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DOI:10.1097/HJH.0000000000001329

Endothelin-1-induced endothelial mesenchimal transition via endothelin type B receptor stimulation: implication for chronic kidney disease

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Lariviére *et al.* [1], using a rat remnant kidney model of chronic kidney disease (CKD) with calcium/phosphate-rich diet associated with vitamin D supplementation, have reported that endothelin-1 plays a role in medial vascular calcification and stiffness, at least in part, through the modulation of vascular smooth muscle cell (VSMC) differentiation and vascular inflammation, thereby suggesting that endothelin-1 system may be a potential therapeutic target for improving cardiovascular morbidity in patients with CKD [1,2]. These authors have, in fact, shown that endothelin-1 production occurs not only in the endothelial cells, but also in the VSMCs, where endothelin-1 may act in an autocrine and/or paracrine manner to induce VSMC differentiation into osteoblast-like cells [1]. Moreover, the treatment with the ET_A receptor subtype of endothelin-1 atrasentan prevented the expression of the osteoblastic differentiation markers BMP-2 and osteocalcin along with prevention of macrophage infiltration into the media layer and blunted expression of inflammatory cytokines [1].

These protective effects of ET_A receptor subtype antagonism were associated with reduction of SBP and pulse pressure, leading to improvement of aortic stiffness, in rats with CKD supplemented with calcium/phosphate and vitamin D compared with CKD rats not supplemented. However, no changes were observed between groups in serum creatinine levels or creatinine clearance and in calcium/phosphate balance. Based on these results the authors concluded that the decline in renal function could be related to the mineral imbalance [1].

We would like to point out that the results of our recent study may provide an additional explanation for Lariviére *et al.* [1] conclusions.

In transgenic TG(mRen2)27 rats developing fulminant angiotensin II-dependent hypertension with prominent cardiovascular and renal damage [3], we have shown that endothelin-1 induces epithelial-to-mesenchymal transition (EMT), a process allowing the phenotypic switch of the epithelial cells to a mesenchymal phenotype, finally leading to tubulointerstitial fibrosis (TIF), acting via ET_B receptor of endothelin-1 [4]. The role of ET_B receptor subtype was supported by in-vitro experiments using human HK-2 proximal tubular cells showing that the selective ET_B receptor antagonist BQ-788 was able to prevent endothelin-1-induced EMT, proved by the blunted expression of the epithelial marker E-cadherin and by the increase of the mesenchymal marker αSMA, along with an increase of collagen synthesis and metalloproteinase activity [4].

Therefore, the block of ET_A receptor subtype could facilitate the bond of endothelin-1 in excess to ET_B subtype, which is the predominant subtype in the renal tubules [4,5], thereby favouring EMT and TIF.

The key role of the ET_B receptor subtype in EMT and TIF, in addition to provide an additional explanation for Lariviére *et al.* [1] conclusions, could also provide a further interpretation for the unfavourable results obtained with the ET_A selective antagonist avosentan in type 2 diabetic patients with overt nephropathy in the ASCEND trial [6], suggesting that the favourable antiproteinuric effects of the ET_A blockade in the glomeruli could have been counterbalanced by the unfavourable ET_B-mediated effects on the tubules.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

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Journal of Hypertension 2017, 35:1326–1330

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DOI:10.1097/HJH.0000000000001344