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Voluntary post weaning exercise restores metabolic homeostasis in offspring of obese rats

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Abstract *Aim:* Physical exercise reduces obesity, insulin resistance and dyslipidemia. We previously found that maternal obesity alters central appetite circuits and contributes to increased adiposity, glucose intolerance and metabolic disease in offspring. Here we hypothesized that voluntary exercise would ameliorate the adverse metabolic effects of maternal obesity on offspring.

Methods and Results: Sprague–Dawley females fed chow (C) or high-fat diet HFD (H) were mated. Female offspring from C dams were weaned onto chow (CC); those from H dams recieved chow (HC) or HFD (HH). Half of each group was provided with running wheels (CC_{EX}, HC_{EX}, HH_{EX}; $n = 10–12$).

Maternal obesity increased body weight (12%), adiposity, plasma lipids and induced glucose intolerance (HC vs CC; $P < 0.05$). These were exaggerated by postweaning HFD (HH vs HC; $P < 0.01$), showed doubled energy intake, a 37% increase in body weight, insulin resistance and glucose intolerance (HH vs HC; $P < 0.01$). Exercise reduced fat mass, plasma lipids, HOMA and fasting glucose in HC_{EX} (vs HC; $P < 0.05$) and HH_{EX} (vs HH; $P < 0.01$). Values in HC_{EX} were indistinguishable from CC, however in HH_{EX} these metabolic parameters remained higher than the sedentary HC and CC rats ($P < 0.01$). mRNA expression of hypothalamic pro-opiomelanocortin, and adipose tumour necrosis factor α and 11β-hydroxysteroid dehydrogenase type 1 were reduced by exercise in HH_{EX} (vs HH; $P < 0.05$).

Conclusion: While voluntary exercise almost completely reversed the metabolic effects of maternal obesity in chow fed offspring, it did not fully attenuate the increased adiposity, glucose intolerance and insulin resistance in offspring weaned onto HFD.

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Acronyms

AgRP	Agouti related protein
ARC	Arcuate nucleus
ATGL	Adipose triglyceride lipase
BMI	Body mass index
CRH	Corticotrophin releasing hormone
FFA	Free fatty acid
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GTT	Glucose tolerance test
HFD	High fat diet
HOMA	Homeostasis model assessment
11βHSD-1	11β-Hydroxysteroid dehydrogenase type 1
LSD	Least significant difference
mTOR	Mammalian target of rapamycin
NPY	Neuropeptide Y
Ob-Rb	Leptin receptor
POMC	Pro-opiomelanocortin
PPARγ	Peroxisome proliferator activated receptor gamma
PVN	Paraventricular nucleus
RP	Retroperitoneal
rRP	Right retroperitoneal
SOCS3	Suppressor of cytokine signalling
TNF-α	Tumour necrosis factor alpha
WAT	White adipose tissue
Y1 receptor	Neuropeptide Y type 1 receptor

Introduction

Obesity in women confers increased risk to maternal health and pregnancy outcomes [1] and there is growing evidence for transmission of obesogenic and diabetogenic traits [2–4]. Maternal obesity alters hormones and has long-lasting consequences for offspring hypothalamic appetite regulation and metabolism [2,5]. Maternal obesity is also associated with elevated blood pressure in offspring [6], increasing the risk of metabolic syndrome.

Dysregulation of the central mechanisms that control energy balance plays a major role in the development of obesity. Insulin and leptin normally regulate neuropeptides in the hypothalamic arcuate nucleus (ARC) that control food intake [7]. However, the high leptin levels in obesity fail to bring about weight loss due to central leptin resistance [8]. Although genetic makeup influences hypothalamic appetite regulation and thus body weight [2,5,9], physical activity and diet are also important factors contributing to energy homeostasis [10,11]. Expression of neuropeptide Y (NPY), a major hypothalamic orexigenic peptide, was altered by exercise [12,13].

Exercise has also been shown to ameliorate hypertension and reduce the risk of cardiovascular disease. Obesity-related hypertension has been linked to increased sympathetic activation, possibly related to hyperleptinemia and hyperinsulinemia [14]. Other adipocyte derived mediators such as tumour necrosis factor-α (TNF-α) have effects on endothelial function [15]. 11β-hydroxysteroid dehydrogenase-1 (11βHSD-1) also plays a key role in cardiovascular risk by converting cortisone to its active form, cortisol [16]. Exercise is known to modulate 11βHSD-1 and TNF-α expression [17,18], possibly ameliorating hypertension.

Our previous studies [5,19] showed that high fat diet (HFD) fed offspring from obese dams showed greater metabolic risk than those consuming chow [5,19]. As beneficial impacts of physical exercise on metabolism, adiposity and leptin sensitivity have been demonstrated [12,18], we hypothesized that exercise would ameliorate the adverse effects of maternal obesity. To our knowledge, this is the first study documenting the impact of exercise on offspring of obese rats. As maternal obesity may have important trans-generational impacts, female offspring were studied. Given the role of physical exercise on appetite control [12], hypothalamic appetite regulators were examined. As obesity is associated with increased production of inflammatory cytokines and corticosterone, we measured adipose mRNA expression of leptin, TNF-α and 11βHSD-1.

Methods

Animal experiments were approved by the Animal Care and Ethics Committee of the University of NSW. Female Sprague–Dawley rats (8 weeks) were housed at 20 ± 2 °C, 12/12 h light/dark and fed either standard chow (C) (11 kJ/g, 14% fat, 21% protein, 65% carbohydrate by energy, Gordon's Specialty Stockfeeds, Australia) or two commercial high fat pelleted diets (H) SF01-025 (18.3 MJ/kg, 40.7% fat, 14.3% protein, 44.9% carbohydrate), SF01-020 (20 MJ/kg, 43% fat, 17% protein, 40% carbohydrate, Specialty feeds, Glen Forest, Australia) for 5 weeks.

At 14 weeks females were mated with chow fed male Sprague–Dawley rats. Dams continued on their assigned diet throughout pregnancy and lactation. At weaning, female offspring from chow fed dams were fed chow (CC); offspring from obese dams were fed chow (HC) or HFD (HH). Half of each group was provided with a running wheel (CC_{EX}, HC_{EX}, $HH_{EX;}$ $n = 10–12$); the remainder were sedentary (CC, HC, HH; $n = 10–11$). Distance traveled was calculated from wheel rotations every 24 h. To avoid stress due to social isolation, all rats were housed 2–3 per cage; exercised rats shared one wheel per cage. Offspring were killed at 14 weeks of age.

Offspring data

Energy intake: average 24-h intake (g) was calculated weekly from 4 to 13 weeks by carefully collecting and weighing food remaining in the cage, subtracting this from the known amount given to calculate total kJ.

Glucose tolerance test (GTT): at 11 weeks GTT was performed after 6 h fasting. Wheels were locked 18 h prior to GTT. After baseline blood glucose measurement (Accu-Chek Glucometer), rats received 2 g glucose/kg (30% w/v) by intraperitoneal injection. Blood samples were taken at