SIGNIFICANCE STATEMENT

Angiotensin-converting enzyme (ACE) can regulate inflammation through mechanisms independent of angiotensin II synthesis, and ACE's catalytic N- and C-domains can process substrates other than angiotensin I. The authors investigated the relative contributions of the N- and C-domains to the sodium retention and renal inflammation associated with diabetic kidney disease. They found that diabetic mice lacking a functional N-domain (NKO) had less sodium retention in response to a saline challenge, decreased activity of the epithelial sodium channel, and less renal inflammation compared with diabetic wild-type mice or diabetic mice lacking a functional C-domain. They also provide evidence that the protective NKO phenotype is mediated through accumulation of the anti-inflammatory tetrapeptide N-acetyl-seryl-asparyl-lysyl-proline. These findings suggest that blocking the ACE N-domain improves diabetic kidney disease independently of renal angiotensin II.