RENAL AUTOREGULATION consists of several mechanisms that cooperate to keep renal blood flow constant in situations of changing renal perfusion pressure. Adaptations of the tone of renal resistance vessels elicited by alterations in renal perfusion pressure also buffer alterations in glomerular capillary pressure and, consequently, protect the glomerular filtration rate against the volatility of systemic arterial blood pressure. Two mechanisms predominantly account for the renal autoregulatory capacity: the myogenic response and tubuloglomerular feedback (TGF) mechanism. The myogenic response, also known as the Bayliss effect, is characterized by the rapid contractile response of vascular smooth muscle cells when intravessel pressure increases. This mechanism is not specific for the kidney and, with a few exceptions, is observed in most other vascular beds. The TGF mechanism is kidney specific; this component of renal autoregulation links the tubular salt concentration at macula densa cells of the thick ascending limb of Henle’s loop to preglomerular resistance. Thus, when the tubular salt (respective chloride) concentration at the macula densa increases, a signaling cascade is initiated that results in an increase in the afferent arteriole tone and eventually in a compensatory decline in the single nephron filtration rate. Compared with the myogenic mechanism, the TGF response mediates the slow component of renal autoregulation with a response time in the range of 20–30 s.

The mechanisms of renal autoregulation have been studied intensively, although less progress has been made in assessing the systemic conditions that may interfere with the intrarenal autoregulatory system. In a recent issue of the American Journal of Physiology-Renal Physiology, Fellner et al. (4) contribute to this field by addressing the influence of a chronic high-salt diet on the renal autoregulatory capacity. When rats were fed a diet containing 8% NaCl (compared with 0.8% NaCl in the control group), the autoregulatory capacity of the kidney was largely compromised, as determined in vitro using an elegant isolated perfused juxtamedullary nephron preparation. This result was confirmed in vivo by measurements of the glomerular filtration rate and renal blood flow after manipulation of renal perfusion pressure. Moreover, the autoregulation in rats that received a high-salt diet was largely restored in the presence of apocynin. Based on the data, the authors suggested that NADPH oxidase-dependent formation of ROS is causally involved in the impairment of renal autoregulation during high oral salt intake. However, there has been some controversy regarding the specificity of apocynin, as this drug was suggested to be inefficient in inhibiting NADPH oxidase in endothelial and vascular smooth muscle cells, due to the low conversion of the compound into the active dimer (5). In this case, apocynin may instead serve as an antioxidant and a scavenger of peroxides. Regardless of the exact mechanism for the effect of apocynin, it appears likely that the formation of ROS is crucially involved in the desensitization of renal resistance vessels during high salt intake.

Although clearly beyond the scope of this study, it remains to be determined what the mechanistic link may be among high-salt diet, the formation of ROS (and other potential mechanisms acting in parallel), and compromised autoregulatory capacity. Assuming that hormones account for this linkage, the relevant hormone should fulfill at least two prerequisites: 1) its generation should depend on oral salt intake and 2) it should affect the formation of ROS in blood vessels (or at least in close proximity to blood vessels) and/or should modulate vascular constrictor reactivity. Atrial natriuretic peptide (ANP) and ANG II may represent such hormones, among many others. Indeed, ANP levels are increased, whereas ANG II levels are decreased, during a high-salt diet compared with a standard diet. Furthermore, ANP may inhibit or enhance the formation of ROS, depending on the cell type (3, 7), although the effect on renal endothelial and vascular smooth muscle cells remains unclear. In contrast to ANP, ANG II is known to increase oxidative stress [which would not meet the above criteria because ANG II levels are low during a high-salt diet (1)], and low ANG II levels may compromise vascular reactivity. Thus, pharmacological inhibition of the renin-angiotensin system or genetic ablation of the ANG II type 1 receptor may blunt TGF-mediated control of preglomerular resistance and, consequently, eliminate the slow component of autoregulation. In this context, the TGF mechanism was estimated to contribute ~50% to the total renal autoregulatory capacity (6).

The question that arises is what is the evolutionary advantage that may have led to the development of reduced renal autoregulation, when the salt intake is high? The answer to this question is certainly speculative, but Fellner et al. (4) suggest that reduced autoregulation during a high-salt diet may support the renal excretion of large amounts of salt to eventually facilitate salt homeostasis. This assumption appears very reasonable, although it implicates the following problem: renal autoregulation serves to keep renal blood flow and glomerular filtration constant over a wide range of different renal perfusion pressures. In addition, renal autoregulation is a protective measure that buffers pressure peaks within the glomerular capillaries, which are prone to pressure-induced lesions. Thus, a deleterious impact on glomerular capillaries (and possibly the entire filtration barrier) due to reduced autoregulatory capacity may represent the price we have to pay for more efficient excretion of large amounts of salt. It should also be noted in this context that the use of rat chow containing 8% NaCl (7), although a common and reasonable experimental
approach to obtain clear results, most likely represents the upper limit of what is tolerated by the animal and, therefore, may indicate the end point of the regulatory range. Translated into the human situation, a diet containing 8% salt corresponds to a daily salt intake of ~50 g NaCl or more, which is substantially more than the estimated 5–12 g typically ingested in the Western hemisphere (2).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: H.C. drafted manuscript; H.C. edited and revised manuscript; H.C. approved final version of manuscript.

REFERENCES


