Insulin Resistance Induced by Early Life Overnutrition is Reversed by Calorie Restriction
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Abstract

Overnutrition of the rat during the suckling period results in the development of hyperinsulinemia, adult-onset obesity and insulin resistance. To investigate insulin resistance in the skeletal muscle of adult male rats, the litter size was reduced from 12 (NL) to 3 (SL) male pups/dam from postnatal day 3 to day 21. Both NL and SL rats were fed lab chow ad libitum until day 140. Another SL group was pair-fed (SLPF) to NL rats starting from day 21. On day 94, ½ of the SL/PF rats continued being pair-fed, while the remaining SLPF rats were allowed ad libitum feeding of chow (SLPF/AL). Insulin receptor substrate-1 (IRS-1) levels were significantly reduced in skeletal muscle of SL rats but pair-feeding normalized IRS-1 levels in SLPF rats. However switching to ad libitum feeding maintained IRS-1 levels similar to that of NL. These results show that pair-feeding was adequate to reverse insulin resistance in SLPF rats.

Introduction

Obesity is a large concern from both public and economic standpoints today, especially in Western societies. Statistics show that 35.7% of the adult population in the U.S. alone is classified as obese (w/ BMI’s > 30), which is an increase from previous time periods. The presence of obesity puts people who have it at higher risk for several metabolic disorders such as hypertension, adverse lipid concentrations and type II diabetes. Even though genetics, sedentary lifestyle, and increased consumption of high-caloric foods are the major causes underlying the current obesity epidemic, epidemiological data and results from animal models suggest that altered nutritional experiences during early periods in life (i.e. fetal and suckling period) can potentiate development of obesity and metabolic diseases later in the offspring’s life. The maturation of organs such as the pancreas and the hypothalamic neuronal system in rodents is completed only in the immediate postnatal period, so it is during this period that malnutrition can affect developmental programming. While these early adaptations enable the organism to endure the nutritional stress, in the long run they are disadvantageous. It has been demonstrated that cross-fostering of normal rats offprings by a diabetic dam resulted in metabolic disorders in adulthood.

A rat model for metabolic programming effects due to changes in nourishment during the suckling period is the small litter (SL) mode in which the litter size is reduced to 3 pups/dam. Overnutrition induced by the reduction of litter size for newborn pups resulted in increased levels of serum insulin and leptin and increased body weight gains during the suckling period. Insulin resistance also resulted. It has been shown that deviations in insulin-stimulated glucose uptake can play a major role in the pathogenesis of insulin resistance. This condition is proven to be associated with alterations in the components of the insulin signaling cascade including reduced serine phosphorylation of the insulin receptor and IRS (insulin receptor substrate) proteins. These effects persisted in the postweaning period with the manifestation of obesity and other metabolic disorders in adulthood.

Methods

Western blotting: Skeletal muscle samples were homogenized in ice-cold lysis buffer and supernant was obtained by centrifugation. Total protein in supernant was measured by BCA method (Bio-Rad, Hercules, CA, USA). Proteins were separated using SDS-PAGE and detected using specified antibodies.

Previous Findings

Body weights of NL and SL rats from postnatal day 3 (d3) to d24 (A); NL: n 26; SL: n 34 PF (left). Body weights (B; n 9 – 12/group) and mean weekly food intake (C; n 9 – 12/group) of NL, SL, SLPF, and SLPF/AL rats from d28 to d140. Results are expressed as means ± SE.

Summary

• Overnutrition of rats in the postnatal period leads to the reduction of the levels of IRS-1 in skeletal muscle, indicating a defect in the insulin-signaling pathway. This may contribute to the development of insulin resistance reported in SL rats.
• Pair-feeding normalized IRS-1 levels in skeletal muscle in SL rats, and was sufficient in reversing the developmental programming effects brought by overnutrition in the postnatal period.
• Serine (S302) phosphorylation of IRS-1 is not affected by overnutrition during the postnatal period. This is an odd finding in view of insulin resistance in SL rats.

Results

A Western blot of IRS-1 (non-phosphorylated)

B

C

D

Gel I (3 animals/treatment) Gel II (3 animals/treatment)

Insulin Signaling Pathway

Skeletal muscle of adult male rats, the litter size was reduced from 12 (NL) to 3 (SL) male pups/dam from postnatal day 3 to day 21. Both NL and SL rats were fed lab chow ad libitum until day 140. Another SL group was pair-fed (SLPF) to NL rats starting from day 21. On day 94, ½ of the SL/PF rats continued being pair-fed, while the remaining SLPF rats were allowed ad libitum feeding of chow (SLPF/AL). Insulin receptor substrate-1 (IRS-1) levels were significantly reduced in skeletal muscle of SL rats but pair-feeding normalized IRS-1 levels in SLPF rats. However switching to ad libitum feeding maintained IRS-1 levels similar to that of NL. These results show that pair-feeding was adequate to reverse insulin resistance in SLPF rats.