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INCREASED EXPRESSION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARs) IN RESISTANCE ARTERIES OF SPONTANEOUSLY HYPERTENSIVE RATS
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PPARs are ligand-activated transcription factors found in different tissues. In blood vessels, PPAR expression and function is unknown. We hypothesized that PPARs could modulate vascular remodeling in hypertension and investigated the abundance of PPARα and PPARγ in mesenteric arteries from 6-week old and adult 16-week old SHR and age-matched WKY. Cultured mesenteric vascular smooth muscle cells (VSMCs) were also studied. mRNA level was evaluated by RT-PCR and protein expression by Western blot analysis. PPARα and PPARγ are expressed in VSMCs from intact tissue and cultured cells. PPARα expression was almost undetectable in VSMCs in cell culture. In comparison to other tissues, PPARα and PPARγ level in mesenteric arteries was 5-10 fold less abundant in WKY but of similar level as in other tissues in SHR. In vessels from SHR, PPARα and PPARγ mRNA (PPAR/GAPDH) was significantly greater in comparison to WKY (0.90±0.05 and 1.11±0.07 vs. 0.51±0.01 and 0.44±0.02, p<0.05). PPARα and PPARγ mRNA (PPAR/GAPDH) was greater in young SHR than WKY (0.54±0.07 vs. 0.10±0.01 and 6.80±0.80 vs. 2.03±0.43, p<0.05) and in adult SHR (3.67±0.42 vs. 1.89±0.12 and 9.45±0.69 vs. 6.19±0.38, p<0.05). Expression of PPARγ in cultured VSMCs was 3-fold higher in SHR than in WKY. Thus, resistance arteries from young and adult SHR have increased expression of both PPAR-isoforms, which may play a role in vascular remodeling.

Key Words: PPAR, Resistance arteries, SHR

O-2
THE FATTY ACID TRANSPORTER CD36 IS A MAJOR DETERMINANT OF THE INSULIN SENSITIZING ACTIONS OF PIOGLIITAZONE IN THE SPONTANEOUSLY HYPERTENSIVE RAT
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Pioglitazone, like other thiazolidinediones, is an insulin sensitizing agent that improves glucose tolerance and lowers fatty acid levels in patients with type II diabetes. However, the relative importance of various target genes in the insulin sensitizing actions of TZDs remains to be defined. To investigate the role of the Cd36 fatty acid transporter gene in the insulin sensitizing actions of TZDs, we compared the antidiabetic effects of pioglitazone in spontaneously hypertensive rats (SHR) that have a naturally occurring mutation in Cd36 versus its antidiabetic effects in a congenic strain of SHR expressing wild type Cd36. All rats were fed a high fructose diet to promote impaired glucose tolerance. One group received a semipurified diet that contained pioglitazone (300 mg/kg of diet) and the other group received the semipurified diet without pioglitazone. Blood samples were obtained two weeks later. In fructose fed congenic SHR harboring wild type Cd36, administration of pioglitazone induced significantly greater reductions in circulating levels of glucose, insulin, and fatty acids than in SHR harboring mutant Cd36. Thus, congenic SHR expressing normal Cd36 appear to be much more sensitive to the antidiabetic effects of pioglitazone than SHR lacking Cd36. These findings are consistent with the hypothesis that in SHR fed a high fructose diet, the Cd36 fatty acid transporter represents one of the major targets involved in the antidiabetic actions of pioglitazone.

Key Words: Insulin resistance, thiazolidinediones, diabetes

O-3
ABDOMINAL ADIPOSITY PREDICTS ENDOTHELIAL DYSFUNCTION IN UNCOMPLICATED OBESETY: AN ANALYSIS OF TRADITIONAL AND NOVEL RISK FACTORS
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Background: Vascular endothelial dysfunction has been demonstrated in obesity, however its etiology is unclear. The high prevalence of other cardiovascular risk factors in overweight adults often confounds and masks any possible direct relationship between excess adiposity and endothelial dysfunction. To provide mechanistic insight into the etiology of obesity-related endothelial dysfunction, we determined the predictors of fasting and postprandial endothelial function in overweight adults devoid of all other traditional cardiovascular risk factors. An underlying systemic inflammatory state and atherogenic lipoprotein alterations were evaluated as potential mechanisms linking uncomplicated obesity to endothelial dysfunction.

Methods: Thirty-two otherwise healthy overweight adults (BMI > 27 kg/m 2) underwent determination of LDL particle size (LDLPS), C-reactive protein (CRP), anthropometric measurements and endothelial function by flow-mediated dilatation of the brachial artery (FMD). As humans spend the majority of their time in a postprandial state, postprandial lipemia (PL) and FMD were measured 4 hours after a high fat mixed meal (1630 kcal, 71 g total fat).

Results: Blood pressures and fasting levels of lipoproteins, glucose, insulin and fatty acids were normal. The waist/hip ratio (w/h) was the sole significant predictor of FMD ($r = -0.58, p=0.001$), despite no significant correlation between BMI and FMD. At comparable levels of BMI, obese subjects with a w/h > 0.85 had a significantly blunted FMD compared to those with a w/h < 0.85 (3.93 ±2.85% vs. 8.34 ±5.47%, p=0.016). CRP, PL and LDLPS did not predict fasting FMD, nor did they differ between w/h groups. We found no appreciable alteration in postprandial from fasting FMD (6.31 ±4.62% vs. 6.25 ±5.47%, p=0.95).

Conclusions: Increased abdominal adiposity determined by a simple w/h ratio is a powerful predictor of endothelial dysfunction even in otherwise healthy overweight adults; a finding unexplained by alterations in conventional risk factors, systemic inflammation or atherogenic lipoproteins. These findings suggest a direct relationship between abdominal adiposity and impaired vascular endothelial function. As even small and often subtle increases in the w/h ratio are related to decreases in endothelial function, future studies of vascular endothelial function should account for the independent effects of abdominal adiposity (w/h).

Key Words: Endothelial function, Obesity, Systemic Inflammation