Nitric oxide in the kidney

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BASTRON AND KALOYANIDES (2) had already investigated the effects of sodium nitroprusside in the isolated kidney 8 years before the postulate of an endothelium-derived relaxing factor was made by Furchgott and Zawadzki (14). More recent studies aim at the importance of nitric oxide (NO) for kidney development (36, 37) and kidney function during pregnancy, efferent and afferent renal nerve activity (21), renal hemodynamics (17) and excretion (26, 39), as well as renal injury and pathophysiology (6, 25).

Renal vascular resistance is low in pregnancy, possibly relying on NO (7, 20, 33), which could be released by relaxin (9). Hefer et al. (16) found that mice either deficient for endothelial NO synthase (eNOS) or over-expressing angiotensinogen and mice with mutations in both genes showed higher blood pressures throughout pregnancy compared with common laboratory strains (16). This increased blood pressure was not of renal origin; at least the measured renal functional parameters did not significantly change. At first sight, this might seem surprising: a reduced renal arterial smooth muscle cell contractility has been observed in pregnant rats. In these pregnant rats, unspecific inhibition of NO synthesis enhances renal vascular cell contraction contractility, presumably by increases of intracellular Ca$^{2+}$ concentration (30). NOS inhibition increases vascular resistance in many beds in the pregnant rabbit (3). It also abrogates the reduced myogenic reactivity of small renal vessels from gravid rats (15). The latter occurs without affecting myogenic reactivity in arteries from virgin animals (15). However, it seems that neuronal NOS (nNOS), and not eNOS, is the NOS isoform that helps maintain renal perfusion and filtration during pregnancy (1). As of yet, the relevance of NO for many kidney functions is not clear. For instance, NO has been reported to stimulate, inhibit, and to not change renin levels (23, 32). This might rely on the potential of NO to inhibit phosphodiesterase 3 (5, 35), which, in turn, degrades cAMP. Moreover, NO blockade increases blood pressure (4, 18, 41), which reduces renin release (34, 38) by a different mode of action than does NO.

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NO is also essential in regulating proximal tubular reabsorption of fluid, sodium, bicarbonate, and phosphate. NO controls most renal transporters and the permeability of the proximal tubule. Whether the renal tubules, particularly the proximal tubule, produce NO under basal conditions is still unclear. However, it seems that the proximal tubule is exposed to NO and...
that great amounts of NO are released by a variety of stimuli (25). This may also be of pathophysiological importance: enhanced production of NO, perhaps iNOS from macrophages, may participate in hypoxic/ischemic proximal tubular injury (25). Glomerular NO production is also increased by ischemia (40). In this context, NO seems to stem from the eNOS isoform and has a protective influence. Unspecific blockade of the NO isoforms enhances the severity of renal ischemia. A protective effect of NO in certain forms of renal failure is supported by experiments using vena cava occlusion (6). This procedure leads to acute renal failure by impairing renal venous draining. The renal outer medulla is pivotal in the pathophysiology of ischemic renal failure. The long-term outcome relies more on this region of circulation than on glomerular filtration. Remarkably, renal failure by vena cava occlusion is aggravated by NO depletion (6). N-acetyl-L-cysteine, a free radical scavenger, enhanced outer medullary blood flow in this model of renal failure and ameliorated the renal failure. The effect of the free radical scavenger, however, relied on an intact NO production (6).

Taken together, NO plays an important role for maintaining volume, electrolyte, and blood pressure homeostasis. This is brought about by controlling the local renal circulation, modulating renal efferent and afferent nerve activity, and by directly affecting the reabsorption of fluids and electrolytes. Changes occurring during pregnancy and in various pathophysiological states, such as acute renal failure or salt-sensitive hypertension, critically depend on the renal NO systems.

REFERENCES


