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New clues towards solving the mystery of endothelin and blood pressure regulation

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There is no shortage of data suggesting that endothelin-1 (ET-1) has a profound influence on blood pressure, both in an acute and chronic setting, but many of the mechanisms appear complex and have been difficult to resolve. An increase in plasma ET-1 concentrations and/or activity is seen in a number of rodent models with hypertension, and treatment with an endothelin receptor antagonist reduces blood pressure in the vast majority of settings regardless of whether hypertension is present or whether circulating ET-1 concentrations are elevated.¹ The measurement of plasma ET-1 can provide clues to the activity of the ET-1 system, but the interpretation is complex because 1) endothelial release of ET-1 is overwhelmingly towards the basal side of the cell, and 2) ET-1 binds irreversibly to both ET_A and ET_B receptors present on vascular smooth muscle and endothelial cells, respectively.¹ Importantly, it appears that most of this ET-1 is bound by ET_B receptors, which has led investigators to conclude that the ET_B receptor functions as a clearance receptor such that the loss of ET_B function, through pharmacological blockade, gene deletion, or in some cases, functional down-regulation can lead to large increases in plasma ET-1 concentrations.¹ The primary source of circulating ET-1 is derived from the vascular endothelium, which is shown by a large reduction (but not complete loss) of plasma ET-1 in endothelial cell specific ET-1 knockout mice, as well as an increase in plasma ET-1 in mice with ET-1 overexpression by endothelial cells.² However, the question remains as to which function of endothelial cell-derived ET-1, dilator or constrictor, has the most predominant role. Fortunately, studies by Rautureau et al. in the current issue of *Hypertension* provide an important piece of the puzzle regarding endothelial ET-1 and arterial pressure by the development of an inducible, endothelial cell-specific ET-1 over-expressing mouse (ieET) that has elevated circulating ET-1 and hypertension.³

Numerous genetic models have been developed to study the role of endothelin in vascular, renal, and neural physiology.¹ Many of the first gene deletion models revealed a very important role for ET-1 and its receptors in fetal development, but did not survive to adulthood. Vascular endothelial cell-specific deletion of ET-1 gene expression, the VEET mouse, was first reported to result in lower arterial pressure,² but subsequent studies from the same laboratory in these same mice reported these animals as having normal arterial

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pressure⁴ (our laboratory has unpublished observations that the VEET mice have normal blood pressures when on a normal diet; observations of variable blood pressures in the VEET mice emphasize the inconsistency and difficulty of chronic blood pressure measurements in mice). To the surprise of many, transgenic overexpression of ET-1 by endothelial cells driven by the Tie-2 promoter had no effect on blood pressure even though there were profound effects on vascular inflammation, oxidative stress and other abnormalities.⁵ These studies all highlight the major difficulty with using genetically manipulated mice that developmental adaptation to the loss or over-expression of various genes is too often dismissed or not addressed. Rautureau et al developed two distinct models where over-expression of endothelial-derived ET-1 over-expression (ieET) was induced in adulthood and observed significantly elevated arterial pressure.³ Thus, without developmental adaptation, it appears that increased ET-1 production by the vascular endothelium leads to hypertension, via activation of the ET_A receptor.

Inducible over-expression of endothelial ET-1 results in extremely large increases in plasma levels of ET-1 that may account for differences between gene induction and chronic infusion models. Our laboratory has published several papers where we have given an intravenous infusion of ET-1 for a two-week period and not observed any effect on arterial pressure when measured by telemetry.⁶ We presume that the amount of ET-1 infused may not equal the level of ET-1 exposure seen in the ieET-1 model. However, we did observe increases in inflammatory markers and modest, but significant effects on glomerular permeability that were all driven by ET_A receptor activity. Rautureau et al demonstrated that the hypertension observed in the ieET-1 model could be reversed by atrasentan consistent with the ET_A receptor mediating the hypertensive effects of ET-1. It is important to note that the plasma levels of ET-1 observed in the ieET mouse are at least 8-12 fold higher than control mice and are in the range observed when ET_B receptors are blocked with an antagonist or genetically deleted. These levels are much higher than typically seen in disease models where ET-1 is believed to be over-active.

One of the complicated aspects to understanding how ET-1 affects blood pressure is the opposite effect that its receptors produce on blood pressure.¹ The ET_A receptor is found most abundantly on vascular smooth muscle and is thought to increase blood pressure by raising vascular resistance. On the other hand, endothelial ET_B receptors function to account for the vasodilatory effects of ET-1 and provide a means of clearing ET-1 from the circulation, thus protecting against over-stimulation of ET_A receptors. Furthermore, renal epithelial ET_B receptors promote natriuresis and diuresis by reducing tubular Na⁺ uptake, in turn, reducing blood pressure. Even less well-known are the effects of ET_A and ET_B receptors modulating the sympathetic nervous system that impact arterial pressure responses, at least in response to acute stress.⁷ An additional important finding of the current study by Rautureau et al, is that systemic ET-1 negatively feeds back on ET_A and ET_B receptors in vascular tissue to reduce expression, yet appears to have a positive effect on ET_A and ET_B receptor expression in renal tissue (Figure 1). One could speculate that the vascular response is a true negative feedback system in response to increased ligand, while the increase in renal receptor expression may be a compensatory effect to counteract the hypertension by promoting natriuresis. These findings emphasize the idea that maintaining a balance between ET_A and ET_B receptor function is key to maintain proper physiologic

function, and that receptor imbalance, not elevated ET-1 per se, may be the key initiator of pathophysiological situations such as hypertension. Along these lines, our laboratory has reported evidence for angiotensin II dependent down-regulation of the renal ET_B receptor,⁸ which could account for salt-sensitivity in this model as well as the observations that ET_A blockade can counteract the hypertensive effects of angiotensin II.

Going forward, it is clear that the models developed by Rautureau et al will be invaluable tools for future work in this area. As the authors indicated, it will be important to investigate the long-term effect of chronic endothelial ET-1 elevation as well as models with other complicating features such as hyperglycemia. In the kidney, there are fundamental physiological questions about the role of endothelial versus epithelial cell ET-1 that may control renal hemodynamics, especially in response to a high salt diet. Furthermore, there are reports of elevated ET-1 outside of the kidney in response to a high salt diet⁹ that may have implications for non-renal adaptations that may occur in places such as the skin (unpublished observations). It seems counterintuitive to have a powerful vasoconstrictor such as ET-1 to be increased during high salt intake; however, ET-1 may be functioning in other roles aside from vasoconstriction, such as facilitating inflammation that is important for sodium storage in the skin.¹⁰ In addition, increasing renal perfusion pressure clearly can promote natriuresis, which is consistent with the overall function of the ET-1 system as a regulator of sodium balance as opposed to simply blood pressure regulation per se.

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References

1. Kohan DE, Rossi NF, Inscho EW, Pollock DM. Regulation of blood pressure and salt homeostasis by endothelin. *Physiol Rev.* 2011; 91:1–77. [PubMed: 21248162]
2. Kisanuki YY, Emoto N, Ohuchi T, Widyantoro B, Yagi K, Nakayama K, Kedzierski RM, Hammer RE, Yanagisawa H, Williams SC, Richardson JA, Suzuki T, Yanagisawa M. Low blood pressure in endothelial cell-specific endothelin 1 knockout mice. *Hypertension.* 2010; 56:121–128. [PubMed: 20516397]
3. Rautureau, Y.; Coelo, SC.; Fraulob-Aquino, JC.; Huo, G.; Rehman, A.; Offermanns, S.; Paradis, P.; Schiffrin, EL. Hypertension. in press; 2015. Inducible human endothelin-1 overexpression in endothelium raises blood pressure via endothelin type A receptors.
4. Heiden S, Vignon-Zellweger N, Masuda S, Yagi K, Nakayama K, Yanagisawa M, Emoto N. Vascular endothelium derived endothelin-1 is required for normal heart function after chronic pressure overload in mice. *PLoS One.* 2014; 9:e88730. [PubMed: 24523936]
5. Amiri F, Viridis A, Neves MF, Iglarz M, Seidah NG, Touyz RM, Reudelhuber TL, Schiffrin EL. Endothelium-restricted overexpression of human endothelin-1 causes vascular remodeling and endothelial dysfunction. *Circulation.* 2004; 110:2233–2240. [PubMed: 15466627]
6. Saleh MA, Boesen EI, Pollock JS, Savin VJ, Pollock DM. Endothelin-1 increases glomerular permeability and inflammation independent of blood pressure in the rat. *Hypertension.* 2010; 56:942–949. [PubMed: 20823379]
7. D'Angelo G, Pollock JS, Pollock DM. Endogenous endothelin attenuates the pressor response to acute environmental stress via the eta receptor. *Am J Physiol Heart Circ Physiol.* 2005; 288:H1829–1835. [PubMed: 15563533]

8. Kittikulsuth W, Pollock JS, Pollock DM. Loss of renal medullary endothelin b receptor function during salt deprivation is regulated by angiotensin ii. *Am J Physiol Renal Physiol*. 2012; 303:F659–666. [PubMed: 22674027]
9. Tsai YH, Ohkita M, Garipey CE. Chronic high-sodium diet increases aortic wall endothelin-1 expression in a blood pressure-independent fashion in rats. *Exp Biol Med (Maywood)*. 2006; 231:813–817. [PubMed: 16741004]
10. Titze J. A different view on sodium balance. *Curr Op Nephrol Hyper*. 2015; 24:14–20.

Figure 1.

Hypothetical schematic of vascular endothelial derived ET-1 overproduction influence on blood pressure. Overexpression of endothelial derived ET-1 reduces both ET_A and ET_B receptor expression on systemic vasculature, yet maintains normal vessel reactivity to ET-1. In contrast, upregulation of ET_A and ET_B receptors occurs in renal tissue, although the specific cell type is not known. Given the large amount of receptor expressed in renal tubular epithelium, the increase in receptor expression in the kidney could be a compensatory mechanism for the increase in blood pressure since renal tubular ET-1 promotes natriuresis. In addition to renal and vascular ET-1 receptors, evidence suggests that ET_A and ET_B receptors on peripheral nerves may modulate blood pressure, but this mechanism is very poorly understood in terms of blood pressure regulation and how vascular endothelium may or may not impact nervous system ET_A and ET_B receptor activity is unknown.