Renin

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THE RENIN-ANGIOTENSIN SYSTEM (RAS) has a central place in this journal because it integrates cardiovascular and renal function in the control of blood pressure and salt and volume homeostasis. The classical controllers of renin release from the kidney are the following.

First, the macula densa mechanism, which couples the tubular chloride concentration inversely to the plasma renin concentration (PRC) in the rat (13). Local changes in RAS help determine the sensitivity of the tubuloglomerular feedback mechanism and the set point for autoregulation of renal blood flow (29).

Second, the sympathetic nervous system, which stimulates renin secretion through β-adrenergic receptors on the juxtaglomerular cells (6).

Third, the pressure-sensitive mechanism for renin release, whose activation in vivo is associated with activation of the sympathetic nervous system (35) and release of hormones, such as oxytocin, which stimulate renin release in rats via a β-adrenergic receptor-dependent mechanism (10, 11).

Mice maintain a constant arterial pressure during alterations in sodium intake by changing the activity of the RAS, and when the RAS is clamped, the blood pressure becomes salt sensitive (5). Technically, it is important that in mice RAS activity is better correlated to PRC than plasma renin activity (PRA). Increasing sodium intake in conscious mice inhibits PRC, plasma ANG II, and aldosterone, but has no effect on PRA (5). In humans, too, a reduction in RAS activity after an oral salt load explains the adaptation of salt excretion to salt intake (1). In addition to its role in long-term salt homeostasis, the RAS defends cardiovascular function in acute hypotension and hypovolemia. Fainting in healthy volunteers after exposure to lower body negative pressure is associated with a sluggish response of the RAS (8).

Nitric oxide (NO) promotes salt excretion. Inhibition of NO synthase (NOS) in conscious dogs increases blood pressure and decreases salt and volume excretion independently of renin (25), and NO helps to prevent salt-sensitive hypertension in the Dahl salt-resistant rat and decreases salt sensitivity of blood pressure in the Dahl salt-sensitive rat (34). The importance of NO and RAS in pregnancy was emphasized by the demonstration of increased blood pressure in pregnant mice with deletion of the endothelial NOS gene or with four copies of the angiotensinogen gene or combinations of these (9). The effect of NO on salt excretion is probably not mediated by inhibition of renin secretion, because enhancing NO’s second messenger cGMP by inhibition of phosphodiesterase-5 stimulates renin secretion (27). The RAS and NO also interact in growth control. Thus pretreatment with NOS inhibitors prevents the ability of angiotensin-(1–7) to inhibit angiogenesis in the mouse (17).

In addition to salt excretion, water and sodium intake are also affected by the RAS: ANG II stimulates water intake, and thirst evoked by arterial hypotension in rats depends on pressure-sensitive renin release (30). Conversely, the ability of ANG II to stimulate thirst is inhibited by increases in arterial pressure (31). Administration of DOCA and intracerebroventricular infusion of renin result in elevated sodium intake (20).

Central administration of ANG II increased blood pressure in conscious rats (2) and sheep, where inhibition of renal sympathetic nerve activity and PRA was also seen (19). In conscious dogs with one kidney denervated, ANG II infusion caused sodium retention. Sodium excretion from the innervated kidney was lower, suggesting that baroreflexes inhibit renal sympathetic nerve activity during ANG II-induced hypertension and that, in the absence of these reflexes, ANG II had sustained renal sympathoexcitatory effects (14). The effects of ANG II on dog kidney function are not mediated by endothelin (3). In conscious rats, the gain of baroreceptor-mediated bradycardia is increased by blockade of brain AT2 receptors (36).

The constituents of the RAS are highly active in the fetal kidney. At embryonic day 14, the metanephros contains renin and ANG II and both ANG II receptors (AT1 and AT2). Renin is found in cells scattered within the mesenchyme (24). A functioning fetal and early postnatal RAS is a prerequisite for normal nephrogenesis in the rat. Insulin-like growth factor (IGF)-I may be critically involved in this process, because angiotensin-converting enzyme (ACE) inhibition suppresses renal IGF-I expression and treatment with IGF-I normalizes renal function and histology after early ACE inhibition (23). In fetal sheep, infusion of IGF-I increased renin synthesis and secretion (18). In the sheep
fetus, the concentrations of ANG I and renin are higher than in the ewe, whereas the ANG II concentration is comparable (22). Similar to the situation in the ewe, infusion of ANG II into the fetus increases blood pressure and lowers PRC and renin gene expression (21). The sympathetic control of renin secretion is functional in the sheep fetus, because denervation reduces the PRC, but it does not affect renal renin content or expression (7). Furthermore, denervation does not interfere with pressure control of renin release and synthesis (26). Asphyxia is another stimulator of renin secretion in the adult and has the same effect in fetal sheep (16). In hydropnephrotic neonatal rats, ANG II stimulates renal TGF-β1 expression through AT1 receptors and clusterin expression via AT2 receptors. The latter response is opposite to that of the adult rat, suggesting preponderance of AT2 receptors in the developing kidney (37).

Renin has been suggested to be involved in the hypertrophic responses in hypertension and heart failure, but renin is clearly not mandatory for this, because ventricular hypertrophy develops in a rat salt-overload model with a suppressed renin system and stimulation of the renin system by a low-sodium diet did not cause ventricular hypertrophy (12). In heart failure, the falling blood pressure and increased sympathetic activity activate the RAS, which contributes to the salt and water retention. In rats with heart failure induced by an aortocaval shunt, the activation of the sympathetic nervous system was blunted by injection of an AT1 antagonist into the nucleus of the solitary tract (NTS). Furthermore, that ANG II in the NTS contributes to the sympathetic activation (28). In dogs with pacing-induced heart failure, a fixed normal-level ANG II concentration led to a higher peripheral resistance, filtration fraction, and norepinephrine concentration. A further increase in ANG II led to antinatriuretic, sympathoexcitatory, and dipsogenic responses, suggesting that ANG II plays a critical role in the transition from compensated to decompensated heart failure (15).

Components of the RAS are also present and functional in fish. The angiotensinogen gene is expressed in kidney and liver of rainbow trout, and ACE inhibition causes vasodilation, an increased glomerular filtration rate, and decreased water reabsorption (4). On the other hand, there are also differences between fish and mammals: in seawater-adapted eels, infusion of an ACE inhibitor depressed drinking and arterial blood pressure independently of plasma ANG II (32). The response may be explained by the formation of bradykinin-like peptides, which unlike in mammals inhibit drinking and increase blood pressure in the eel (33).

REFERENCES


