Interaction and sexual dimorphism of ETB/NOS signaling in cardiovascular and renal disease

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The renal collecting duct is critical in the fine-tuning mechanism of sodium homeostasis. ET, ETB receptors, and nitric oxide synthase (NOS) are all highly expressed in the collecting duct. Our laboratory is interested in the ET/ETB/NOS signaling mechanism regulating sodium homeostasis and blood pressure. Utilizing collecting duct-specific knockout mice, we found that collecting duct ET/ETB activation leads to the stimulation of collecting duct NOS1 pathway to mediate inhibition of sodium reabsorption via epithelial sodium channel activity, while vascular endothelial cell ET knockout mice do not activate collecting duct NOS1. Moreover, the collecting duct NOS1 pathway does not appear to regulate the ET/ETB pathway. The alternative splice variant, NOS1beta, is exclusively expressed in the collecting duct of mice. Thus far, our experiments have not detected a sexual dimorphism in the ET/ETB/NOS pathway in the transgenic mice. However, in rats distinct male and female regulatory pathways of ET/ETB signaling mediated sodium homeostasis are detected. ETA and ETB mediated natriuresis is present in female rats, while only ETB mediates natriuresis in male rats. NOS1 specific activity is significantly higher in female rats compared to male rats. However, NOS1 activity in male rats is ETB dependent while NOS1 activity in female rats is independent of the ET/ETB pathway. Collecting ducts in rats express two NOS1 variants, full-length NOS1alpha and NOS1beta. This difference in NOS1 activity and variant expression may mediate the sexual dimorphism observed in the ET/ETB mediated natriuresis in rats but not seen in mice. In conclusion, the ET/ETB/NOS signaling pathway is critical to maintain fluid and electrolyte homeostasis in both males and females.


Endothelin is getting older: How aging links endothelin with disease

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Aging is a physiological process reflecting the accumulation of changes responsible for the sequential alterations that accompany advancing age and the associated progressive increases in the chance of disease and death (PNAS 1991; 88: 5360). Accordingly, the American Heart Association has identified age above 45 years in men and above 55 years in women as an independent risk factor for cardiovascular disease. Within the last century life expectancy in man has doubled to more than 80 years. Increased longevity will result in an overall shift of the world population in the decades to come (Cardiovasc Res 2005; 66: 187) which will pose additional challenges to healthcare providers and societies.

Endothelin-1 (ET-1), a cytokine-like pro-inflammatory mitogen with vascular activity and predominant member of the endothelin peptide family, was discovered 25 years ago at the University of Tsukuba in Japan (Nature 1988: 332: 411). ET-1 not only has physiological functions such as embryonic development, nociception and natriuresis, but also contributes to disease progression – mainly via ETA receptor activation. The prevalence of vascular and renal disease in humans show a clear age-dependency (Nephrol Dial Transplant 2005; 20: 485), and GFR in humans decreases by 1% per year after age 45.

Research of the past decade has provided new insights into molecular mechanism underlying age-dependent changes in cardiovascular and renal physiology (Pflugers Arch 2010; 460: 825). It is now well established that cellular senescence is associated with an overall activation and production of pro-inflammatory cytokines and growth factors (including ET-1), which propagate the development of (patho-)physiological processes such as vascular hypertrophy, cardiomyocyte injury, renal cell injury, and sarkopenia, among others. New research indicates that aging-associated cellular changes are not inexorable, but that aging – similar to arterial hypertension and obesity – can be considered a modifiable risk factor (JCI 2013; 123; 906), in which molecular mediators such as peptides with cellular and vascular activity may also be involved.

Indeed, preclinical studies targeting either cellular activity or production of ET-1 – using ERAs or ARBs, respectively – have demonstrated that aging-associated changes in vasculature and kidney can indeed be reversed in part (Hypertension 2004; 44: 974; Nephrol Dial Transplant 2006; 20: 485), suggesting that the endothelin system plays an important role in aging physiology and cellular senescence. The clinical implications of these findings and interventions to promote healthy aging starting in youth will be discussed.

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Endothelin-1 over-expressed mice

Development of osteoarthritis-like changes in transgenic Chunyi Wen1, LimCho Steven Pei2, Baretella Oliver2, Sookja Kim Chung2, Aimin Xu3, ChunHoi Yan4, KowungYuen Chiu5, Weijia William Lu6

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