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4.6 Angiotensinogen Promoter Variants and Tissue-Specific Regulation of Angiotensinogen Expression in Human Kidney and Visceral Adipose Tissue

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Introduction. Angiotensinogen (AGT), the precursor of angiotensin II and other vasoactive peptides, is involved in essential hypertension especially when obesity-related. Although AGT is primarily synthesized in the liver, its mRNA is abundant in adipose tissue and the local synthesis play a key role also in kidney function. AGT gene promoter polymorphisms have been associated with essential hypertension and with altered AGT transcription in vitro. In the present study we investigated the association among AGT promoter variants and AGT expression levels in human visceral adipose tissue (VAT) and kidney to verify whether AGT promoter variants are associated with different tissue-specific AGT expression in vivo.

Methods. Samples of adipose and kidney tissues were obtained from 35 consecutive non-diabetic patients (mean age 64.8 ± 12.5 years) undergoing renal surgery for intracapsular renal cell carcinoma (T1/T2, NO, MO). AGT gene expression was studied by RealTime Taq-Man assay and normalized by GAPDH mRNA levels. Genomic sequence of the AGT geneprompter (from -368 to +26) was sequenced in each patient to identify variants. Statistical models were constructed considering age, gender and BMI.

Results. Two novel SNPs (-175GA and -163GA) in strong linkage disequilibrium (LD = 0.90) when present together (n=17) were associated with about 4-fold lower AGT expression only in VAT (p=0.033). Patients with the known -20C variant had 3-fold higher AGT expression only in kidney medulla (P=0.038) when compared to patients with -20A homozygotes. The other known SNPs (-6AG;-217GA) were not associated with different level of AGT expression.

Conclusions. Our data support the hypothesis that AGT promoter variants affect transcriptional activity in a tissue-specific way. Two novel AGT promoter variants (-175A and -163A) in strong linkage disequilibrium appear to down-regulate AGT expression in human VAT whereas the -20C variant is associated with higher AGT expression in kidney. Moreover, the proximity and linkage of -175A and -163A variants suggest that might destabilize the binding of specific nuclear factors.