

Perivascular Adipose Tissue Diminishes Nitric Oxide Bioavailability in Metabolic Syndrome

DeVallance, E., Branyan, KW., Seldomridge, A., Lemaster, KA., Skinner, RC., Asano, S., Setola, V., Frisbee, JC., Chantler, PD. West Virginia University, Morgantown, WV.

Metabolic syndrome (MetS) is a major risk factor of cardiovascular disease. Over the past decade compelling evidence has been collected suggesting a unique depot of adipose tissue called perivascular adipose tissue (PVAT) plays an active roll in vascular function. PVAT is known to release a multitude of vaso-active substances. Just like endothelium, PVAT produces nitric oxide (NO) from the enzyme endothelium nitric oxide synthase (eNOS). In order for eNOS to function properly it must be coupled in a homo-dimer configuration assisted by the co-factor tetrahydrobiopterin (BH4). A three-step process produces BH4 locally with GTP-cyclohydrolase-1 (Gch1) catalyzing the rate-limiting step. The production of NO from the PVAT surrounding the aorta may contribute directly to vascular tone. Furthermore other factors release from PVAT may effect aortic endothelium's production of nitric oxide. **PURPOSE:** To show MetS causes a disruption in normal expression of eNOS and its cofactor BH4 causing a decrease in PVAT derived NO. Further, to reveal healthy PVAT exudate augments endothelium NO production while obese PVAT exudate blunts endothelium NO production. **METHODS:** Lean (LZR) and Obese (OZR) Zucker Rats were utilized for our model of health and MetS. PVAT expression for eNOS and BH4 were measured by qPCR. NO bioavailability was assessed using a DAF-FM diacetate assay. **RESULTS:** Similar to previous findings in visceral adipose, MetS caused an up-regulation of eNOS, 1.8 fold increase in OZR from LZR ($p \leq 0.001$). However, this was accompanied by a 1.6 fold decrease in Gch1 expression in OZR ($p \leq 0.001$). NO production from OZR PVAT was decreased 36% ($p \leq 0.01$). Aortic ring segments treated with exudate from the surrounding PVAT caused a relative 20% increase of NO in LZR and a 20% decrease in OZR. PVAT treated aortic rings from OZR had a 54% decrease in relative NO release ($p \leq 0.001$). **CONCLUSIONS:** MetS decreases PVAT released NO despite an increase in eNOS expression. This may be attributed to the mismatched expression of Gch1, which may lead to a lower BH4, greater uncoupling of PVAT eNOS, and reactive oxygen species production. Furthermore PVAT exudate treatment had opposite effects on endothelium NO production. This decrease in bioavailable NO may contribute to the greater aortic tone associated with MetS.

This study was supported by the American Heart Association (IRG 14330015, PRE 16850005, EIA 0740129N), and the National Institutes of Health (1P20 GM109098, U54GM104942; RR 2865AR; P20 RR 016477).