Does endoplasmic reticulum stress mediate endothelin-1-induced renal inflammation?

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De Miguel C, Pollock JS. Does endoplasmic reticulum stress mediate endothelin-1-induced renal inflammation? Am J Physiol Regul Integr Comp Physiol 305: R107–R109, 2013. First published May 15, 2013; doi:10.1152/ajpregu.00184.2013.—Endothelin-1 (ET-1) is the most potent vasoconstrictor peptide known. It exerts its actions through two pharmacologically different receptors: ETA and ETB receptors. In the renal vasculature, there is a majority of ETB receptors in the efferent arteriole, whereas a greater amount of ETA receptors are located in the afferent arteriole. The nephron is rich in ETB receptors, especially in the thick ascending limb and collecting ducts, while containing a smaller amount of ETA receptors. High levels of circulating or renal ET-1 have been described in cardiovascular diseases such as hypertension or diabetes, diseases also associated to renal inflammation. Despite extensive evidence associating high levels of ET-1 to increased renal inflammation, the molecular mechanism(s) by which ET-1 leads to renal immune infiltration and/or immune activation remains unknown. In this minireview, we propose that the ET-1/ETA pathway mediates an increase in renal endoplasmic reticulum (ER) stress, initially a survival mechanism that if prolonged, leads to the eventual death of the cell via apoptosis.

endothelin-1; endoplasmic reticulum stress; renal inflammation

RECENTLY, ENDOPLASMIC RETICULUM (ER) stress has been implicated in the development of a variety of cardiovascular and renal diseases, many of which are also associated with elevated endothelin-1 (ET-1) levels. There is also extensive evidence that links increased ET-1 levels with renal immune cell infiltration and/or immune activation. This review summarizes this evidence and proposes the working hypothesis that ET-1 induces renal inflammation and/or immune activation by stimulating renal ER stress through the ETA receptor (Fig. 1).

Endothelin and Renal Inflammation

ET-1 is a very potent vasoconstrictor peptide that exerts its biological actions through the activation of two G protein-coupled receptor subtypes: ETA and ETB receptors. The affinity of ET-1 for each receptor subtype has been shown to be the same (Kd = 0.01–0.5 nM) (4). The vasoconstrictor effects of the ETA receptor are mainly mediated by a Gq protein, whereas the vasodilatory effects of ET-1 through the ETB receptor are largely mediated via a Gi protein (8).

Upregulation of the ET-1 system is implicated in many cardiovascular diseases, such as hypertension, vascular disease, pulmonary hypertension, heart failure, renal disease, or diabetic nephropathy (14). Interestingly, many of these disorders have been reported to have an important inflammatory component to their development. The kidney, in particular the renal medulla, contains the highest concentration of ET-1 in the body, and progressive renal damage is described in transgenic animals overexpressing ET-1 (6). ET-1 stimulates renal hypertrophy, fibrosis, and inflammation predominantly through the activation of the ETA receptor (16, 17). Recently, our laboratory reported that chronic infusion of a nonpressor dose of ET-1 in Sprague-Dawley rats results in elevated circulating and renal levels of inflammatory mediators, such as ICAM-1 or monocyte chemoattractant protein-1 (MCP-1), as well as increased renal infiltration of macrophages and T-lymphocytes (13). Interestingly, the proinflammatory effects exerted by ET-1 in these studies were attenuated by the administration of an ETA receptor blocker, highlighting the involvement of this receptor in the development of the ET-1-induced proinflammatory state. We also demonstrated that ETA receptor activation mediates renal infiltration of T cells in a hypertensive angiotensin II-infused animal model (1). Despite a large body of evidence linking the ET-1 system with renal inflammation, the mechanism by which ET-1 leads to this inflammation remains unclear.

ER Stress and Renal Inflammation

The ER is known to be a key cellular organelle in the modification, maturation, and folding of proteins into their active conformations. The ER is also a very sensitive sensor of stress in the cell (5). Homeostasis in the ER can be disrupted by
physiological and/or pathophysiological conditions (14), leading to the accumulation of misfolded proteins in the ER, a situation known as ER stress (20). To maintain ER function, the cell initiates a protective mechanism known as adaptive unfolded protein response (UPR), which is directed to temporarily stop further protein transcription and translation, in an attempt to gain time for the ER to fold the accumulated misfolded proteins. Glucose-regulated protein 78 (GRP78, also known as BiP) is the molecular sensor that detects misfolded proteins within the ER, physically binding to them and initializing the three parallel signaling arms of the UPR by activating three ER membrane-associated proteins: inositol-requiring enzyme 1 (IRE1), protein kinase-like ER kinase (PERK), and activating transcription factor 6 (ATF6). If the conditions triggering ER stress are too severe or prolonged in time, the cell activates the so-called apoptotic UPR to remove damaged cells, which may lead to organ malfunction if too many cells are affected (5).

Among the triggers that have been implicated in ER stress are hypoxia, ischemia, and oxidative stress, all of which are linked to the development of cardiovascular and renal diseases. There is also accumulating evidence of a pathophysiological role of ER stress in acute kidney injury, renal ischemia-reperfusion injury, or diabetic nephropathy (7). Substantial evidence also indicates that ER stress is interconnected with inflammatory signaling pathways. For instance, activation of the UPR is reported to be coupled to the production of proinflammatory cytokines like MCP-1, TNF-α, IL-6, or IL-8 (18). In addition, other studies have shown that the tree branches of the UPR can lead to the activation of the central inflammatory mediator NF-κB, which induces the transcription of other inflammatory genes (21).

**ET/ET<sub>A</sub> Pathway and ER Stress**

Given that elevated renal levels of ET-1 and renal inflammation are highlights of renal disease, our working hypothesis is that ET-1 induces renal inflammation by elevating ER stress in the kidney (Fig. 1). The elevated ER stress levels in turn lead to the production of inflammatory mediators and renal inflammation. A recent study supports this idea by demonstrating that cultured pulmonary aortic smooth muscle cells (PASMCs) show activation of the UPR and cytokine production after exposure to ET-1 (19). Among the upregulated proinflammatory cytokines were IL-6, IL-2, and chemokine (C-C motif) ligand 5 (CCL-5). Interestingly, these effects of ET-1 were ameliorated by treatment with an ET<sub>A</sub> receptor blocker, whereas treatment with an ET<sub>B</sub> receptor antagonist did not have any effect. One of the possible mechanisms by which activation of the ET<sub>A</sub> receptor could lead to renal ER stress is by generation of oxidative stress. Extensive evidence indicates that ET<sub>A</sub> receptor activation stimulates superoxide production via NADPH oxidase (15), and that cross-talk exists between oxidative stress and ER stress (11). Moreover, stimulation of the UPR in response to oxidative stress is an adaptive mechanism to preserve cell function and survival during renal dysfunction (9). Modulation of renal ER stress through the ET system may be a novel therapeutic target against the development of renal disease in situations like hypertension or diabetes.

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**AUTHOR CONTRIBUTIONS**

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