Metabolism Clinical and Experimental xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Research advances in metabolism 2017

1. Introduction

The scope of this article is to present the most important recent advances in the field of metabolic research aiming to inspire the inception of creative research ideas and the start of novel research projects. We have therefore selected some of the most exciting original articles and reviews published in 2017 in *Metabolism*. We are including articles referring to the pathophysiology of important metabolic diseases, such as obesity, Non-alcoholic fatty liver disease (NAFLD), dyslipidemia, diabetes and its complications, as well as to novel mechanisms that can be targeted therapeutically or treatments that can be potentially further evaluated in sophisticated clinical settings.

Abbreviations: PTP1B, protein tyrosine phosphatase 1B; CNS, central nervous system; HFD, high fat diet; NPY, neuropeptide Y; AMPK, 5' AMP-activated protein kinase; BAT, brown adipose tissue; AF, albiflorin; hAMSCs, human adipose tissue-derived mesenchymal stem cells; PPAR$_\gamma$, peroxisome proliferator-activated receptor gamma; CEBPA, the CCAAT/enhancer-binding protein-alpha; AMPK, 5' AMP-activated protein kinase; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; RhM, rhesus monkeys; DysMet, metabolic dysfunction; CDPP, Curcumin-3,4 Dichloro Phenyl Pyrazole; C/EBP α, CCAAT/enhancer binding protein α; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FA, fatty acid; LPS, lipopolysaccharide; WT, wild type; DKO, double-knockout; FABP4/5, fatty acid binding protein 4 and 5; WD, western diet; LV, left ventricle; ROS, reactive oxygen species; NEFA, non-esterified fatty acids; FGF, fibroblast growth factor; IL-6, interleukin 6; PTP1B, protein tyrosine phosphatase; STZ, streptozotocin; PPARα, peroxisome proliferator-activated receptor α; TGF-1β, transforming growth factor 1β; ACC, acetyl-CoA carboxylase; CVD, cardiovascular disease; CKD, chronic kidney disease; XO, xanthine oxidase; WD, western diet; NAFLD, nonalcoholic fatty liver disease; STING, stimulator of interferon genes; (NF)-κB, nuclear factor κB; IRF, interferon regulatory transcription factor; IR, insulin resistance; NASH, non-alcoholic steatohepatosis; AGEs, advanced glycosylation end-products; SIRT1, Sirtuin 1; BCAAs, branched-chain amino acids; TG, triglyceride; CDHF, choline-deficient high fat diet; NFIL3, Nuclear factor interleukin-3; FGF21, fibroblast growth factor 21; CREB, cAMP response element protein; MS, Multiple sclerosis; GLUT-1, glucose transporter-1; CD4, cluster of differentiation 4; ATP, adenosine triphosphate; T2D, type 2 diabetes; CV, cardiovascular; HR, heart disease; LCKD, low-carbohydrate high fat ketogenic diet; FFAs, free fatty acids; CAN, cardiovascular autonomic neuropathy; HRV, heart rate variability; LF, low frequency; HF, high frequency; BMI, body mass index; DI, disposition index; NG, normoglycemic (NG); GIP, gastrointestinal peptide; PP, pancreatic polypeptide; IGF-1, insulin-like growth factor 1; IGFBP, insulin-like growth factor binding protein; PON-1, paraoxonase-1; PREVEND, prevention of renal and vascular end-stage disease; Lp (a), lipoprotein (a); PCSK9, proprotein convertase subtilisin/kexin type 9; HeFH, heterozygous patients with FH; AN, anorexia nervosa; HA, amenorrhea; GH, growth hormone.

2. Basic Research Studies

2.1. Knocking Down Amygdalar PTP1B in Diet-induced Obese Rats Improves Insulin Signaling/Action, Decreases Adiposity and may Alter Anxiety Behavior [1]

Protein tyrosine phosphatase 1B (PTP1B) is an ubiquitously expressed enzyme which has been associated with impaired insulin and leptin signaling [2]. The expression of PTP1B is increased in central nervous system (CNS) of mice fed a high fat diet (HFD) and knocking it down (either in whole nervous system or in hypothalamus) reduces adiposity [3,4]. Mendes et al. aimed to investigate whether PTP1B is also related to the anxiety disorders observed often in obesity and high-fat feeding through regulation of CNS function [1]. For this purpose, eight week old male Wistar rats were fed initially with HFD or chow for eight weeks and were subsequently treated for seven days with oligonucleotide antisense to knock down PTP1B levels. HFD increased significantly the expression of PTP1B in amygdala, a region of the brain that has been associated with the anxiety disorders observed in rodents. Knocking down PTP1B led to weight loss and decrease of fat mass without affecting lean mass. This was the result of increased energy expenditure in the light cycle of rats and reduced daily food intake probably through improvement of insulin signaling and alterations in neuropeptide expression (i.e. oxytocin and NPY). Regarding behavioral changes, PTP1B knock down led to improvement of important parameters of anxiety (e.g. enhance latency for food intake both in novel and known environment, tendency to spend more time in the center of the arena, increased time spent in open arms of elevated plus maze). These findings reveal a potential new target for improving obesity and the obesity-mediated anxiety disorders i.e. by regulating CNS function through PTP1B reduction.

2.2. Albiflorin Ameliorates Obesity by Inducing Thermogenic Genes via AMPK and PI3K/AKT In vivo and In vitro [5]

Activation of brown adipose tissue (BAT) or differentiation of white adipose tissue (WAT) to BAT are being investigated as possible mechanisms to increase body energy expenditure and subsequently prevent from obesity [6,7]. Albiflorin (AF) is a monoterpene glycoside and has been shown to reduce epididymal adiposity and improve impaired glucose metabolism in obese mice fed an HFD [7]. Jeong et al. investigated whether AF can protect from obesity and whether this is achieved through regulation of BAT activity [5]. Treatment of human adipose

https://doi.org/10.1016/j.metabol.2018.01.018

Please cite this article as: Perakakis N, et al, Research advances in metabolism 2017, Metabolism Clinical and Experimental (2018), https://doi.org/10.1016/j.metabol.2018.01.018

tissue-derived mesenchymal stem cells (hAMSCs) with AF significantly reduced lipid droplets and the expression levels of important genes related to adipogenesis i.e. of peroxisome proliferator-activated receptor gamma ($PPAR_{\gamma}$) and the CCAAT/enhancer-binding protein-alpha (CEBPA). Additionally, it enhanced markers related to differentiation of the adipocytes to beige phenotype. Treatment of obese mice due to HFD with AF reduced body weight and white adipose tissue by activation of BAT through regulation of thermogenic and mitochondrial genes and activation of 5' AMP-activated protein kinase (AMPK) and PI3K/AKT pathway. Collectively, AF may be a good candidate for the development of an anti-obesity treatment based on the increase of energy expenditure.

2.3. siRNA-mediated Inhibition of SREBP Cleavage-activating Protein Reduces Dyslipidemia in Spontaneously Dysmetabolic Rhesus Monkeys [8]

Diabetic dyslipidemia is characterized by insulin resistance with increased low-density lipoprotein (LDL)-C and triglycerides (TG) and reduced high-density lipoprotein (HDL)-C [9,10]. SREB cleavage-activating protein (SCAP) is a membrane protein that activates transcription factors related to lipid biosynthesis and lipid clearance [11–13]. In vitro and in vivo experiments have demonstrated reduced circulating LDL-C, TGs and proprotein convertase subtilisin/kexin type 9 (PCSK9) after inhibition of SCAP [14–16]. Murphy et al. evaluated in their work the effect of SCAP inhibition on the lipid profile of primates and specifically on rhesus monkeys (RhM) with metabolic dysfunction (DysMet Rhm) [8]. For this purpose, they treated DysMet Rhm with siRNA oligonucleotide-lipid nanoparticles designed to disrupt hepatic SCAP translation. The treatment resulted in 20% reduction of LDL-C, 30–40% of PCSK9 and >25% of triglycerides. Additionally, it reduced palmitate synthesis rate without affecting cholesterol synthesis rate. This study is the first demonstration of the positive effects of SCAP inhibition in primates with impaired lipid profile and reveals a new target for developing an effective treatment against diabetic dyslipidemia.

2.4. Curcumin-3,4 Dichloro Phenyl Pyrazole (CDPP) has Anti-adipogenic and Anti-dyslipidemic Effects by Activation of the Reverse Cholesterol Transport [17]

Curcumin is a natural polyphenol that has several beneficial effects such as antioxidant, anti-inflammatory, anti-mutagenic, anti-microbial, and anti-cancer properties. One of the major problems for using curcumin against diseases is its poor bioavailability due to inadequate absorption, rapid metabolism and elimination [17]. In order to overcome this problem, Gupta et al. synthesized curcumin derivatives and evaluated their bioavailability and functional properties. Among them, Curcumin-3,4-Dichloro Phenyl Pyrazole (CDPP) demonstrated much higher bioavailability and gastrointestinal stability compared to curcumin. Furthermore, CDPP inhibited the differentiation of preadipocytes while it did not affect lipolysis. This was achieved by an inhibition of the AKT/mTOR pathway, as well as by a reduction of gene and protein expression of important regulators of adipogenesis, such as the PPARγ and CEBPA, fatty acid synthase and fatty acid binding protein-4. Finally, CDPP blocked cell cycle arrest of preadipocytes in G1/S transition and in S phase probably through down regulation of ERK1/2 pathway. Increased oxygen consumption of mature adipocytes after CDPP treatment proved that CDPP caused increased energy utilization, which was also confirmed with increased UCP1 and PGC1α expression in the cells. In the past, hypolipidemic effects of curcumin had been observed using animal and human models. Specifically, curcumin has been associated with increased cellular cholesterol efflux and "reverse cholesterol transport", which is a procedure characterized by transport of excess cholesterol from peripheral tissue to liver and intestine [18]. Some of the mechanisms of these effects involve an increase of cholesterol efflux from adipocytes by regulating the PPARc-LXR-ABCA1 pathway [19] and the upregulation of low density lipoprotein receptor in liver cells [20]. Similar to curcumin, in the current study, CDPP demonstrated significant anti-dyslipidemic and hepatoprotective effects in vivo in HFD fed Syrian golden hamsters. Specifically, it reduced serum triglycerides, total cholesterol, LDL as well as aspartate aminotransferase (AST) and alanine aminotransferase (ALT). These effects were achieved by attenuation of adipogenesis and stimulation of reverse cholesterol transport through activation of the PPARα-LXRα-ABCA1 pathway. Altogether, CDPP overcomes the problem of reduced bioavailability observed in curcumin products, while maintaining the antidyslipidemic and hepatoprotective effects of curcumin.

2.5. Robust Suppression of Cardiac Energy Catabolism With Marked Accumulation of Energy Substrates During Lipopolysaccharide-induced Cardiac Dysfunction in Mice [21]

In healthy conditions, 70% of the energy required for heart function is supplied by fatty acid (FA) oxidation and only 30% by glucose oxidation [22,23]. In heart failure, FA oxidation is reduced and this reduction is compensated by increased glucose catabolism. Similarly, in cardiovascular dysfunction during sepsis, FA uptake and oxidation are decreased, but it is unclear whether glucose metabolism can compensate for these changes or it is impaired due to insulin resistance. Umbarawan et al. aimed to clarify how the observed changes in FA and glucose catabolism during sepsis affect cardiac function [21]. For this purpose, a systemic reaction similar to sepsis was induced with a lipopolysaccharide (LPS) injection in wild type (WT) and in double-knockout mice for fatty acid binding protein 4 and 5 (FABP4/5) (DKO mice). FABP4/5 bind to FAs and facilitate their transport, cellular uptake and metabolism. DKO mice demonstrate low FA uptake and increased glucose uptake in myocytes. In this study, cardiac function was determined by echocardiography along with serum parameters, gene expression, heart uptake of glucose and lipids, metabolome analyses and trace studies. Contrary to the initial hypothesis, sepsis in DKO mice was associated with a more profound deterioration of cardiac contractile function compared to WT mice, mainly due to decreased FA uptake and impaired glucose and ketone metabolism, despite the high glucose uptake. These results indicate that the shift from FA to glucose metabolism for maintaining energy sufficiency in the heart observed during sepsis, may have detrimental rather than favorable effects.

2.6. Enhanced Endothelium Epithelial Sodium Channel Signaling Prompts Left Ventricular Diastolic Dysfunction in Obese Female Mice [24]

Cardiac diastolic dysfunction is frequently observed in patients with obesity and with type 2 diabetes and is associated with increased risk for acute cardiovascular events [25]. Coronary microvascular endothelial dysfunction leads to cardiac diastolic dysfunction by activation of the endothelial cell mineralocorticoid receptors (ECMR) [26]. A signaling target of ECMR is the epithelial sodium channel (EnNac) located on the surface of endothelial cells [27,28]. Jia et al. aimed to investigate, whether cardiac fibrosis and maladaptive remodeling observed in obesity is a result of upregulated coronary vessel EnNaC signaling [24]. For this aim, four week-old female C57Bl6/J mice fed with Western Diet (WD) were treated with or without amiloride (antagonist of EnNaC) for 16 weeks. Amiloride-treatment prevented the diastolic dysfunction observed by WD, indicated by lower diastolic relaxation time and higher initial filling rate. Additionally, it attenuated unfavorable changes in cardiac remodeling by preventing the increase of F-actin and coronary arterial fibronectin observed in WD. Furthermore it prevented the increase of endothelial permeability, inflammatory response, oxidative stress and left ventricle (LV)-interstitial fibrosis by regulating tight junction proteins of the endothelium, macrophage polarization, reactive oxygen species (ROS)-generation and profibrotic signaling cascades respectively. Collectively, these findings demonstrate an important role for EnNaC in cardiac diastolic dysfunction observed in obesity.

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