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Author: S. Raidal and S. Echols
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The advantages and disadvantages of excreting uric acid

Shane R. Raidal, BVSc, PhD, FACVSc

School of Agriculture and Veterinary Sciences, Charles Sturt University, Wagga Wagga, NSW, 2650, Australia

M. Scott Echols, DVM, Diplomate ABVP- Avian Practice

Westgate Pet and Bird Hospital, 4534 Westgate Blvd, Suite 100, Austin, Texas 78745, USA.

Summary

To understand and diagnose renal disease in birds it is first important to understand the biochemical and physiological peculiarities of uricotely. The synthesis of uric acid and excretion of urine with a high protein component is a metabolically expensive strategy that must have significant trade-offs to birds and other animals that have chosen this pathway for excreting nitrogenous waste products. Birds rely heavily on post-renal modification of urine to conserve water and salt balance so it is important to remember that damage to organs other than the kidney may present with signs that might be otherwise attributable to renal dysfunction. In this paper we review the biochemical and physiological aspects of uricotely that are important for understanding the normal function of the avian renal system.

Body fluid regulation and nitrogenous waste excretion

Veterinarians graduate with a fairly good introduction to the physiology of the mammalian renal system but in the animal kingdom mammals are odd (Braun 1998; Raidal & Raidal 2006). They have the capacity to produce concentrated urine containing potentially toxic concentrations of soluble nitrogenous waste products as it leaves the kidney. Consequently the mammalian ureter and bladder have to be impermeable to both water and urea to prevent dilution of the urine and reabsorption of "excreted" waste. It is important to remember that there is no *post-renal* modification of mammalian urine and the need for other solute secretory organs such as salt glands is redundant. This is primarily made possible by the enhanced urine osmotic concentrating capacity

achieved by the anatomical differentiation of renal cortex and medulla along with the development of the loop of Henle to efficiently recycle soluble urea. Mammals have the clever advantage of being able to utilise urea as a major osmolyte for the actual process of concentrating urine. The mammalian kidney is thus an efficient primary organ of osmoregulation and nitrogenous waste excretion and whilst it has 4 main functions: the removal of nitrogenous wastes (principally urea); regulation of water balance and blood pressure; electrolyte homeostasis (particularly Na^+, K^+, Cl^- and Ca^+ ions); and acid-base homeostasis it is the first that identifies it as unique amongst the vertebrates.

Other vertebrates including birds utilise multi-organ osmoregulatory mechanisms with significant post-renal urine modification occurring to conserve water, ionic and pH homeostasis and nitrogenous waste excretion (Figure 1). As it reaches the cloaca urine is refluxed retrograde into the colon for resorption of water. If birds and reptiles excreted urea as the chief nitrogenous waste product it would just be reabsorbed from the cloaca and colon. Marine reptiles and birds also may possess nasal glands that excrete salt (Na^+ and Cl^- ions) to help them conserve water and sharks have rectal glands that perform a similar function. In fish the gills and the opercular epithelium are important excretory and osmoregulatory organs with the kidneys assuming a lesser role since they are able to excrete ammonia directly into the environment.

Elimination of nitrogenous wastes

Animals can be classed as ammonotelic, ureotelic or uricotelic, depending on whether they predominantly excrete ammonia or the more metabolically expensive but less toxic urea or uric acid, respectively. However, this can be a loose distinction since many have the capacity to excrete nitrogenous wastes in more than one form, or even all three when conditions are appropriate (Lee et al 1991, Lim et al 2004). These excretory strategies have evolved to deal with the elimination of ammonia (NH_3) which is a highly toxic byproduct of amino acid metabolism. Because it is a base, it rapidly accepts a H^+ ion to form ammonium (NH_4^+) at physiological pH and both NH_3 and NH_4^+ are toxic (Cameron and Heisler, 1983). Hydrated NH_4^+ has the same ionic radius as the hydrated K^+ ion, and due to their K^+-like behavior, NH_4^+ can affect the membrane potential of neurons and other cells (Binstock & Lecar, 1969; Cooper & Plum, 1987) as well as result in toxic accumulations of glutamine and disruption of essential cellular functions. Across the animal kingdom the ammonia concentration of body fluids is typically low (50–400 μmol/L) (Cooper and Plum, 1987; Cameron and Batterton, 1978; Weihrauch et al., 2004) and concentrations exceeding 1 mmol/L total ammonia (NH_3 and NH_4^+) are usually toxic to mammalian cells (Hrnjez et al., 1999).

Reptilian type nephrons

To understand the avian kidney it is important to have some knowledge of reptilian-like nephrons. Like in birds the kidneys of reptiles are the chief site of osmoregulation and nitrogenous waste excretion. And there is significant post-renal modification of urine in the cloaca and or the urinary bladder, in those reptiles that have one. Reptilian nephrons have an incipient juxta-glomerular apparatus, some aglomerular nephrons, and a thin very short intermediate segment which connects the proximal and distal convoluted tubules. In reptiles (Bradshaw & Bradshaw 2002; Mahlmann et al 1994), and birds, arginine vasotocin (AVT) is the predominant antidiuretic hormone of the 10 neurohypophyseal hormones reported in other species (arginine vasopressin, arginine vasotocin, lysine vasopressin, glumitocin, aspartocin, valitocin, isotocin, oxytocin and mesotocin). AVT may have a dual effect in the reptilian kidney, first to dilute the urinary fluid in the thin-intermediate segment, prior to its entering the collecting duct system, and then facilitating water reabsorption along an osmotic gradient as the urine passes through the final segments of the nephron. The intermediate segment may thus prove to be the evolutionary homologue of the thin-ascending limb of the loop of Henle in the mammalian and avian kidney (reference?).

The relative length of the distal tubules is longer in reptiles adapted to dry environments and tubular reabsorption of fluid is primarily from the distal segments of the nephron. In freshwater turtles, the diuretic frusemide produces diuresis by doubling urine volume and increasing Na^+, Cl^- and K^+ excretion principally by inhibiting tubular reabsorption in the distal segments of the nephron (Stephens & Robertson 1985). Turtles also lack a tubular mechanism for altering renin release but there is a well-developed renin angiotensin system in reptiles (Cho et al 1987; Cipolle & Zehr 1984; Wilson 1984). Seasonal variations in renin levels in relation to the physiological phase of the animals: active animals demonstrated high renal and plasma renin concentration, while lower values were obtained in hibernating animals (Vallarino 1984).

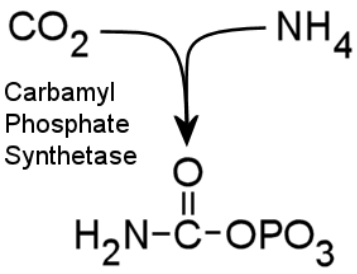
The turtle urinary bladder is analogous to the collecting and distal tubules of the mammalian kidney and it has been used frequently as an experimental model in renal physiology (Drenckhahn et al, 1987; Henke et al., 1990). The epithelium of both the turtle bladder and the mammalian collecting duct can generate a steep gradient for H^+ ions between blood and urine. Secretion of H^+ into the urine is coupled to a basolateral efflux of HCO^-_3 that appears to be exchanged mainly against Cl^-. Knowledge of the large urinary bladders in terrestrial chelonids extends back to 1676 when the Parisian comparative anatomist Claude Perrault, observed the extraordinary size of the urinary bladder in the Indian giant tortoise (Jérgensen 1998). During arid conditions desert chelonids do not void but store urine in the bladder where urine osmolality gradually rises. Potassium ions are precipitated with uric acid as urates and the bladder can thus function both to store nitrogenous waste and K^+ as well as water which can be reabsorbed as needed. However, plasma osmolality gradually rises (Dantzler & Schmidt-Nielsen, 1966) mostly due to and increase in urea concentration. Urine is only voided following rain when copious drinking restores bladder volume with hyposthenuric urine. In 1799 Townson observed that dehydrated freshwater turtles imbibed water by anal drinking (Jérgensen 1998) but more recent evidence indicates that this is not a method of hydration but rather so that the urinary bladder can supplement respiratory exchange of O_2 and CO_2 (King & Heatvole 1994a,b).

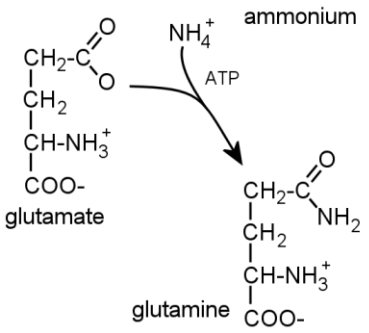
Uricotely in birds and reptiles

In reptiles and birds excretion of ammonia is achieved via the amino acid (& neurotransmitter) glutamate via its conversion to glutamine, glycine and aspartate for incorporation into the purine synthetic pathway. This pathway is much more energy expensive than the urea cycle of mammals with the main advantage being the excretion of relatively insoluble nitrogen-rich uric acid which is not reabsorbed from the cloaca in the adult or from the allantois in the avian embryo. In the egg urate occurs, not as a watery colloid gel as in the adult but as a crystalline anhydrous deposit in the allantois. This permits efficient recycling of the transporting water and electrolytes and segregation of nitrogenous waste material. If urea, about 40,000 times more soluble than uric acid, was the main nitrogenous waste product in avian and reptilian embryos it would readily diffuse back into the blood in potentially toxic concentrations.

Detoxification of ammonia

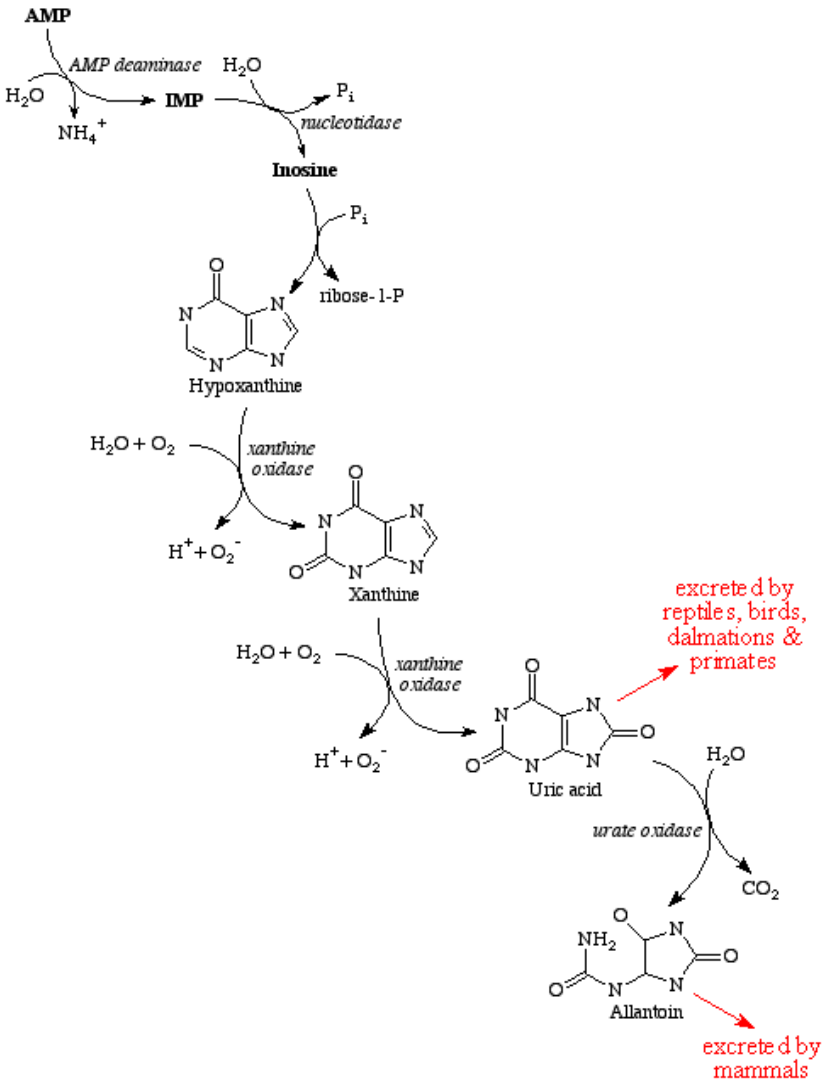
In contrast to mammals the primary ammonia-detoxifying enzyme in avian liver is mitochondrial glutamine synthetase (GS) and it is broadly distributed throughout most hepatocytes (Smith & Campbell 1988), much like its counterpart carbamoyl-phosphate synthetase I (CPS) in mammalian liver. With CPS, mammals are readily able to detoxify NH_4 by converting it, along with two molecules of ATP and one molecule of CO_2 into carbamyl phosphate which combines with ornithine to enter the urea cycle as citrulline. Birds lack mitochondrial CPS and so are unable to fuel the urea cycle in the same manner as mammals. Birds instead use their mitochondrial GS to convert ammonia into glutamine. Both citrulline (mammals) and glutamine (birds) leave the mitochondria where they are then converted into urea and uric acid, in mammals and birds, respectively.





Mammals **Birds**

In mammals it is a then a relatively simple process to produce urea via the intermediates of arginosuccinate and arginine. The final step which cleaves arginine into urea and ornithine is catalysed by the enzyme arginase and the regenerated ornithine can re-enter the mitochondria thus completing the urea cycle. It takes 3 molecules of ATP to produce one molecule of urea but there is efficient recycling of substrates and the by-product of 2 NADH molecules from the conversion of glutamate to NH_4^+ and α-ketoglutarate and the recycling of fumarate into malate can regenerate ATP. In effect the urea cycle releases slightly more energy than it consumes. In contrast the production of uric acid is a relatively complex and energy expensive process consuming 5 molecules of ATP.



Note that the predominant site of uric acid synthesis in birds is the hepatocyte and that xanthine oxidase is an important cytoplasmic enzyme that is required first for the conversion of hypoxanthine to xanthine and then for converting xanthine to uric acid. Presumably avian hepatocytes have high concentrations of this enzyme so it may well be that measurement of plasma xanthine oxidase activity could be a sensitive & specific measure of hepatocellular damage in birds.

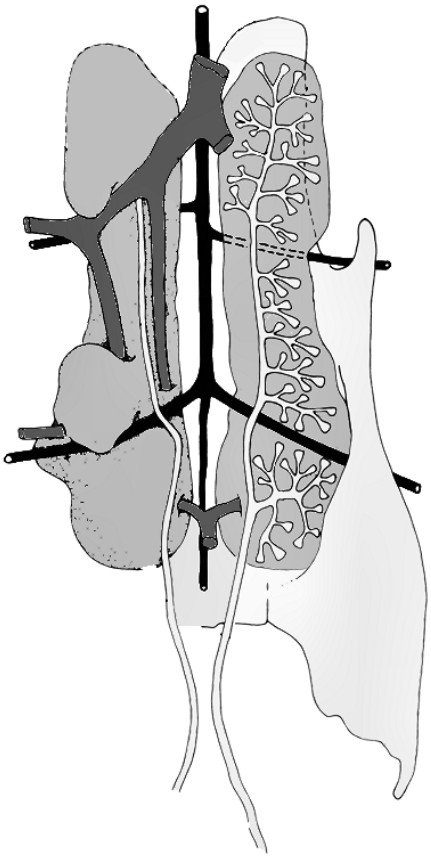
The urea cycle in birds

It is important to note that birds do not lack any of the urea cycle enzymes and arginine, an essential amino acid in birds, can still be broken down by arginase to form urea. However, avian arginase is predominantly mitochondrial and not cytoplasmic as in mammals and the highest concentrations occur in the kidney rather than the liver (Traniello et al 1975; Kadowaki et al 1976; Kadowaki &

Nesheim 1978). Avian arginase can be upregulated in birds fed high protein diets and is inhibited by ATP so when energy is not limited urea is not produced (Ruiz-Feria et al 2001; Koutsos et al 2001). In low ambient temperatures some birds may conserve energy by increasing urea excretion and lowering uric acid excretion, hummingbirds can even excrete up to 50% of waste nitrogen as ammonia provided that water intake is not limited (Preest, & Beuchat, 1997; van Tets et al 2001; Roxburgh & Pinshow 2002; McWhorter et al 2003).

In birds and reptiles most of the amino nitrogen and all of the purine nitrogen is excreted as uric acid (mainly by the liver) which at physiological pH forms soluble salts (urates) with ammonia, Na^+, or K^+ ions. The molecule is relatively insoluble and this is a relatively risky property for a waste product that has to be transported in the plasma from the liver to the kidney. Once it reaches the kidney uric acid is actively excreted by the tubular epithelial cells. Most birds excrete about 80% of renal nitrogen as dihydrates of uric acid in a supersaturated colloidal suspension with the remainder excreted as urea or ammonium which enters the urine by glomerular filtration. Avian urine contains about 5 mg/mL of protein which helps, at a metabolic expense, to maintain uric acid in colloidal suspension. These can be seen microscopically as spheres of variable size but usually measuring 1-2 µm in urine and faecal wet-preps. The spheres are made of lamellated colloidal material that sequester Na^+ and K^+ and which does not contribute to the urine osmotic pressure. The osmolality of the carrier fluid component is largely due to Na^+, K^+ and Cl^- . So this is why urine specific gravity measurements are not a reliable indicator of "urine concentration capacity" in birds. Also during times of dehydration, the urine can be refluxed from the cloaca into the colon for further water reabsorption. In a bird that is polyuric it is worth checking the faeces for evidence of retrograde urine reflux by looking for urate spheres in faecal wet-preps and they can also be seen in caecal contents, in those birds that have caeca (Roberts & Baudinette 1984).

Avian renal anatomy

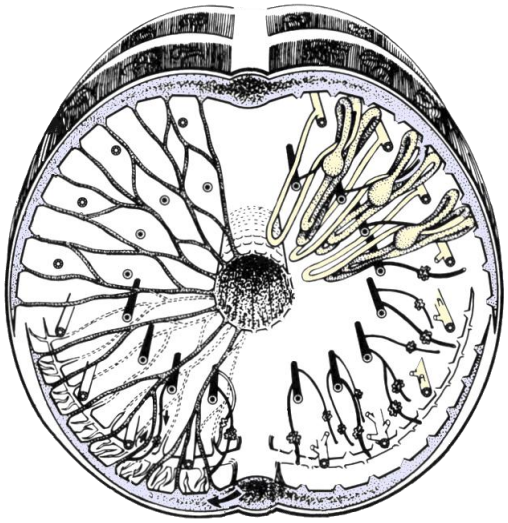


For a comprehensive review of the comparative renal anatomy of invertebrates and vertebrates see Holz & Raidal (2006). In birds, the kidneys lie symmetrically in the renal fossae of the synsacrum and extend as far as the lungs cranially and to the end of the synsacrum caudally (Getty 1975). They are covered by a thin peritoneal serosa except in extremely obese birds are surrounded by invaginations of the abdominal airsac. The kidneys of birds are relatively larger than the kidneys of mammals and comprise 1-2.6% of avian body weight compared to only 0.5% of mammalian body weight. Each kidney is divided into cranial, middle and caudal divisions or lobes that are supplied by major blood vessels although in most passerines the middle and caudal lobes are fused. In other species such as

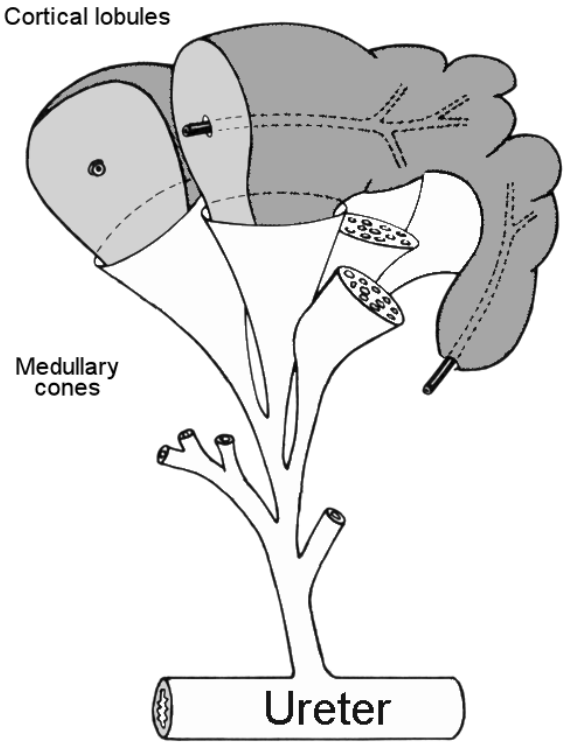
herons, puffins and penguins there may be fusion of the left and right caudal lobes. Within each renal lobe there are 13 to 17 lobules, separated by interlobular veins.

Classical regions of renal cortex and medulla can be difficult to identify grossly in each lobe because cortical-type tissue predominates but medullary cones can be identified histologically. Each medullary cone receives collecting ducts from several adjacent lobules and the collecting ducts coalesce to form medullary collecting ducts. These ducts then combine from several adjacent lobules into a single cone shaped collecting duct and the lobules that drain into this duct together comprise the renal lobe. These large collecting ducts coalesce to form the ureter which is thus branched to service each medullary cone. The avian kidney thus resembles a series of ice-cream cones lined up in parallel rows.

The ureter lies on the ventral surface of the kidney in association with the blood vessels, except in the cranial division where it is embedded into the parenchyma. Distally, the ureter empties into the urodeum. There is no urinary bladder to store urine instead much of the fluid is refluxed into the coprodeum and from there into the lower alimentary tract. The one exception is in the ostrich whereby the coprodeum does not receive faeces but instead functions like an absorptive reptilian-like urinary bladder with final modification of urinary solutes occurring here. This is facilitated by a well-developed recto-coprodeal sphincter. Ostriches thus can pass 2 types of droppings, one containing faeces and one containing just urine (Deeming 1999).



Birds have two types of nephrons (Dantzler 1985). The cortical nephron is similar to the reptilian nephron because it lacks a loop of Henle, has a short intermediate segment and is oriented perpendicular to the collecting duct. The medullary nephron has a loop of Henle inserted between the proximal and distal tubule and is similar to mammalian nephrons being arranged parallel to the collecting ducts. In the different species proportions vary from 10% mammalian-type nephrons in Gambel's quail (*Callipepla gambelii*) up to 30% in European starlings (*Sturnus vulgaris*). The appearance of a loop of Henle means that birds, like mammals, can produce urine that is



hypertonic compared with blood.

The kidney is provided with arterial blood via the cranial, middle and caudal renal arteries, which provide blood to the cranial, middle and caudal kidney lobes respectively. These branch to form intralobular arteries, which give rise to the afferent arterioles. The efferent arterioles empty into the peritubular capillary plexus, which drains into the intralobular veins.

The cranial and caudal renal portal veins form a ring that encompasses both kidneys by joining the external iliac and caudal renal veins. Venous blood enters this ring via the internal vertebral venous sinus, the caudal mesenteric vein, external iliac veins, ischiadic veins, and internal iliac veins. The afferent renal branches leave this ring and penetrate the renal parenchyma where they become the interlobular veins, which drain into the peritubular capillary plexus. From here blood enters the intralobular veins, efferent renal veins and finally the cranial and caudal renal veins. These open into the common iliac vein (Canny 1998).

The renal portal valve is situated within the common iliac vein. When this valve is open blood is diverted away from the kidneys into the caudal vena cava, and when it is closed blood is shunted through the kidneys. The valve is inhibited by adrenaline and stimulated by acetylcholine (Benson & Forest 1999).

Avian renal physiology

At first reckoning avian kidneys seem to have a *limited capacity* to concentrate urine compared to mammals. There are two types of nephron, each composed of a glomerulus and a tubular system. Cortical or reptilian type nephrons (RTNs) are the main type (60 to 90%) and they lack a loop of Henle. Juxtamedullary or mammalian type nephrons (MTNs) are less numerous, they possess a loop of Henle with thick and thin limbs; convoluted proximal and distal tubules; and are arranged parallel to each other, their loops of Henle are bound with the vasa recta into medullary cones to allow for countercurrent exchange. Thus, urine can be concentrated to some extent as it passes through the loop of Henle. In contrast RTNs are not arranged in parallel and are confined to the renal cortex, they can only produce urine which is isotonic or hypotonic to plasma. However, all collecting ducts pass through a medullary cone in their path towards a ureteral branch, so that urine can be concentrated to some extent, regardless of which nephron it originated from. Desert-dwelling species generally have more MTNs (up to 40%) than birds with ready access to water. Many desert and water bird species also have a nasal gland which actively secretes salt. In these species the nasal gland is the major site of sodium ion secretion. Sea-birds can survive by drinking salt water and may refuse to drink fresh water.

Individual avian nephrons have a low GFR compared to mammals but the number of nephrons per kidney is much higher in birds so that overall GFR is similar. Normally more than 95% of the water of the original filtrate is reclaimed by tubular reabsorption. Variations from this are achieved by regulation of GFR or reabsorption both of which are controlled by AVT. AVT release from the neurohypophysis is stimulated greatly by a rise in ECF osmolality but only moderately by a decrease in ECF volume, such as due to haemorrhage. Considerable recent research has been done to investigate the value of using AVP in mammals with hypovolaemic shock (Lurie et al 2002; Voelckel et al 2003). In birds that have experienced blood loss or injury AVT or AVP may prove to be a treatment for restoring blood pressure and improving survival rates. This is because AVT release from the neurohypophysis is stimulated greatly by a rise in ECF osmolality but only moderately by a decrease in ECF volume, such as due to haemorrhage. Endotoxin induced pyrexia also significantly increases circulating AVT concentrations in ducks (Gray & Maloney 1998) which led to speculation that it might have some antipyretic action. Alternatively such elevations might be involved in stimulating the pituitary-adrenal (PA) axis. As in some mammals (Oritz et al 2003) it is noteworthy that AVP is a potent stimulator of the PA axis in pigeons (Westerhof et al 1996) and it might prove to be a safer way of increasing circulating endogenous corticosterone concentrations as an alternative to exogenous glucocorticoids in those clinical situations where such treatment may be warranted.

It is also worth noting that AVT is also responsible for controlling ovipositioning in hens with the highest concentrations associated with the onset of uterine contractions. In this respect AVT does the function of mesotocin which is the avian equivalent of oxytocin (Goldstein & Skadhauge 1999).

The avian nephron has a juxtaglomerular complex and with salt and volume depletion this releases renin to stimulate the conversion of angiotensin-I to angiotensin-II which promotes aldosterone mediated Na^+ absorption, K^+ excretion, decreased GFR and decreased urine flow. Unlike in mammals the alternative release of aldosterone from the adrenal gland is not stimulated directly by elevations in blood K^+. Birds also produce atrial natriuretic peptide which acts to increase Na^+ excretion.

The renal-portal system is a feature which birds share with reptiles (Goldstein & Skadhauge 1999).. It consists of a ring of veins which receive blood from the pelvic limb, colon and some of the structures in that region. The renal-portal ring is connected to the hepatic portal system, the caudal vena cava and the intervertebral venous sinuses. The renal-portal system is separated from the systemic circulation by a valve which is innervated by adrenergic and cholinergic fibers. When the valve is closed it prevents blood from directly entering the caudal vena cava and therefore most of the blood enters the kidney or the hepatic portal system. Much of the blood flows into the kidneys, where it mixes with arterial blood from the efferent glomerular arteriole and participates with perfusion of the peritubular network but does not supply the glomeruli. Up to two thirds of the blood supply to the kidney comes via the renal portal system and up to 50% of renal blood flow can come from the ischiac and external iliac veins (Goldstein & Skadhauge 1999)..

In response to hypovolaemia, shock or with sympathetic stimulation (ie flight or fight response) the valve opens and blood is diverted into the vena cava. The plasma osmolality rises and stimulates AVT which causes constriction of the afferent glomerular arterioles of the RTNs. Thus the nephrons with the least capacity to concentrate urine are no longer functioning. The shunting of blood to the peritubular network, allows the kidney to continue excreting uric acid even though the GFR is greatly reduced. The MTNs, not all of which are functional during normal hydration are recruited so that glomerular filtration occurs in those nephrons best capable of producing concentrated urine.

The high protein diet of carnivorous birds such as raptors and penguins leads to them having higher reference blood uric acid ranges and postprandial elevations can also occur. Avian urine is usually acidic because there is very efficient reabsorption of bicarbonate (Goldstein & Skadhauge 1999).

Dehydration usually does not notably elevate blood uric acid concentrations until GFR is decreased to the point that uric acid is not able to be flushed through the nephron. Dehydration can be difficult to assess in birds because even in closely related some species the primary effect may be haemoconcentration or a rise in plasma osmolarity. In one study that compared the effects of water deprivation between a desert adapted quail species (stubble quail) and a closely related but wet grassland adapted quail species (king quail) the desert adapted species was better able to cope with dehydration in terms of being able to maintain normal plasma osmolarity but still had evidence of haemoconcentration (Roberts & Baudinette 1984). The king quail on the other hand suffered considerable weight loss associated with a 20% rise in plasma osmolarity after a much shorter period of water deprivation (Table 1) and could not survive even when green food was supplemented in the face of total water deprivation. Stubble quail, on the other hand, were able to survive and maintain body weight without the availability of drinking water, providing supplementary green food was provided.

Table 1. The effects of water deprivation on body weight and plasma ionic concentrations in stubble quail (*Coturnix pectoralis*) and king quail (*Coturnix chinensis*) fed seed only for 20 days (Roberts & Baudinette 1984)

	Stubble quail (n=8)	**King quail (n=16)**
Days without water	20	10
Body weight	85.6	80.5
Plasma osmolarity	101.2	119.9
PCV	115.5	102.1

Plasma Cl^-	100	115.9
Plasma Na^+	115.8	96.6
Plasma K^+	134.8	127.4

* Note that final values are expressed as a percentage of original values.

The kidneys, intestinal tract, salt glands, skin and respiratory tract all contribute to osmoregulation in birds.

Conclusion

The avian renal system is perhaps the most divergent from mammals and the underlying physiology and biochemistry of uricotely needs to be understood by the avian clinician in order to investigate the pathophysiology of renal failure. Mammalian concepts such as pre-renal, renal and post-renal azotaemia may not be applicable to birds because they have unique physiological mechanisms that are counter-intuitive to such paradigms. In most cases of hyper-uricaemia in birds the lesion will reside in the kidney.

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