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Integrated stress response activation by sleep fragmentation during late gestation in mice leads to emergence of adverse metabolic phenotype in offspring

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ABSTRACT

Background. Late gestational sleep fragmentation (SF) is highly prevalent particularly in obese women, and induces metabolic dysfunction in adult offspring mice. SF induces activation of the integrated stress response (ISR), which might be involved in metabolic disorders. We hypothesized that adult offspring of double mutant mice (DM) involving the critical ISR genes CHOP and GADD34 would be protected from developing obesity and insulin resistance following SF.

Methods. Time-pregnant CHOP/GADD34 DM and wild type (WT) mice were randomly assigned to sleep control (SC) or SF conditions during the last 5 days of gestation. At 24-weeks of age, body weight, fat mass, and HOMA-IR were assessed in the offspring. Tregs lymphocytes, Lyc6c^{high}, M1 and M2 macrophages were examined in visceral white adipose tissues (vWAT) using flow cytometry. The effects of plasma exosomes on adipocyte cell line proliferation, differentiation and insulin sensitivity were also evaluated.

Results. SF-WT male showed significant increases in body weight, vWAT mass and HOMA-IR compared to SC-WT mice, while SF had no effect in SF-DM mice. Inflammatory macrophages (Ly-6c^{high}) and the ratio of M1/M2 macrophages were increased while FoxP3+ Tregs counts were decreased in SF-WT but not in SF-DM mice. Exosomes from SF-WT, but not from the SF-DM offspring increased pre-adipocyte proliferation and differentiation, and decreased *in vitro* adipocyte insulin sensitivity.

Conclusion. Activation of the ISR during late gestation, as induced by late gestational SF, appears to underlie some of the transgenerational modifications in metabolic genes ultimately contributing to a metabolic syndrome phenotype in adult offspring.

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Abbreviations: CHOP, C/EBP homologous protein; DM, double mutant; ER, endoplasmic reticulum; eIF2α, eukaryotic initiation factor 2; FoxP3+, Forkhead box P3+; GADD34, growth-arrest and DNA-damage-inducible protein 34; HOMA-IR, Homeostasis model assessment of insulin resistance; ITT, insulin tolerance tests; ISR, integrated stress response; PERK, protein kinase-like ER kinase; SC, sleep control; SVF, stromal-vascular fraction; vWAT, visceral white adipose tissue; WT, wild type.

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1. Introduction

Obesity is a significant and increasing public health concern in the United States and worldwide [1,2]. Familial behaviors and genetics represent important factors that explain a substantial component of the variance in the well-recognized transgenerational susceptibility to obesity [3]. The direct impact of maternal dietary changes, obesity and its comorbidities on fetal development represent a new paradigm proposed to explain the transmissible character of metabolic diseases. Indeed, the impact of maternal obesity goes beyond the newborn period, whereby altered fetal programming during critical windows of gestation may impose long term detrimental effects on the offspring as well as on subsequent generations [4,5].

Maternal sleep disorders may constitute another gestational condition that adversely impacts the offspring's long term metabolic homeostatic regulation. Gestational sleep disorders are highly prevalent during late gestation [6,7], and their occurrence is particularly increased in obese women [8,9]. Indeed, pregnancy is associated with physiological changes including progressive weight gain and upward displacement of the diaphragm, placing pregnant women at risk for the development of sleep-disordered breathing [10–12]. As each apnea finishes with an arousal from sleep, SF is a frequent condition during late gestation and is susceptible to induce not only adverse metabolic maternal outcomes [13], but also likely to impact fetal metabolic development with long-term manifestations into adulthood. We have previously shown that late gestational sleep fragmentation (SF) in mice increases body weight and induces insulin resistance in adult progeny [14].

SF induces the integrated stress response (ISR) in adult mice, and consequently could impact metabolic function end energy homeostasis [16]. The cumulative evidence to date indicates that the ISR is intimately involved in the pathogenesis of obesity-associated metabolic diseases, such as diabetes [17] and dyslipidemia [18]. Obesity has been reported to induce the ISR that in turn leads to impaired insulin signaling [19]. The ISR is a highly preserved signaling pathway initiated in the endoplasmic reticulum (ER) upon phosphorylation of the alpha subunit of eukaryotic initiation factor 2 (eIF2α) at serine 51 in response to diverse stress conditions [20]. Under various pathological conditions including obesity and sleep disorders, ISR can be induced by unfolded protein accumulation in the ER lumen through activation of three signaling pathways which are initiated by three ER transmembrane sensors including double-stranded RNA-dependent protein kinase-like ER kinase (PERK). PERK phosphorylates eIF2α resulting in translational attenuation. Phosphorylation of eIF2α increases ATF4 expression, which results in activation of C/EBP homologous protein (CHOP), a pro-apoptotic transcription factor. CHOP in turn activates GADD34 (growth-arrest and DNA-damage-inducible protein 34), which acts to dephosphorylate eIF2α as a negative feedback thereby leading to termination of the protective component of the acute ISR [18].

Exosomes represent another potential mechanism linking sleep disorders, obesity and metabolic dysfunction. Exosomes are 30–100 nm vesicular structures that contain a wide variety of proteins, lipids, RNAs, non-transcribed RNAs, miRNAs and small RNAs [21]. Exosomes are released by a large variety of cells into their environment and also to the blood stream. Recent studies have involved exosomes in the vascular dysfunction associated with sleep apnea in children [22]. Indeed, plasma exosomes isolated from children with OSA and endothelial dysfunction induced marked *in vitro* and *in vivo* functional and structural alterations in endothelium that were mediated by altered exosomal miRNA cargo. For example, reductions in exosomal expression of hsa-miR-630 emerged as a significant effector of endothelial dysfunction [22]. Exosomes have also been shown to participate in the insulin resistance induced by a high fat diet in mice [23]. To this effect, exosomes isolated from mice fed with a palm oil enriched diet modified *in vitro* expression of genes involved in the cell cycle and muscle differentiation [23]. To the best of our knowledge, no data are available on the role of exosomes in the gestational SF-induced metabolic dysfunction in offspring.

The aim of the study was to investigate the role of the ISR in metabolic phenotype that characteristically occurs among the progeny of SF-exposed mice. Therefore, we evaluated the metabolic status of adult offspring from CHOP/GADD34-null pregnant mice exposed to SF as compared to wild type (WT) mice.

2. Materials and Methods

2.1. *Pregnant Female Mice*

All experiments were approved by The University of Chicago Institutional Animal Care and Use Committee (IACUC 72169). Male and female C57B6J (WT) mice were purchased from The Jackson Laboratory (Bar Harbor, ME) for breeding. Time-pregnant CHOP/GADD34 double mutant (DM) were used. These mice were generated through crossing of single mutants generated in David Ron's laboratory (http://ron.cimr.cam.ac.uk/RONMICE_JAX.html [24–26] to each other to generate mice that were heterozygous for both mutations. Double heterozygotes were interbred to generate the homozygous double mutants on a C57B6J background. All animals were allowed to recover within the animal care facility in which SF procedures would be carried out for 7 days. Animals were fed a normal chow diet and housed in a controlled environment with 12-h light–dark cycles (7:00 A.M. – 7:00 P.M.) in constant temperature (24 ± 0.2 °C) with *ad libitum* access to food and water. For all measurements and assessments, experimenters were blinded to the identity of the mice being tested.

Individual 3-month-old male and virgin female mice were used for breeding to generate only one litter. Male mice were removed once inspection of the female revealed the presence of a copulation plug (day 1 of gestation). After 14 days of pregnancy, the mice were divided into two groups: late gestational control sleep (SC) mice were housed in standard housing conditions, and sleep fragmented mice were exposed to an SF paradigm for 5 days (days 14–19 of gestation). Thus, 4

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