl) ratio has traditionally been used as an indicator of total protein catabolism (26). Although many species of mammals undergo fasts of long duration at specific times in their lives, most show no change or an increase in the blood urea-to-creatinine ratio when fasting (52). The decline of the blood urea-to-creatinine ratio to <10 during a prolonged fast is probably unique to the bear family [American black bear, polar bear, and grizzly bear (4, 46, 52)]. Barboza et al. (4) compared urea kinetics and protein turnover rates between autumn hyperphagia and winter dormancy in the black bear and grizzly bear. Urea production in winter was ~17% of that in autumn, reflecting a diminished rate of deamination/oxidation of amino acids.

In autumn, ~7.5% of produced urea was hydrolyzed in the intestine and just >1% of the released nitrogen was used for protein synthesis. In contrast, in dormant bears, virtually 100% of the urea produced was hydrolyzed and all the nitrogen was reutilized for synthesis. Whole body protein turnover rates were similar between autumn and winter. Nelson (44) extensively studied nitrogen metabolism in the black bear, and the data indicate that urea nitrogen is recycled through essential and unessential amino acids and plasma protein and back into urea. It is not clear whether the bear utilizes metabolic pathways present in all mammals. Wolfe et al. (77) speculated that the bear may have pathways for recycling urea nitrogen other than intestinal hydrolysis, and the ability of the bear to synthesize essential amino acids from urea nitrogen may be unique (44).

Harlow et al. (27) and Tinker et al. (71) measured muscle function and structure in hibernating black bears, and the results are consistent with the metabolic adaptations described by Barboza et al. (4) and Nelson (44). Although inactivity in humans, for example, as a result of confined bed rest, leads to skeletal muscle atrophy and impaired strength, the black bear does not suffer a similar deterioration. Dormant bears

---

Table 2. Nitrogen metabolism/excretion features in a “typical” mammal and in mammals with a high protein intake

<table>
<thead>
<tr>
<th></th>
<th>Typical Mammal</th>
<th>White-Tailed Prairie Dog</th>
<th>Marten</th>
<th>Vampire Bat</th>
<th>B. brevicauda</th>
<th>S. arcticus</th>
<th>S. cinereus</th>
<th>M. hoyi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass, g</td>
<td></td>
<td>1,200</td>
<td>1,150</td>
<td>26</td>
<td>20.1</td>
<td>5.4</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Ratio</td>
<td>5–25</td>
<td>5.86</td>
<td>2.78</td>
<td>0.83</td>
<td>1.82</td>
<td>0.61</td>
<td>0.84</td>
<td>0.71</td>
</tr>
<tr>
<td>Blood urea concn, mmol/l</td>
<td>2–10</td>
<td>12.1</td>
<td>16.2</td>
<td>27–57</td>
<td>1.82</td>
<td>0.61</td>
<td>0.84</td>
<td>0.71</td>
</tr>
<tr>
<td>%Intestinal hydrolysis</td>
<td>20–55†</td>
<td>~5*</td>
<td>~5*</td>
<td>0*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Ratio, GFR (ml/min) ÷ urinary nitrogen excretion (g/day). †Percentage of injected urea hydrolyzed to CO₂.
lose <23% of muscle strength over 130 days, whereas humans would suffer an estimated 90% strength loss over the same period (27). Muscle structure and protein content were studied by taking (muscle) biopsies in hibernating bears during early and late winter (71). There was a modest net loss of muscle protein during hibernation, but it was not as great as predicted from small mammal hibernator and immobilization disuse models. On the other hand, muscle fiber number and cross-sectional area were unchanged, and there was only a small change in the proportion of slow-twitch aerobic fibers to fast-twitch anaerobic fibers. Clearly, bears employ a unique physiological strategy to maintain muscle tone during extended periods of inactivity while in hibernation (71), and one mechanism is synthesis of new amino acids and protein from urea nitrogen (27, 44).

The bear’s proficiency in fully reutilizing urea nitrogen while undergoing a prolonged fast appears to be unparalleled. In other mammals, fasting is associated with less-complete nitrogen conservation adaptations, although the data are limited. In humans, a 96-h fast did not lead to any significant changes in urea production or hydrolysis compared with a standard food intake of 1.2 g protein·kg⁻¹·day⁻¹ (29). Cahill et al. (11) studied six normal men who fasted for 8 days. Blood urea levels increased ~30% by day 4 and then fell back to baseline. Urinary nitrogen excretion displayed parallel changes. Blood urea-to-creatinine ratios remained unchanged at 25 at baseline and day 8. Hence, in both of these studies, short-term fasting was not associated with increased nitrogen conservation. In contrast, a 7-day fast in the golden-mantled ground squirrel (70) was associated with a 60% reduction in urea excretion and a 10-fold increase in urea hydrolysis, changes indicative of enhanced nitrogen conservation.

Owen et al. (49) studied 11 obese subjects who fasted for 5 wk. Liver and kidney metabolism were carefully studied during this period. Estimated glucose production after 5 wk of starvation was significantly reduced to 86 g/day. Approximately all the lactate, pyruvate, glycerol, and amino acid carbons that were removed by the liver and kidney were converted to glucose. Although urea kinetics were not measured, urea production and hydrolysis can be estimated from the collected data. About 31% of the synthesized glucose was derived from amino acid carbons. The liver contributed ~55% and the kidney 45% to total glucose production. Because hepatic and renal blood flows were similar, as were splanchnic and renal arterial-venous differences for α-amino nitrogen concentrations, it can be assumed that the liver accounted for 17% (31 × 0.55) or 14.6 g of glucose derived from amino acids. This amount of glucose would be equivalent to a urea production rate of 4.3 g urea N/day, because the ratio of grams of glucose formed to grams of urea nitrogen is 3.40 (35). After 5 wk of fasting, mean urea nitrogen excretion was 1.55 g/day. Hence, urea kinetic parameters (in g urea N/day) in this group of subjects would be as follows: urea production = 4.3, excretion = 1.55 (36% of production), and hydrolysis = 2.75 (64% of production).

The average weight of the subjects at the end of the fast was 115 kg. With use of the allometric equation given in Table 1, an individual of this weight with a “normal” diet would have a predicted urea production rate of 19.1 g urea N/day. In summary, prolonged fasting (5 wk) in humans is associated with an estimated 77% reduction in urea production rate and an increase in hydrolysis from ~30% (29) to 64%. These changes would result in enhanced nitrogen conservation but not nearly to the same extent as that displayed by the bear.

In the bear, a preparatory phase for winter sleep occurs in early fall, when food is available (46). Such a phase is necessary, because the bear could not duplicate the dormant state during the summer when starved outside under ambient temperature or housed in winter sleeplike conditions (in the dark and in the cold) (47). However, there is no published information available as to how the bear switches metabolic pathways from the summer “active” state to the winter dormant state. Because a colonic urea transporter has been identified (54, 66, 80), one could speculate that upregulation of this transporter could increase movement into the colon and thus increase the extent of intestinal hydrolysis.

In summary, the bear during winter sleep adapts to a situation comparable to chronic renal failure. GFR is significantly reduced, and the small volume of urine formed is completely reabsorbed by the bladder. Urea production continues, but urea nitrogen is completely salvaged and reutilized for protein synthesis. How the bear accomplishes this feat is not well understood, but the relevance of these metabolic adaptations to possible treatments for renal failure in humans is obvious. However, as discussed in mammalian design features, nitrogen released by urea hydrolyzed in humans can be utilized for synthetic processes other than urea formation. For example, Meakins and Jackson (42) found that, in humans ingesting a 30-g protein diet, supplementation with oral urea doubled the rate of urea hydrolysis but did not increase endogenous urea production. Only 10% of the released nitrogen was used for urea reformation.

Perhaps the study that most directly addresses the question of chronic renal failure and urea nitrogen reutilization is that of Varcoe et al. (72).

Varcoe et al. (72) measured urea kinetics and incorporation of urea nitrogen into albumin in normal subjects and patients with chronic renal disease. The normal control group had a mean urea clearance of 49 ml/min and mean blood urea concentration of 3.6 mmol/l, whereas the patients with chronic renal failure had a mean urea clearance of 6 ml/min and a mean blood urea concentration of 25 mmol/l. In the normal group, ~0.2% of urea nitrogen released by hydrolysis was incorporated into albumin, whereas for patients with chronic renal failure the values were 0.68 and 1.66% when daily protein intake was 70 and 30 g, respectively.

In addition, absolute rates of urea nitrogen incorporation into albumin were in the same order: for pa-
patients with chronic renal failure, 99 and 61.1 μmol/h for protein intakes of 30 and 70 g, respectively, and for normal subjects, 6.4 μmol/h. Inasmuch as albumin synthesis represents ~5% of total body protein synthesis (22), if urea nitrogen were made available to general protein synthesis to the same extent as albumin synthesis, then ~4% of urea nitrogen could go to protein synthesis in normal subjects and 13.6 and 33% in patients with chronic renal failure on a 70- or 30-g protein diet, respectively.

In 1985, Nelson et al. (45) reported on the long-term dietary management of patients with chronic renal failure. Protein intake was 0.38 g·kg\(^{-1}\)·day\(^{-1}\), and 12 of 15 patients remained in this program for ≥2 yr. Baseline mean blood creatinine and urea values were 7.7 mg/dl (680 μmol/l) and 135 mg/dl (22.5 mmol/l), respectively. In the majority of patients, body weight increased, as did serum albumin. Basal metabolic rate remained within normal limits, but there was a significant decrease in the amount of protein used in basal metabolism. Blood urea-to-creatinine ratios declined during diet therapy, and in many of the patients the ratio fell to <10.

Do these observations of Varcoe et al. (72) and Nelson et al. (45) indicate that patients with chronic renal failure, particularly when ingesting a low-protein diet, undergo a bearlike adaptation? This is certainly an intriguing possibility but, at the moment, clearly speculative.

SUMMARY

In mammals, RMR, whole body protein and RNA turnover, urea production, GFR, and urinary nitrogen excretion constitute a set of broad interdependent functions. The signals coordinating these functions are unknown, but ammonia may be one of the signal molecules. Additional features can be added to this framework. A variable fraction of produced urea is transported to the colon, where it undergoes hydrolysis. Some of the ammonia released is reformed back into urea, but most is available for other synthetic processes. Urea excretion by the kidney depends on GFR less urea reabsorption in the distal nephron and bladder. Because urea transporters have been identified in the colon and nephron collecting duct, it is quite plausible to consider GFR plus colonic and collecting duct transport rates as a coordinated system for regulating nitrogen excretion/conservation. For mammals in general, the capacity of processes such as GFR is approximately matched to RMR, whole body protein turnover, and rate of urea production. It is apparent, however, that this matching has limits. In mammals, such as the vampire bat and shrew, which have an exceedingly high protein intake, GFR is not commensurate with the large urea load to be excreted. The vampire bat and probably also the shrew are azotemic. Blood urea concentrations are 27–57 mmol/l in the vampire bat but, unfortunately, have not been measured in the shrew. How have these animals adapted to an azotemic internal environment that would include not only high urea levels but probably also high ammonia levels? Why do these mammals not develop progressive renal failure given their exposure to an intense, chronic hyperfiltration stimulus? The American black bear, on the other hand, has adapted to a prolonged period without intake or urine output. Despite continued amino acid catabolism with urea production, this mammal is able to completely salvage and reutilize urea nitrogen for protein synthesis. It is not known what signals initiate this metabolic adaptation during the bear’s winter sleep or whether the bear possesses unique metabolic pathways not present in all mammals. Clearly, understanding the particular adaptations of the vampire bat, shrew, and bear to their unusual situations could lead to new interventions for the prevention and treatment of chronic renal disease. This approach underlies the principles of biomimicry. Biomimicry is the science that studies nature’s models and then imitates or takes inspiration from these designs and processes to solve human problems. After 3.8 billion years of evolution, nature has learned what works, what is appropriate, and what lasts (6).

REFERENCES

15. Campbell JW. Excretory nitrogen metabolism. In: Environmen-
tal and Metabolic Animal Physiology, edited by Prosser CL. New

16. Cano N, Catelloni F, Fontaine E, Novaretti R, DiCon-
stanzo-Dufetel J, Reynier JP, and Leverve XM. Isolated rat
hepatocyte metabolism is affected by chronic renal failure. Kid-

17. Child SC, Soares MJ, Reid M, Persaud C, Forrester T, and
Jackson AA. Urea kinetics varies in Jamaican women and men
in relation to adiposity, lean body mass and protein intake. Eur J

18. Churchfield S. The Natural History of Shrews. London: Helm,

19. Churchfield S. The Natural History of Shrews. London: Helm,

20. Cooper AJJ and Plum F. Biochemistry and physiology of

21. Danielsen M and Jackson AA. Limits of adaptation to a diet

22. Gersovitz M, Munro HN, Udall J, and Young VR. Albumin
synthesis in young and elderly subjects using a new stable
isotope methodology: response to level of protein intake. Metab-

23. Goodship THJ, Mitch WE, Hoerr RA, Wagner DA, Stein-
man TI, and Young VR. Adaptation to low-protein diets in

24. Harlow HJ. Urea hydrolysis in euthemeric hibernators and
non-hibernators during periods of food availability and depriva-

25. Harlow HJ and Braun EJ. Gastric Na+ K+ ATPase activity
and intestinal urea hydrolysis of the common vampire bat,
Desmodus rotundus. Comp Biochem Physiol 118A: 665–669,
1997.

26. Harlow HJ and Buskirk SW. Comparative plasma and urine
chemistry of fasting white-tailed prairie dogs (Cynomys leucu-
rus) and American martens (Martens americana): representati-

27. Harlow HJ, Lohuis T, Beck TDI, and Laizoo PA. Muscle

28. Hiatt EP and Hiatt RB. The effect of food on the glomerular
filtration rate and renal blood flow in the harbor seal (Phoca

29. Hibbert JM, Jackson AA, and Persaud C. Urea kinetics:
early, severely restricted dietary restriction and changes on urea hydrolysis.

30. Hoppeler H and Weibel ER. Limits for oxygen and substrate

31. Horst R. Observations on the structure and function of the
kidney of the vampire bat (Desmodus rotundus murinus). In:
Physiological Systems in Semiarid Environments, edited by Hoff
CC and Reidel JL. Albuquerque, NM: University of New

32. Isozaki T, Gillin AG, Swanson CE, and Sands JM. Protein
restriction sequentially induces new urea transport processes in
rat initial IMCD. Am J Physiol Renal Fluid Electrolyte Physiol

33. Jackson AA. Salvage of urea-nitrogen in the large bowel: func-
tional significance in metabolic control and adaptation. Biochem

34. Jackson AA, Picou D, and Landman J. The non-invasive
measurement of urea kinetics in normal man by a constant
infusion of 15N15N-urea. Hum Nutr Clin Nutr 38C: 339–354,
1984.

35. Jungs RL, Halperin ML, and Brosnan JT. Quantitative
analysis of amino acid oxidation and related gluconeogenesis in

JM. UT-A urea transporter protein expressed in liver: upregu-

37. Klim RA, Albajari M, Hems R, and Williamson DH. Effects of
chronic uraemia on the formation of glucose and urea plus
ammonia from l-alanine, l-glutamine and l-serine in isolated

38. Langran M, Moran BJ, Murphy JL, and Jackson AA. Ad-
apation to a diet low in protein: effect of complex carbohydrate
upon urea kinetics in normal man. Clin Sci (Lond) 82: 191–198,

39. Lindstedt SL. Energetics and water economy of the smallest

40. McDonald MD and Wood CM. Reabsorption of urea by the
kidney of the freshwater rainbow trout. Fish Physiol Biochem

41. McFarland WN and Wimsatt WA. Renal function and its
relation to the ecology of the vampire bat, Desmodus rotundus.

42. Meakins TS and Jackson AA. Salvage of exogenous urea
nitrogen enhances nitrogen balance in normal men consuming
225, 1996.

43. Menyhart J and Grof J. Urea as a selective inhibitor of

44. Nelson RA. Nitrogen turnover and its conservation in hiberna-
tion. In: Living in the Cold, edited by Malan A and Canguilh-

45. Nelson RA, Anderson CF, Hunt JC, and Margie J. Nutri-
tional management of chronic renal failure for two purposes:
postponing onset and reducing frequency of dialysis. In: Chronic
Renal Disease, edited by Cummings NB and Klahr S. New York:

46. Nelson RA, Beck TDI, and Steiger DL. Ratio of serum urea
to serum creatinine in wild black bears. Science 226: 841–842,
1984.

47. Nelson RA, Jones JD, Wahner HW, McGill DB, and Code
CF. Nitrogen metabolism in bears: urea metabolism in summer
starvation and in winter sleep and role of urinary bladder in
water and nitrogen conservation. Mayo Clin Proc 50: 141–146,
1975.

48. O’Connor WJ and Summerill RA. The excretion of urea by

49. Owen OE, Felig P, Morgan AP, Wahren J, and Cahill GF
Jr. Liver and kidney metabolism during prolonged starvation.

50. Picou D and Phillips M. Urea metabolism in m eu nished
and recovered children receiving a high or low protein diet. Am J

51. Pitts RF. Physiology of the Kidney and Body Fluids. Chicago, IL:

52. Ramsay MA, Nelson RA, and Sterling I. Seasoned changes
in the ratio of serum urea to creatinine in feeding and fasting polar

53. Reeds PJ and Lobley GE. Protein synthesis: are there real

54. Ritzhaupt A, Wood IS, Jackson AA, Moran BJ, and
Shirazi-Beechey SP. Isolation of a RT-PCR fragment from
human colon and sheep rumen RNA with nucleotide sequence
similarity to human and rat urea transporter isoforms (Ab-

55. Robertson OH, Krupp MA, Thomas SF, Favour CB, Hane
S, and Wexler BC. Hyperadrenocorticism in spawning migra-
tory and nonmigratory rainbow trout (Salmo gairdneri): com-
parison with Pacific salmon (genus Oncorhynchus). Gen Comp

56. Robertson OH and Wexler BC. Histological changes in the
organs and tissues of migrating and spawning Pacific salmon

57. Rosenbaum RM. Urinary system. In: Biology of Bats, edited


59. Schmidt-Nielsen K. Scaling: Why Is Animal Size so Important?

60. Schmidt-Nielsen K. Scaling: Why Is Animal Size so Important?


