



Salt, hypertension and chronic kidney disease



Scott A. Brown, VMD, PhD, Dipl. ACVIM

College of Veterinary Medicine, University of Georgia, Athens, Georgia, USA

Dr. Brown received his veterinary degree in 1982 from the University of Pennsylvania. He completed an internship and residency in Small Animal Internal Medicine at the Teaching Hospital of the University of Georgia in 1986 and received Board Certification in Internal Medicine from the American College of Veterinary Internal Medicine in 1987. From 1984 to 1989, Dr. Brown received a PhD in Renal Pathophysiology from the University of Georgia. Since 1989 Dr. Brown has been a faculty member of the University of Georgia with a joint appointment in the Department of Physiology and Small Animal Medicine where he is currently a Professor of Physiology. His research interests are progression of chronic kidney disease and systemic hypertension.

It has been proposed that high blood pressure, high salt (NaCl) intake, and extracellular fluid volume expansion might be linked in cats with chronic kidney disease (CKD). Sodium and chloride are the major electrolytes of extracellular fluid and generally restricted to this fluid compartment. Thus, changes in total body NaCl content eventually lead to corresponding changes in extracellular fluid volume. Since extracellular

fluid volume is a major determinant of the level of blood pressure, the regulation of body NaCl content is a central factor in control of blood pressure. Because of the importance of body NaCl content, it is not surprising that salt balance is very complex, depending on renal, hormonal, and neural regulatory mechanisms.

Changes in body NaCl content are caused by net differences between intake and output. There is, unfortunately, very little physiologic regulation of gastrointestinal intake or fecal output.

Thus the central mechanisms for sodium regulation reside in the kidney, where variations in NaCl input lead to compensatory alterations in urinary excretion (1). While the ability of the kidney to maintain total body NaCl balance is an inherent renal mechanism, it can be modulated by a variety of neurohumoral factors and by disease processes. For example, there are volume sensors in the atria, right ventricle, and a variety of blood vessels. The distension of these volume receptors (usually due to expansion of the extracellular fluid volume) leads to increased renal sodium excretion, mediated by secretion of atrial natriuretic hormone and also by alteration in renal nerve activity. There are additional key hormonal factors that regulate renal handling of NaCl. These include angiotensin and aldosterone, both of which decrease renal sodium excretion.

As noted above, cats with CKD have a high prevalence of systemic hypertension (2,3). Since changes in renal function can alter blood pressure through effects on sodium excretion and body fluid homeostasis, it has been hypothesized that dietary salt supplementation could aggravate hypertension in cats with CKD by inducing volume expansion.

Indeed, the effects of dietary NaCl intake on blood pressure have been studied. In many strains of rats with reduced renal mass, high NaCl intake increases blood pressure and this is referred to as salt-sensitivity (4). However, some strains of rats are salt-insensitive (5) as their kidneys are able to compensate for alterations in NaCl intake, preventing a change in blood pressure. Interestingly, most people are relatively salt-insensitive as well. Studies in normal dogs demonstrate that increasing NaCl intake from 8 to 120 $\mu\text{mol}/\text{kg}$ does not affect blood pressure, suggesting that normal dogs are salt-insensitive (6). This means that in normal dogs, regulation of body NaCl content by the kidney is efficient and capable of responding appropriately to changes in NaCl intake. While it could be surmised that dogs with CKD might be salt-sensitive, experimental studies of dogs with induced azotemia similar to IRIS Stages II and III CKD indicate that this is not the case (7), since variation in NaCl intake failed to affect blood pressure. While it is likely there will be individual animal variation due to genetic, environmental, and disease factors, normal dogs and dogs with stages I-III CKD appear unlikely to be particularly salt-sensitive.

What about cats with CKD? Are they salt-sensitive like certain rat strains or are they more similar to dogs and people? In a recent experimental study of induced azotemia similar in degree to IRIS Stages

II and III CKD in cats, salt intake had no effect on blood pressure (8). Further, the lowest level of NaCl intake was associated with the lowest values for GFR, inappropriate hypokalemic kaliuresis, and activation of the renin-angiotensin-aldosterone system. These findings of salt insensitivity of blood pressure were remarkably similar to those observed in normal cats (8). Taken together, studies in dogs and cats suggest that neither blood pressure nor systemic hypertension are salt-sensitive in either species. As both sets of study subjects had azotemia similar to Stage III or earlier CKD, more studies are needed to determine if cats or dogs with Stage IV CKD are also salt-insensitive.

It was not surprising that dietary NaCl restriction activates the renin-angiotensin-aldosterone axis in cats with CKD as this hormonal system acts to prevent changes in body sodium balance. While activation of this hormonal system minimizes effects of salt restriction on blood pressure, angiotensin II (9,10) and aldosterone (11,12) may cause cardiac and renal fibrosis and contribute to the progression of CKD. Potentially deleterious effects of activation of this hormonal system deserve attention in our clinical patients. Certainly, inhibitors of the renin-angiotensin-aldosterone axis, such as ACEI and/or antagonists of receptors for aldosterone or angiotensin II, should be considered whenever low NaCl intake is utilized.

REFERENCES

1. Brown SA, Brown CA, Jacobs G, et al. Effects of the angiotensin converting enzyme inhibitor benazepril in cats with induced renal insufficiency. *Am J Vet Res* 2001; **62**: 375-383.
2. Elliott J, Barber PJ, Syme HM, et al. Feline hypertension: clinical findings and response to antihypertensive treatment in 30 cases. *J Small Anim Pract* 2001; **42**: 122-129.
3. Syme HM, Barber PJ, Markwell PJ, et al. Prevalence of systolic hypertension in cats with chronic renal failure at initial evaluation. *J Am Vet Med Assoc* 2002; **220**: 1799-1804.
4. Sterzel R, Luft FC, Gao Y, et al. Renal disease and the development of hypertension in salt-sensitive Dahl rats. *Kidney Int* 1988; **33**: 1119-1129.
5. Rapp JP. Development of inbred Dahl salt-sensitive and inbred Dahl salt-insensitive rats. *Hypertension* 1987; **9 Suppl 1**: 1-21-23.
6. Krieger JE, Liard JF, Cowley AW. Hemodynamics, fluid volume, and hormonal responses to chronic high-salt intake in dogs. *Am J Physiol* 1990; **259**: H1629-H1636.
7. Greco DS, Lees GE, Dzendzel G, et al. Effects of dietary sodium intake on blood pressure measurements in partially nephrectomized dogs. *Am J Vet Res* 1994; **55**: 160-165.
8. Buranakarl C, Mathur S, Brown SA. Effects of dietary sodium chloride intake on renal function and blood pressure in cats with normal and reduced renal function. *Am J Vet Res* 2004; **65**: 620-627.
9. Mezzano SA, Aros CA, Droguett A, et al. Renal angiotensin II up-regulation and myofibroblast activation in human membranous nephropathy. *Kidney Int Suppl* 2003, pp. 39-45.
10. Weber KT, Brilla CG. Myocardial fibrosis and the renin-angiotensin-aldosterone system. *J Cardiovasc Pharmacol* 1992; **20 Suppl 1**: 48-54.
11. Sato A, Saruta T. Aldosterone-induced organ damage: plasma aldosterone level and inappropriate salt status. *Hypertens Res* 2004; **27**: 303-310.
12. Zhou X, Ono H, Ono Y, et al. Aldosterone antagonism ameliorates proteinuria and nephrosclerosis independent of glomerular dynamics in L-NAME/SHR model. *Am J Nephrol* 2004; **24**: 242-249.