ROLE OF ANGIOTENSIN 1B RECEPTORS IN INDUCING REGIONAL DISPARITIES IN HYPERTENSIVE AORTIC REMODELING

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Introduction

Hypertensive arterial remodeling using angiotensin II (AngII) infusion in mice has been studied for over 20 years, uncovering the role of the renin-angiotensin system in blood pressure control. Although there are numerous studies on how AngII leads to hypertension development, central artery stiffening, and formation of abdominal aortic aneurysms (AAAs), many key questions remain unanswered, such as the role of AngII receptors on tissue-level consequences. Among the two primary AngII receptors, AT1R and AT2R, the former is expressed in two isoforms, AT1aR and AT1bR. Deletion of AT1aR suppresses AAA formation while deletion of AT1bR does not [1]. Interestingly, these effects are not mirrored by effects in vasoconstriction. AT1bR in smooth muscle cells mainly contributes to AngII-induced local vasoconstriction, whereas AT1aR has no clear effect thereon. AT1aR and AT1bR density has been shown to vary along the aorta, increasing from the proximal to the distal aorta, but it is still unclear how this affects the differential regional hypertensive remodeling response of the aorta. Our study aims to clarify this aspect by analyzing histo-mechanical metrics in multiple aortic regions in AT1bR gene-deficient mice, without or with AngII infusion.

Methods

We contrasted 14- and 28-day infusions of AngII at a rate of 1000 ng/kg/min in adult male and female wild-type (WT) and AT1bR null (*Agtr1b*$^{-/-}$) mice by *ex vivo* histo-mechanical characterization in the ascending (ATA) and descending (DTA) thoracic aorta and the infrarenal abdominal aorta (IAA). Aortic segments were characterized functionally by biaxial extension-distention tests and isobaric vasoactive tests to obtain fundamental biaxial mechanical metrics [2]. Immunohistochemical quantifications allowed layer-specific analysis of composition and infiltration of pan-inflammatory cells (macrophages, monocytes, and T-cells). Sample-specific analyses allowed identification of crosstalk between biomechanics and histology.

Results and Discussion

Mechanical and histological metrics revealed that baseline properties and AngII-induced remodeling were independent of sex in *Agtr1b*$^{-/-}$ mice. Focusing then on male mice, AngII-induced changes in aortic morphology and mechanics differed by region and genotype. A marked AngII-induced thickening of ATA but little thickening of IAA was seen in both genotypes. Despite no differences in the level of blood pressure elevation between AngII-infused WT and *Agtr1b*$^{-/-}$ mice, we observed marked thickening of the DTA in WT but not *Agtr1b*$^{-/-}$ mice. After AngII infusion, distensibility, elastic energy storage, energetically preferred axial stretch, and axial material stiffness decreased the most in ATA, less so in DTA, and little in IAA, independent of genotype. By contrast, biaxial wall stresses, circumferential material stiffness, and energy dissipation revealed marked variations within the DTA of AngII-infused WT but not *Agtr1b*$^{-/-}$ mice. Vasoactive tests revealed that the vasoconstriction to AngII was higher in IAA in WT mice, but this result was blunted in all regions in *Agtr1b*$^{-/-}$ mice. Histology showed that AngII-induced wall thickening was preferentially adventitial in the WT thoracic aorta, but more medial in *Agtr1b*$^{-/-}$ DTA. This distinctive behavior correlated with an increase in adventitial cell area. Immuno-histochemistry revealed a marked increase in the pan-leukocyte markers in the ATA of all AngII-infused mice and in the DTA of WT mice, as well as a marked increase in the macrophage marker in all three segments of the aorta of AngII-infused WT mice. Conversely, DTAs of *Agtr1b*$^{-/-}$ mice showed only a moderate number of leukocytes after AngII infusion that was in line with the distinctive thickening and mechanical behavior, as also all aortic regions of *Agtr1b*$^{-/-}$ did not show increases in macrophages after AngII infusion.

Therefore, in the context of aortic remodeling through AngII-induced hypertension in mice, AT1b receptor deletion surprisingly revealed to have differential effects along the aorta, particularly at the level of the DTA, where negative remodeling was significantly attenuated through modulation of the inflammatory response. It is thus necessary to continue to study the role of AngII in differentially influencing the multiple cell types that contribute to regional disparities in aortic remodeling.

References

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