Learning from Failure: New Therapy for Diabetic Nephropathy and Beyond?

By David M. Pollock

I take only about 5 years after the discovery of the endothelin (ET) peptide to develop potent and selective endothelin receptor antagonists (ETRAs). This was about 20 years ago, and there are now two antagonists currently approved for use in pulmonary hypertension. Other targets have demonstrated tremendous promise in preclinical studies, but patient exp irations and failures in several clinical studies have discouraged most of the big pharmaceutical companies from further investigation of these drugs as therapies. The failures include a wide range of disorders, including heart failure, prostate cancer, and even resistant hypertension. The latter target remains a strong possibility, but unlikely because of financial reasons.

Endothelin-1 functions through ETA receptors primarily located on vascular smooth muscle to produce the well-known vasoconstrictor effects, but perhaps more importantly as a promoter of cell growth and inflammation. In healthy conditions, these effects are held in check by ETB-dependent vaso dilation and anti-inflammatory effects. Many investigators believe that the loss of this mechanism-based, given that other mechanisms must remain front and center in this saga of disease, including CKD.

References

David M. Pollock, PhD, is affiliated with the Section of Experimental Medicine in the Department of Medicine at Georgia Regents University in Augusta. He is president-elect of the American Physiological Society.