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Clarifying Endothelin Type B Receptor Function

David M. Pollock, Markus P. Schneider

Endothelin (ET) receptors have become the targets for the treatment of a variety of cardiovascular disorders and a mixed ET type A (ET_A)/ET type B (ET_B) receptor antagonist, bosentan, is currently being used to effectively treat pulmonary hypertension. An ongoing debate has revolved around the question of whether selective ET_A receptor blockade would be preferable to using the mixed antagonist. The functional role of ET-1 is complicated by the opposing actions of the ET_A and ET_B receptor in the vasculature, as well as the kidney. ET_B receptor function is further complicated by the presence of vasoconstrictor ET_B receptors on vascular smooth muscle in some vascular beds, whereas ET_B receptors on endothelium and renal tubules have vasodilator and natriuretic activities. ET_B receptors also serve to clear ET-1 from the circulation and, thus, minimize vasoconstrictor activity. Despite the well-recognized effects of ET_B receptors to oppose ET_A-mediated actions, it is not clear whether blocking both ET_A and ET_B receptors at the same time is detrimental or advantageous compared with selective ET_A blockade. Indeed, ET_A selective antagonists are also expected to soon receive approval for treatment of pulmonary hypertension. Although this may indicate that both strategies work in pulmonary hypertension, the pros and cons of selective versus mixed antagonists are much less clear in arterial hypertension and heart and kidney failure.

Previous studies have shown that pharmacological blockade or genetic deficiency of ET_B receptors results in salt-sensitive hypertension in rats.^{1,2} More recent studies have now provided information on the location(s) of the ET_B receptors responsible for this effect. Ahn et al³ demonstrated salt-sensitive hypertension in mice where ET-1 expression was selectively knocked out in the renal collecting duct. It was not clear, however, whether ET-1 originating from the collecting duct acts on ET_B receptors of vascular elements within the renal medulla or in an autocrine fashion on ET_B receptors of collecting duct cells. In the current issue of *Hypertension*, Bagnall et al⁴ report that selective deletion of the ET_B receptor from endothelial cells in mice has no effect on blood pressure or salt sensitivity despite reduced endothelial-dependent relaxation. The authors conclude that ET-1 more likely acts in an autocrine fashion on collecting duct cells, as opposed to activating endothelial ET_B receptors on vasa recta, which could facilitate sodium excretion through an increase in medullary perfusion. This conclusion is further supported by reports that ET_B receptors inhibit electrolyte reabsorp-

tion in vitro.⁵⁻⁷ Strictly speaking, a role for increased medullary perfusion in the renal response to a high-salt diet mediated by the ET_B receptor cannot be completely ruled out yet. It is conceivable that activation of ET_B receptors on tubular cells causes vasa recta to dilate through a "tubulovascular crosstalk" mechanism similar to that described previously for buffering angiotensin II-mediated vasoconstriction in the renal medulla and mediated by NO.⁸ Although some questions do remain about the precise mechanisms, the studies by Bagnall et al,⁴ together with previous results from other groups, indicate a major role for renal tubular ET_B receptors in mediating ET-1-induced natriuresis.^{3,4,7}

In addition to giving new insight into the renal mechanisms, the current study also seems to dramatically reduce the likelihood of vascular endothelial ET_B receptors mediating salt-sensitive hypertension during systemic ET_B receptor blockade. Interestingly, previous cross-transplantation experiments in ET_B receptor-deficient rats showed that salt sensitivity in this model depended on the deletion of extrarenal ET_B receptors.⁹ This raises the possibility that a yet-unidentified extrarenal ET_B receptor may have a protective effect against salt-sensitive hypertension, in addition to the ET_B receptor on renal tubular cells.

Although it has been assumed for quite some time that the endothelial ET_B receptor is responsible for clearing circulating ET-1, the functional ramifications of this concept have been difficult to discern with other models in rats, such as pharmacological ET_B receptor blockade or ET_B receptor deficiency.^{1,2} Endothelial-specific ET_B knockout mice have elevated levels of circulating ET-1, which provide even more definitive evidence for a role of ET_B receptors on endothelium in clearing ET-1 from the circulation. However, it is now also important to realize that the resulting elevations in circulating ET-1 do not account for the hypertension produced by pharmacological or genetic disruption of the ET_B receptor as documented previously.^{1,2} Several laboratories have shown that hypertension produced by ET_B receptor blockade or high-salt intake in ET_B receptor-deficient rats can be blocked by ET_A receptor antagonism.^{2,10,11} Although an obvious argument is that a lack of ET_B receptors displaces ET-1 to produce greater ET_A receptor-dependent vasoconstriction, this cannot account for the hypertension in these models given these new findings. Just because ET_A receptor blockade reduces blood pressure in a model of hypertension does not signify that the hypertension was produced by increased ET_A receptor activation. It is also not clear how a shift of ET-1 from the ET_B to the ET_A receptor could explain the salt dependence of these models. Again, these new results favor a renal mechanism for the salt-sensitive hypertension observed with ET_B receptor blockade or genetic deficiency of ET_B receptors.

Although this study represents an important advance in our understanding of how ET-1 controls blood pressure, there are a number of questions about ET_B receptor function that remain. It should be noted that control mice in the current study were salt sensitive, and so it will be important to establish that a lack of

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endothelial ET_B receptors does not result in salt-dependent hypertension in mice with a salt-resistant genetic background. Another issue that no one has yet addressed is whether gastrointestinal absorption of salt is altered in animals lacking ET_B receptor function. ET-3, which selectively acts on ET_B receptors, has been shown previously to inhibit intestinal sodium reabsorption in dogs.¹² The precise location of the ET_B receptor responsible for this effect can now be further investigated with this new model or other tissue-specific models. Finally, there is emerging evidence for ET_B receptor influence within the sympathetic nervous system that may participate in short-term blood pressure control.¹³

Throughout the literature, there are many references to the phenomenon known as “endothelial dysfunction.” It is quite commonly referred to as a reduced vasodilator response to acetylcholine administration, and so it is clear that we must now include reduced ET_B receptor function as one possible cause of the dysfunction. Even more intriguing, reduced endothelial-dependent vasodilation in endothelial cell ET_B receptor knockout mice does not translate into hypertension. These results add important new information to the ongoing debate of whether endothelial dysfunction is a cause or a consequence of hypertension. Similarly, vascular overexpression of ET-1 in mice has been shown to lead to endothelial dysfunction in the absence of hypertension.¹⁴ Whether the absence of hypertension is specific to the endothelial dysfunction induced by increased expression of ET-1 or deletion of endothelial ET_B receptors remains to be determined. It will also be important to investigate what changes in ET_A receptor activity, if any, occur within the vascular system when the ET_B receptor is absent from the endothelium.

In summary, the work of Bagnall et al⁴ represents an important advance in the understanding of how ET-1 controls blood pressure and the response to salt and provides a valuable new tool for exploring ET_B receptor function. Because so much focus has been on the negative effects of ET_A receptor activation in cardiovascular disease, function of the ET_B receptor on the endothelium has been a relatively underinvestigated aspect of the ET system. Although many questions remain, the work from this group and others, including results with the collecting duct-specific knockout mice, clearly establish an important role for renal epithelial ET_B receptors in regulating salt excretion. This study should provide an impetus for more focus on ET_B receptor function in control of vascular function and also

represents another important piece of the puzzle that will eventually answer the question as to when and where ET_B receptor blockade may be helpful or harmful.

Disclosures

None.

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