ABSTRACT
1438

HYPERTENSION AFFECTS SIMILARLY AORTIC AND ERECTILE TISSUE REMODELING IN SPONTANEOUSLY HYPERTENSIVE RATS

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ABSTRACT

Introduction and Objectives: Vascular remodeling precedes the onset of hypertension (HTN) and participates in the long-term resistance changes associated with HTN. Structural changes in the erectile tissue may contribute to the impairment of corporal smooth muscle relaxation and thus to the pathophysiology of HTN-associated ED. The present study examines the progressive remodeling of aortic and erectile tissue from WKY and SHR at 6, 12 and 24 weeks of age (n=12).

Methods: Total protein and collagen content of aortic and erectile tissue samples were quantified by colorimetry, collagen phenotypes by pepsin solubilization, fractionation by SDS-PAGE and densitometric analysis and smooth muscle cell population by western blot.

Results: Total protein content increased with age in both aortic and erectile tissue of SHR and WKY but decreased in SHR compared to WKY in both type of tissue. There was no difference in aortic α-actin content while it was significantly increased in erectile tissue of SHR compared to WKY. Total collagen content of erectile tissue increased with age similarly in both strains while it was constant in aortic tissue. Major modifications in the distribution of collagen I, III and V occur with time in SHR compared to WKY in both erectile and aortic tissue and were detectable sooner in the erectile tissue compared to the aortic tissue: at 6 weeks vs 12 for collagen I/III ratio and 12 weeks vs 24 for collagen V.

Conclusions: There are consistent parallel changes in the composition of erectile and aortic tissue from SHR. This evolution is often detectable sooner in the erectile compared to the aortic tissue and characteristic of fibrotic remodeling which could participate in the altered mechanical properties of these tissues contributing to both HTN and HTN-induced ED in SHR. This model could be useful to investigate innovative therapeutic strategies targeting HTN-induced remodeling occurring both at the vascular level and at the level of a key target end-organ i.e. the penis.

BACKGROUND

➢ **Epidemiology of ED: The Key Role of Hypertension**

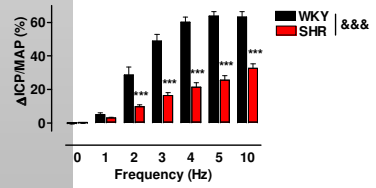
- The prevalence of ED in men with hypertension is significantly higher than in the general population (15% vs 9.6 %)

Feldman et al., J Urol, 151:54-61 (1994)
Jensen et al., Am J Hypertens, 12:271-275 (1999)

- ED is a symptom occurring in 8-10 % of untreated hypertensive patients

Lewis et al., 1st International Consultation on Erectile Dysfunction , WHO (2000)

➢ ***In vivo*** **Erectile Dysfunction in 12-weeks old SHR**



&&& p<0.0001 Two-Way ANOVA
***p<0.001 Bonferroni's complementary analysis

Behr-Roussel et al., Am J Physiol, 2003
Abstract #1435, AUA 2004

➢ **Hypertrophic structural changes in the vasculature precede the onset of hypertension and participate in the long-term resistance changes associated with hypertension**

Folkow et al., Acta Physiol Scand (1970)
Adams et al., Hypertension (1990)

Hypertension in SHR causes structural changes in penile vasculature similar to those in other vascular beds : the penis is not protected from structural changes associated with hypertension

Okabe et al., Int J Impot Res (1999)

⇒ **Structural alteration in the qualitative and quantitative composition of the erectile tissue may participate in the pathophysiology of ED due to hypertension**

OBJECTIVES

To examine the modifications in cellular and extracellular composition (remodeling):

- **Total protein**
- **Total collagen and collagen subtypes (Collagen I, III, V)**
- **Smooth muscle cell population**

in isolated aortic rings and corporal tissue samples of SHR and age-matched normotensive WKY rats

- **at 6 weeks of age : pre-hypertensive state**
- **at 12 weeks of age**
- **at 24 weeks of age : well-established hypertension**

METHODS

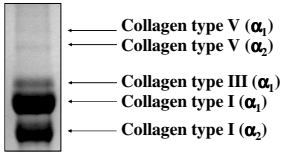
- **Spontaneously Hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats**

➢ **6-weeks old (n=12)**
➢ **12-weeks old (n=12)**
➢ **24-weeks old (n=12)**

Mean arterial pressure under anaesthesia (ketamine/xylazine, mmHg)		
	WKY	SHR
6 weeks	83 ± 2	94 ± 4
12 weeks	96 ± 4	113 ± 4 *
24 weeks	96 ± 4	121 ± 4 *

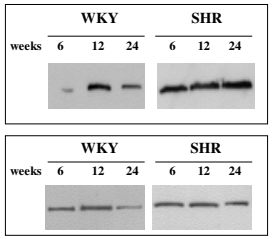
**p<0.05, Two-Way ANOVA WKY versus SHR*

- **Protein content was quantified in proline extract by colorimetric assay with ninhydrine**
- **Collagen content was determined in hydroxyproline extract with Ehrlich's reagent (para-amino benzaldehyde)**
- **Determination of collagen subtypes by pepsin solubilization and fractionation of the resulting mixture by polyacrylamide gel electrophoresis and densitometric analysis**

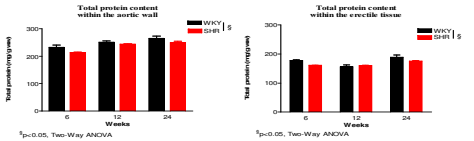


- **Total protein concentration was measured with a Bradford assay and equal amounts of protein (0.3 µg) were separated on 10% denaturing SDS-PAGE, electroblotted on nitrocellulose, probed with a monoclonal anti-α-actin antibody (ABCAM) and detected by enhanced chemiluminescence on autoradiographic film**
- **Densitometric results were expressed in relative optical density of the α-actin protein normalized by an internal standard**

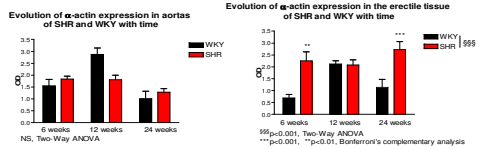
Representative immunoblots of α-actin in the corpus cavernosum (upper panel) and aorta (lower panel) of WKY and SHR at 6, 12 and 24 weeks of age.



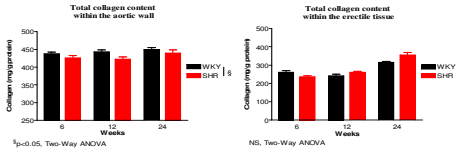
RESULTS



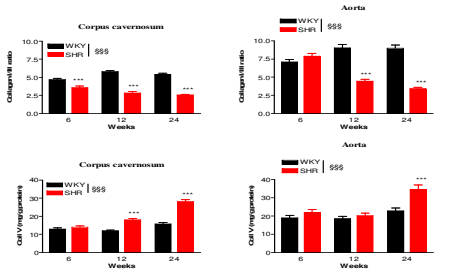
- **Total protein content increased with age in both aortic and erectile tissue**
- **Total protein content is reduced in SHR in both aortic and erectile tissue**



- **No difference in smooth muscle cell population in aortas**
- **Significant increase in smooth muscle cell population at 6 and 24 weeks of age in erectile tissue of SHR**



Total collagen content increased with age similarly in erectile tissue of both strains while it was constant in aortas



- **A specific decrease in collagen I/III ratio and increase in collagen V in SHR with age**
- **Similar modifications in erectile and aortic tissue but detectable sooner in erectile tissue**

CONCLUSION

- **Consistent parallel changes in the composition of erectile and aortic tissue from SHR compared to WKY**
- **Fibrotic degeneration of the erectile tissue, characterized by an increased accumulation of extracellular matrix proteins such as collagen III, could be a possible cause of ED due to hypertension by participating in the impairment of cavernosal relaxation and/or veno-occlusive dysfunction**
- **This fibrotic remodeling is often detectable sooner in the erectile tissue compared to the aortic tissue**
- **This model could be useful to investigate innovative therapeutic strategies targeting hypertension-induced remodeling occurring both at the vascular level and at the level of a key target end-organ i. e. the penis**

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