The kidney and hypertension

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IN 1898, THE AMERICAN JOURNAL OF PHYSIOLOGY first went to press, Tigerstedt and Bergman (36) published experiments suggesting the existence of a humoral substance of renal origin that induces hypertension (see also Ref. 27). Initially, not much attention was paid to these experiments using a cold-water extract from the kidney of a rabbit injected into the jugular vein, but today very many studies published in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology address the plentiful actions of renin and its control (2, 7, 17, 20, 23, 32, 37, 38). Renin is the rate-limiting step in the production of angiotensin II from angiotensinogen. However, the plasma concentration of angiotensinogen is also important, because it is close to the Michaelis-Menten constant. Thus increases in circulating angiotensinogen augment renin and angiotensin II formation, which elevates blood pressure (18). In addition to the well-known direct vasoconstrictor action of angiotensin II, this peptide also exerts vasoconstriction via a central action at the nucleus of the solitary tract (31) or when microinjected into the rostral excitatory region of the ventrolateral medulla, the RVLM. This maneuver leads to a widespread activation of sympathetic vasomotor activity (10). Conversely, if injected into the caudal ventrolateral medulla, angiotensin II causes hypotension, probably by inhibition of the excitatory RVLM neurons (1).

The strongest stimulus for renin synthesis (28) and release (13) is a drop in renal perfusion pressure. This seems to suggest that the renin-angiotensin system (RAS) is important for maintaining sufficient filtration pressure. Moreover, the production of angiotensin II may also be of great importance for upholding blood pressure in the face of varying sodium intake (8). Hypertension caused by the renal release of renin may cause a vicious circle, because the kidney takes damage from the increased pressure levels, which further increases blood pressure. Accordingly, inhibition of angiotensin II decreases blood pressure, prevents renal lesions, and attenuates urinary protein excretion (4). Remarkably, to prevent renal damage in Lyon hypertensive rats, it is sufficient to block the RAS during a narrow therapeutic window, the phase of the sharp blood pressure increase (4). This is the latest phase in the postnatal development of rats that is characterized by an enhanced RAS (33). After discontinuation of RAS blockade, blood pressure takes on higher levels, whereas the development of glomerulosclerosis and urinary protein excretion remains blunted. This indicates that the RAS elicits histopathological changes in the kidney that may be independent of the hypertension (4).

The RAS is only one element of the control system network ultimately making the kidney a pivotal organ for blood pressure control. For instance, in addition to the various other actions of renin (5, 6, 14, 39, 40), it increases renal blood flow, glomerular filtration rate, urinary flow, and sodium excretion when its plasma concentrations are elevated. Furthermore, water intake and aldosterone release are under the control of AM (24, 35). The colocalization of AM expression and the expression of AM receptors in the kidney indicates an importance of AM in modulating renal function as an autocrine and/or a paracrine factor. In some forms of hypertension, plasma, urinary, and intrarenal AM peptide concentrations increase along with augmented levels of AM mRNA and AM receptor mRNA. This can be seen as an attempt to compensate for the malignant hypertensive state via hypotensive, natriuretic, and diuretic actions (25). Indeed, the control of natriuresis and diuresis are often regarded as the crucial step in the regulation of blood pressure by the kidney. Among the many controllers of volume and sodium excretion (3, 11, 15, 21, 26, 30), blood pressure appears to be among the most potent (22). The link between blood pressure and fluid and sodium excretion seems to be located in the renal medullary circulation, which is very particular in its control. When in the well-hydrated state, the renal medullary circulation loses its capacity to autoregulate (22). Accordingly, under these circumstances, hypertension will wash out the osmotic gradient, thereby limiting the amount of fluid excreted. Also, free radicals (9, 12, 29) play an important role in determining renal medullary hemodynamics as may renal nerves (16, 19). Intriguingly, a recent study by Szentesi et al. (29) suggests that NO is very important in counteracting the vasoconstrictor actions of ANG II on the renal medullary circulation (34). These investigators discovered an inherited defect in the ability of the Dahl salt-sensitive (S) rat to produce NO within the outer medulla of the kidney along with a failure of medullary NO concentrations to increase in response to ANG II in Dahl S rats. As a consequence, hypertension occurs in Dahl S rats with small elevations of circulating ANG II that have no effect in normal rats.

Taken together, over 100 years after the first experimental evidence showing that the kidney can influence blood pressure by a humoral factor, a bulk of
evidence now suggests that the kidney is fundamental in the control of blood pressure and the development of hypertension.

REFERENCES


