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, 29), 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 overexpressing 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 Ca2+ 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). Although nNOS inhibition does not alter basal renal blood flow in normal rats (19), this may be different in pregnancy, which would explain the insignificant changes of creatinine clearance in pregnant eNOS-deficient mice (16).

There can be little doubt that renal sympathetic efferent nerves are important for renal function (10, 11, 24, 27, 29). Conversely, many features of the kidney's afferent innervation are still being unraveled (21, 22). nNOS in the kidney is not only localized in the macula densa cells; the renal pelvis also seems to contain nNOS. It is colocalized with substance P and CGRP in renal pelvic sensory nerves (21). Release of substance P produced by increased renal pelvic pressure appears to enhance NO production, which, in turn, results in desensitization of substance P receptors via increased cGMP production. Activation of NO may function as an inhibitory neurotransmitter, regulating the activation of renal mechanosensory nerve fibers by mechanisms related to activation of substance P receptors (21). In theory, this mechanism is a second potential link between nNOS and renal functional changes that can be important during pregnancy or pathophysiological states.

The renal medullary circulation is important for blood pressure (12, 13) and fluid and electrolyte homeostasis (8). Reduction of medullary blood flow, e.g., by local infusion of nNOS antisense, can lead to salt-induced hypertension (28). However, salt-dependent hypertension is also found during inducible NOS (iNOS) inhibition. Moreover, the effect of blocking nNOS on blood pressure without any further challenge has been a matter of dispute (19, 31). Changes in local renal blood flow do not seem to occur when nNOS is blocked (19). An important role of medullary NO production might be associated with the activation of α2-adrenergic receptors: this NO release counteracts the vasoconstrictor effects of norepinephrine in the renal medulla, which is essential for the maintenance of renal medullary blood flow (42).

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.

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 NOS 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


