Physiological actions of renal collecting duct endothelin

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The contribution of endothelin to regulation of renal function under normal physiological conditions is unclear. Many cells in the kidney produce endothelin (9). Endothelin has been reported to have effects that both promote (2, 3, 5–7, 12–14, 16, 18) and reduce (2, 8, 13, 15) urinary sodium excretion and urinary volume. This may be due to the fact that endothelin exerts its effects via two receptor subtypes, ET\textsubscript{A} and ET\textsubscript{B} (4, 13). The fact that endogenously produced endothelin can act via two distinct receptors that have opposite effects has made it impossible to be certain whether endogenous endothelin is natriuretic or diuretic under physiological conditions, or how endothelin produced in specific nephron segments contributes to these processes.

In “Collecting duct-specific knockout of endothelin-1 alters vasopressin regulation of urine osmolality” the authors (3a) deleted the endothelin gene specifically from the collecting duct, thereby eliminating it as a source of endothelin, and tested the resulting effect on the ability of mice to excrete both acute and chronic water loads. Thus this paper demonstrates the technology to dissect the contributions of endothelin from different renal cell types under relatively normal circumstances. The authors found that mice with endothelin deleted from the collecting duct could not eliminate an acute volume load as well as wild-type mice, but there was no difference in the ability of the two strains to eliminate a chronic water load. Infusion of a selective V2 receptor agonist increased urine osmolality, aquaporin-2 phosphorylation, and V2 receptor expression to a greater extent in the knockout mice than the wild-type mice. The authors conclude that endothelin produced by the collecting duct functions as an autacoid to blunt the physiological actions of vasopressin.

Publication of the manuscript “Collecting duct-specific knockout of endothelin-1 alters vasopressin regulation of urine osmolality” represents a milestone in renal physiology for its specific conclusions regarding endothelin and more importantly for the technology that it demonstrates. Historically, we have been divided into two camps: those who study renal function using a reductionist approach using isolated cells and individual segments; and those who study renal function in vivo. The complexity of the kidney, with its nearly 20 different tissue types arranged in a complex geometry that also impacts on function, has slowed progress of both the reductionist and whole animal approaches to understanding the kidney. The advent of technology that allows manipulation of specific genes in specific tissues in the kidney held the promise of being able to study the role of a specific molecule in a specific tissue in renal physiology in vivo with geometry intact. Over the past few years, several advances have been made using such technology. The most rudimentary of these were knockout mice with deletion of a gene whose expression was limited to a few tissues in the body, such as the Na-K-2Cl cotransporter NKCC2. However, homozygous --/- mice were not viable and animals having only one copy of the NKCC2 gene had no overt phenotype (17). The next steps included overexpressing a specific gene such as the renin gene in the proximal tubule (10) and rescue of a deleted gene such as nitric oxide synthase 3 in the thick ascending limb (11). However, in these models, the transgene is not under the control of the native promoter. The potential of gene manipulation technology has now taken another significant step forward with the publication of “Collecting duct-specific knockout of endothelin-1 alters vasopressin regulation of urine osmolality” (3a) and “Collecting duct-specific knockout of endothelin-1 causes hypertension and sodium retention” (1) by the same group. These two papers demonstrate tissue-specific knockout of an autocrine/paracrine factor in the kidney and its physiological consequences. They unequivocally show that endothelin produced by the collecting duct promotes diuresis under physiological circumstances. Thus they move us a significant step closer to the ultimate goal of studying the physiological actions of a single protein in a single cell type at a specific point in time in vivo.

REFERENCES


