Dysfunctional Adipocytes in Cardiovascular Biology

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PDE5 inhibition ameliorates visceral adiposity targeting the miR-22 / SIRT1 pathway: evidence from the CECSID trial
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Background: Visceral adipose plays a significant role in cardiovascular risk. PDE5 inhibitors (PDE5Is) can improve cardiac function and insulin sensitivity in type 2 diabetic patients (T2DM).

Purpose: To investigate whether PDE5Is affect visceral adipose tissue (VAT), specifically epicardial fat (EAT), and what the mechanism involved using microscopy-based profiling of pharmacologically modulated miRNAs.

Methods: a randomized, double-blind, placebo-controlled study was designed in T2DM. 59 diabetic patients were randomized to receive 100 mg/day PDE5 inhibitor or placebo for 12 weeks. Fat biopsies were performed in a subgroup of patients. In a parallel animal study, db/db mice were randomized to 12-week Sedanifen or vehicle and VAT was collected. Main outcomes and measures were anthropometric and metabolic parameters. EAT quantification through cardiac magnetic resonance imaging (CMR), array of circulating 205 miRNAs, qPCR and flow cytometry of VAT.

Results: Compared to Placebo, Sedanifen reduced waist circumference (p=0.024) an EAT by CMR (p=0.006). Microarray analysis identified some miRNAs differentially regulated by Sedanifen, among which a downregulation of miR-22-3p, confirmed by real-time qPCR (p<0.0001). Sedanifen’s modulation of miR-22-3p was confirmed in vitro in HL-1 cardiomyocytes. An up-regulation of SIRT1, a known target of miR-22-3p was found both in serum and subcutaneous fat in Sedanifen-treated subjects. Compared to vehicle, 12-week Sedanifen treatment downregulated miR-22-3p and upregulated SIRT1 gene expression in VAT from db/db mice, shifting adipose tissue cell composition toward a less inflamed profile.

Conclusions: Treatment with PDE5Is in human and murine models of diabetes improve VAT-targeting SIRT1 through a modulation of miR-22-3p expression.

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AMP-activated protein kinase activation partially restores the anti-contractile effect of perivascular adipose tissue in male offspring of obese dams
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Introduction: Maternal obesity preprograms offspring to develop obesity and associated cardiovascular disease although the underlying mechanism is currently unknown. Perivascular adipose tissue (PVAT) reduces vascular contractility in healthy blood vessels and dysfunction has been demonstrated in male offspring of obese dams.

Purpose: We aimed to determine the mechanisms by which an obesogenic maternal diet pre-programmes detrimental vascular changes in her offspring.

Methods: 6 week old female Sprague-Dawley rats were fed a 10% fat diet (controls) or an obesogenic, high fat diet (HFD; 45% fat) for 12 weeks before mating, during pregnancy and lactation. At weaning, offspring were provided with the control 10% fat diet until sacrifice at 12 and 24 weeks of age. PVAT-denuded mesenteric arteries from pups, with or without exogenous PVAT, were mounted on a wire myograph and concentration-response curves were constructed to thromboxane A2 receptor agonist U46619 (10M-3 M) in the presence or absence of 10uM A769662, an activator of AMP-activated protein kinase (AMPK), and/or glucosamine (an O-GlcNAcylation).

Results: Body weight and arterial blood pressure were significantly increased in HFD dams and their 24 weeks old offspring compared to controls but not in 12 weeks old offspring. Without PVAT, vessel contractions to U46619 were reduced in HFD dams’ offspring at both ages, effects mimicked in control arteries by preincubation with 10mM glucosamine. When separately incubated, PVAT from control, but not from HFD offspring, exerted an anti-contractile effect on the corresponding PVAT-denuded arteries at both ages. Pre-incubation of PVAT with glucosamine diminished the anti-contractile effect of PVAT in vessels from control offspring at both ages, PVAT from HFD offspring pre-incubated with glucosamine had no effect on PVAT-denuded vessels but simultaneous AMPK activation within PVAT partially restored anti-contractile capability at both ages.

Conclusions: The diminished anti-contractile effects of PVAT in offspring of HFD dams can be mimicked by incubation of PVAT with glucosamine and partially restored by AMPK-activated protein kinase activation within PVAT.

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Peroxisome proliferator activated receptor (PPAR)alpha-gamma agonist aleglitazar attenuates tumor necrosis factor (TNF)-alpha-mediated inflammation and insulin resistance in human adipocytes
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Background: Adipose tissue inflammation is a mechanistic link between obesity and the related sequelae, including insulin resistance and type 2 diabetes. Co-ligands of peroxisome proliferator activated receptor (PPAR) a and y, combining in a single molecule the metabolic and inflammatory-regulatory properties of a and y agonists, are a promising therapeutic strategy to antagonize adipose tissue inflammation.

Purpose: To investigate the effects of the dual PPARalpha/y agonist aleglitazar on human adipocytes challenged with inflammatory stimuli and rendered insulin resistant.

Methods: Human Simpson-Golabi-Behmel syndrome adipocytes were treated with aleglitazar or the selective agonists for either PPARalpha or y, fenofibrate or rimonabant, for 24 h before stimulation with TNF-alpha. Conditioned media were then tested for MCP-1 by ELISA, the mRNA expression for MCP-1 as well as several other auxiliary pro-inflammatory cytokines were investigated by RT-PCR, the activation status of insulin signaling with regard to activation of mitogen-activated protein (MAP) kinases was assessed by Western analysis with antibodies recognizing the phosphorylated (activated) forms of each kinase.

Results: Aleglitazar, at concentrations as low as 10 nmoL/L, reduced the stimulated expression of several pro-inflammatory mediators including interleukin(IL)-6, -chemokine (C-X-C motif) ligand(CXCL)-1, as well as the expression and release of monocyte chemotactic protein(MCP)-1. Correspondingly, functional monocyte migration assays revealed that aleglitazar reduced monocyte migration, an effect that was consistent with suppression of MCP-1 secretion. Under the same conditions, aleglitazar reversed the TNF-alpha-mediated suppression of insulin-stimulated ser312 IRS-1 phosphorylation and decreased the TNF-alpha-induced ser312 IRS-1 phosphorylation, two major switches in insulin-mediated metabolic activities; also restoring glucose uptake in insulinsensitive adipocytes. These effects were associated with the prevention of activation of serine and threonine kinases involved in the inflammatory-mediated expression of MCP-1, and with a prevention of insulin resistance, involving the p38 mitogen-activated protein (p38 MAPK).

Conclusion(s): Aleglitazar reduces adipose inflammation and dysfunction in insulin signalling in activated adipocytes. Such effects appear to mediate, at least in part, by interference with the activation of p38 MAPK. Although the extent of aleglitazar effect was never superior to those of PPARalpha and y agonist combination, these data suggest that aleglitazar may benefit diabetic and obese patients, and deserve further investigation.