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High Fat Diet Induced Insulin Resistance and Glucose Intolerance is Gender-Specific in IGF-1R Heterozygous Mice

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Abstract

Interactions between genes and environment play a critical role in the pathogenesis of Type 2 diabetes. Low birth weight, due to genetic and environmental variables affecting fetal growth, is associated with increased susceptibility to the development of type 2 diabetes and metabolic disorders in adulthood. Clinical studies have shown that polymorphisms in the Insulin-like growth factor 1 (IGF-1) gene or heterozygous mutations in IGF-1 and IGF-1 receptor (IGF-1R) genes, resulting in reduced IGF-1 action, are associated with low birth weight and post-natal growth. Mice lacking one of the IGF-1R alleles (*Igflr*^{+/-}) exhibit a 10% reduction in post-natal growth, and develop glucose intolerance and insulin resistance as they age. To investigate whether adverse environmental factors could accelerate the onset of the metabolic syndrome, we conducted a short duration intervention of high fat diet (HFD) feeding in male and female *Igflr*^{+/-} and wild-type (WT) control mice. The HFD resulted in insulin resistance, hyperglycemia, and impaired glucose tolerance in males of both genotypes whereas in females exacerbated diabetes was observed only in the *Igflr*^{+/-} genotype, thus suggesting a sexual dimorphism in the influence of obesity on the genetic predisposition to diabetes caused by reduced IGF-1 action.

Keywords

IGF-1; IGF-1R; *Igflr*^{+/-}; SGA; HFD; Type 2 diabetes

1. Introduction

The pathogenesis of type 2 diabetes results from a complex interaction between genetic and environmental factors [1; 2]. Mutations in several candidate genes have been proposed to

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increase the susceptibility of an individual to type 2 diabetes [2], whereas adverse environmental factors including decreased physical activity and consumption of high fat or high calorie diets, increase the risk of developing the metabolic syndrome [2; 3; 4]. Infants born small for gestational age (SGA), also are at increased risk for developing type 2 diabetes in adult life [5; 6; 7]. Environmental factors, such as maternal glucose insufficiency leading to hypercortisolemia, have been implicated in increased diabetes risk in SGA subjects [6]. Resistance to Insulin-like growth factor 1 (IGF-1) action, as seen in subjects expressing heterozygous mutations or hemizygous deletions resulting in loss of function of the IGF-1 receptor (IGF-1R), is now being suggested as a genetic factor that could increase diabetes risk in low birth weight individuals [8; 9; 10; 11; 12]. Igf-1, apart from being a growth factor, also plays an important role in metabolism by suppressing insulin secretion and increasing glucose disposal in the skeletal muscle [13; 14]. Transgenic mice expressing a kinase deficient IGF-1R beta subunit in skeletal muscle exhibit reduced signaling via the IGF-1R and IGF-1R/IR hybrids (the latter due to dominant negative effects) and severe diabetes early in life [15; 16]. In contrast, we have found that mice lacking one of the *Igf-1r* alleles (*Igf1r*^{+/-}) throughout the body exhibit a 10% reduction in post-natal growth, and develop glucose intolerance and insulin resistance as they age (Bokov and Garg et al, submitted to PLoS One, 2011). Therefore, we propose that defects in the IGF-I/IGF-IR signaling pathway in the *Igf1r*^{+/-} mouse could provide a model for elucidation of the association between IGF-1 resistance, reduced birth and post-natal weight and the risk for developing type 2 diabetes later in adult life.

High fat diets (HFD) combine with genetic factors and other variables to reduce insulin sensitivity and promote the development of type 2 diabetes [17]. It has been previously demonstrated that rats born SGA due to intrauterine hypoxia, had increased propensity to develop diabetes when fed a HFD post-natally [18]. This could represent an important model of the hypothesized effect of “obesogenic” diets to increase the risk for the development of insulin resistance in SGA subjects. To investigate whether diet-induced obesity could accelerate the onset of insulin resistance in *Igf1r*^{+/-} mice, we fed *Igf1r*^{+/-} mice and wild-type (WT) controls HFD beginning at 19 months of age for five weeks. Our results demonstrate that HFD feeding exacerbates diabetes in female *Igf1r*^{+/-} mice, thus suggesting a sexual dimorphism in the influence of obesity on the genetic predisposition to diabetes caused by reduced IGF-1 action.

2. Materials and Methods

2.1. Animals and Experimental Design

The *Igf1r*^{+/-} mice were kindly provided by Dr. Argiris Efstradiatis (Columbia University College of Physicians and Surgeons, New York) who derived them in a 129Sv background by homologous recombination targeted ablation of the third exon of the *Igf1r* gene [19]. We obtained *Igf1r*^{+/-} male breeder mice that had been backcrossed 10 times on the C57Bl/6J background. To establish the colony of mice used in this study, *Igf1r*^{+/-} males were bred to C57BL/6 WT (i.e., *Igf1r*^{+/+}) females purchased from the Jackson Laboratory (Bar Harbor, ME). The genotypes of the mice were determined as described by Liu et al. [19]. Male and female *Igf1r*^{+/-} mice and WT were fed *ad libitum* a standard lab chow procured from Harlan, USA (Catalog No. Harlan Teklad LM-485 Mouse/Rat Sterilizable Diet 11.5 kcal% fat) and maintained in micro-isolator cages, 5 to a cage, on a 12-hour dark/light cycle. At 19 months of age, animals were shifted to individual cages and fed a high fat diet containing 60 kcal% fat procured from Research Diets Inc., USA (DIO Diet D12492). Food was changed and food intake and body weight were measured at the same time every week for 5 weeks. The same amount of food was given to all the mice. Prior to initiation of the HFD and again at the end of the five weeks of HFD, blood was collected from the mice for serum analyses and they were subjected to glucose tolerance test (GTT) and insulin tolerance test (ITT).

After an overnight fast, tissues were harvested for RNA analysis and triglyceride (TG) measurements. All procedures involving mice were approved by the Institutional Laboratory Animal Care and Use Committee of the University of Texas Health Science Center (San Antonio, TX).

2.2. Serum Insulin and TGs

Serum insulin was assayed using an Ultra Sensitive Rat ELISA Kit (Catalog No. 90060; Crystal Chem, Downers Grove, IL, USA). Serum TGs were measured using a Triglyceride Assay Kit (Catalog No. 10010303; Cayman Chemical Company, Ann Arbor, MI, USA).

2.3. Glucose and Insulin Tolerance Tests (GTT and ITT)

For GTT, mice were fasted for 12hrs. Blood glucose was measured at 0, 30, 60 and 120min after i.p. injection of 2g/kg body weight of dextrose. ITT was performed by fasting the mice for 4hrs followed by i.p. injection of 0.5U/kg body weight of insulin (Novolin, Novo Nordisk, Princeton, NJ, USA). Blood glucose was measured at 0, 30, 60 and 90min. All blood glucose measurements were done using an Accucheck glucometer (Roche Diagnostics, Indianapolis, IN, USA)

2.4. Real-time PCR

Mice were fasted for 12hrs and tissues were removed and frozen in liquid nitrogen. Total RNA was isolated from the liver, muscle and adipose using RNA STAT-60 (Tel-test, Friendswood, TX, USA) in accordance with the manufacturer's protocol. Single stranded cDNA was synthesized from 2.5ug of RNA using the High-capacity cDNA Archive Kit (P/N 4322171; Applied Biosystems, Foster City, CA, USA). Real-time PCR reaction was performed for each of the following genes, using TaqMan-MGB fas (Mm00662319_m1), cpt-1 (Mm00487200_m1) and cd36 (Mm00432403_m1) and normalized to b2m (Mm00437762_m1) purchased from Applied Biosystems (TaqMan Gene Expression Assays). All samples were run in duplicate and quantitated in an ABI 7500 thermal cycler.

2.5. Tissue TG

Liver tissue (50 mg) was homogenized in 1ml of 2:1 chloroform-methanol and solubilized overnight at 4°C with shaking. 0.5 ml 0.6 % NaCl was added followed by centrifugation at $800 \times g$ for 20 min at 4°C. The organic phase was transferred to a new tube and the samples were dried under nitrogen gas and reconstituted with 100 μ l 1% Triton X-100/PBS. TG concentrations were measured using a Triglyceride Assay Kit (Cayman Chemical Company, Ann Arbor, MI).

2.7. Statistical Analyses

Area under the curve for the GTT and the ITT was calculated using the trapezoid rule. This area under the curve was divided by the total time of observation (120 min for the GTT and 90 min for the ITT) to yield a time-averaged glucose concentration.

Data were analyzed using analysis of variance (ANOVA) for repeated measurements [20]. The effects of gender, genotype, and the gender by genotype interaction were tested using the between-subjects mean square. The effects of diet, the two-factor interactions gender by diet and genotype by diet, and the three-factor interaction gender by genotype by diet were tested using the within-subjects mean square. Residual analyses indicated that all data, except the TG concentrations, were in reasonable accord with the assumptions underlying the ANOVA. Residual analysis suggested a logarithm transformation for the TG concentrations. Because results were similar for statistical analyses of both the

untransformed and transformed data, we show only the results of analyses of the untransformed data.

3. Results

3.1. Body weight

All mice, regardless of genotype, gained weight when fed the HFD diet for five weeks but the effect was not significant in the female WT (Fig. 1; A). Male WT on HFD showed significantly greater weight gain than male *Igf1r*^{+/-} mice on HFD. Female *Igf1r*^{+/-} mice had greater body weight compared to WT on HFD but the effect was not significant. When expressed as relative body weight, male *Igf1r*^{+/-} and WT mice showed the same weight gain on HFD. However, the female *Igf1r*^{+/-} on HFD had significantly greater body weight than the female WT mice on HFD (Fig. 1, B). The amount of food ingested was similar in male and female *Igf1r*^{+/-} and WT mice (data not shown).

3.2. Blood and serum variables

Fasting blood glucose levels did not differ between male or female *Igf1r*^{+/-} and WT mice on the chow diet (Table 1). After five weeks of HFD female *Igf1r*^{+/-} had higher blood glucose than WT mice, which showed no increase in blood glucose on the HFD. In contrast, male *Igf1r*^{+/-} and WT mice both showed increased blood glucose on the HFD but there were no genotype difference in males on the HFD. Serum insulin levels did not differ between male and female *Igf1r*^{+/-} and WT mice on the chow diet (Table 1). After 5 weeks on the HFD, serum insulin levels tended to increase in female *Igf1r*^{+/-} mice, although the increase was not statistically significant. Wild-type female mice showed no change in serum insulin when fed the HFD. In males, HFD feeding significantly increased serum insulin levels to the same extent in *Igf1r*^{+/-} and WT mice. Serum TGs were not different between female *Igf1r*^{+/-} and WT mice on either chow diet or HFD (Table 1). Both *Igf1r*^{+/-} and WT male mice showed significantly increased serum TGs on the HFD diet with no difference between genotypes.

3.3. Genotype, diet and gender effects on glucose and insulin tolerance

GTT and ITT were conducted in male and female mice on chow-diet and again after 5 weeks of HFD [21]. Time averaged glucose values during GTT did not differ between male and female *Igf1r*^{+/-} and WT mice on the chow diet (Fig. 2; A). HFD induced glucose intolerance in all groups except female WT. Thus female *Igf1r*^{+/-} on HFD were more glucose intolerant whereas glucose tolerance in the female WT on the HFD was unchanged from that of female WT mice on the chow diet. In contrast, male *Igf1r*^{+/-} and WT mice exhibited a similar degree of glucose intolerance after 5 weeks of HFD feeding. HFD induced insulin intolerance in a pattern similar to that during GTT (Fig. 2, B). Five weeks of HFD induced a similar decrease in insulin sensitivity in male *Igf1r*^{+/-} and WT mice. However, female *Igf1r*^{+/-} on HFD, but not female WT, developed insulin resistance as assessed by ITT.

3.4. Tissue-specific expression of lipid regulatory genes

Increased fasting glucose and insulin levels in the HFD fed mice led us to determine whether there was any change in the expression of lipid regulatory genes in the liver, muscle and adipose tissue. Female *Igf1r*^{+/-} on HFD had a trend towards increased expression of *fas*, compared to WT, but the effect was not significant (Table 2). Male WT on HFD also exhibited a trend towards increased *fas* expression, compared to *Igf1r*^{+/-}, but the effect was not statistically significant. The expression of liver *cpt1*, a gene involved in fatty acid oxidation, was lower in males compared to females. However, there was no difference in *cpt1*, expression between *Igf1r*^{+/-} and WT in either males or females. Expression of *cd36*, a

gene involved in fatty acid transport, was significantly increased in the liver of females on HFD compared to males on same diet and tended to be higher in the female *Igf1r*^{+/-} as compared to female WT. There was no difference in *cd36* expression between male *Igf1r*^{+/-} and WT mice on the HFD. In the muscle and adipose tissue, *fas* and *cpt1* expression remained unaltered between the genotypes of male and female mice (Table 2).

The results were the same if log-transformed data were analyzed except for an additional significance in the expression of *fas* in the muscle of male *Igf1r*^{+/-} compared to female *Igf1r*^{+/-} (Geometric mean for Female *Igf1r*^{+/-} 1.56 vs. Male *Igf1r*^{+/-} 2.55, $p \leq 0.05$).

3.5. Tissue TG

Increased hepatic expression of *cd36* has been associated with increased TG accumulation during diet induced obesity [22]. We measured liver TGs in male and female *Igf1r*^{+/-} and WT mice. Female *Igf1r*^{+/-} mice on HFD had increased hepatic TGs as compared to WT; however, this difference did not reach significance (Fig. S1). There was no difference in TG levels between male *Igf1r*^{+/-} and WT mice on HFD.

4. Discussion

The pathogenesis of type 2 diabetes involves the interaction of genetic factors such as mutations in genes important in insulin signaling and metabolism, with adverse environmental factors such as western style high fat diets and a sedentary life style [17]. In order to explore gene-environment studies, we conducted a short duration intervention of HFD feeding to *Igf1r*^{+/-} mice, which is the first example of a genetic manipulation with low post-natal weight and exacerbated diabetes on a HFD. Our results demonstrate that feeding a HFD for 5 weeks to 19 months mice resulted in female *Igf1r*^{+/-} mice gaining more weight as compared to the WT mice, and, importantly, loss of protection of female mice from the diabetogenic effects of the HFD. In contrast male mice of both genotypes developed similar increases in obesity and insulin resistance on HFD. Similar results of HFD feeding were obtained in male mice with an overexpression of dominant negative mutant IGF-1R (MKR) mice in which both the IGF-1 and the insulin signaling pathways have been disrupted. However, female MKR mice were not studied [23].

During insulin resistance, hyperglycemia and hyperinsulinemia lead to dysregulation of lipid metabolism resulting in increased expression of genes involved in de novo lipogenesis [24; 25]. High insulin levels in HFD fed male mice of both genotypes positively correlated with increased expression of lipogenic gene *fas* in all three metabolic tissues liver, muscle and adipose. In liver, consistent with increased lipogenesis, males exhibited decreased expression of fatty acid oxidation gene *cpt1*. Serum TGs were elevated in males of both genotypes on a HFD when compared to females which could be a result of increased hepatic TG accumulation and concomitant secretion [26]. Hyperinsulinemia in males, via up-regulation of lipogenic genes, may play a significant role in the ability of insulin to increase triglyceride synthesis in the liver thus resulting in hypertriglyceridemia [26]. Females on HFD exhibited an increased expression of fatty acid transport gene *cd36*, in liver, which is in line with recent reports on the sexual dimorphic expression of this gene in the liver tissue [27]. Interestingly, *cd36* expression was significantly elevated in female *Igf1r*^{+/-} mice compared to WT mice which was associated with elevated levels of hepatic TG suggesting increased fatty acid uptake and dyslipidemia in *Igf1r*^{+/-} mice [22]. In fact, it has recently been demonstrated that liver *cd36* expression was elevated during hyperglycemia and insulin resistance [22; 28].

In summary, our observations may reflect an important sexually dimorphic response to a genetic manipulation where loss of one *Igf1r* allele results in loss of resistance to a HFD in

the female gender. Reduced estrogen is reported to result in susceptibility to HFD-induced obesity [29], but in the 19-month old WT female mice there could be just enough residual estrogen to be protective for a short duration of HFD feeding. The gender differences observed on a HFD could originate from interactions between estrogen and metabolic pathways involved in maintaining glucose and lipid homeostasis [29]. Administration of estradiol to ovariectomized mice fed a HFD controlled insulin resistance by increasing IRS-1 expression and Akt phosphorylation in insulin-stimulated muscle thereby resulting in peripheral insulin sensitivity [30]. Thus future studies will focus on determining estrogen status and effects on insulin sensitivity in *Igf1r^{+/-}* mice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights

- Interaction between genes and environment is critical in pathogenesis of diabetes.
- Reduced IGF-1 action is associated with low birth weight and post-natal growth.
- We examine effects of short duration HFD in male and female $Igf1r^{+/-}$ and WT mice.
- $Igf1r$ heterozygosity results in loss of resistance to HFD in the female gender.

Figure 1.

Body weight of male and female *Igflr*^{+/-} and WT mice on chow and HFD. Mean body weight (A) and body weight relative to weight while consuming the chow diet (B) by gender, genotype, diet, and time on HFD. All measurements were performed in 19 month old male (n = 11–13) and female (n = 5–8) mice fed chow diet at week 0 and HFD for 5 weeks. ○ Female WT, ● Female *Igflr*^{+/-}, △ Male WT, ▲ Male *Igflr*^{+/-} **a** HFD (week 5) significantly different from chow (week 0), same gender and genotype, **b** *Igflr*^{+/-} significantly different from WT, same gender and diet and **c** male significantly different from female, same genotype and diet.

Figure 2.

Glucose and Insulin Tolerance Tests in male and female *Igflr*^{+/-} and WT mice on chow and HFD. Time-averaged glucose concentrations for GTT (A) and ITT (B) by gender, genotype and diet in 19 month old male and female mice on chow diet at week 0 and at the end of 5 weeks of HFD. GTT and ITT were performed as described in the material and methods. The data were obtained from 11–13 male and 5–8 female mice and the mean $\pm$ SE is shown. chow diet, HFD. **a** HFD (week 5) significantly different from chow (week 0), same gender and genotype, **b** *Igflr*^{+/-} significantly different from WT, same gender and diet and **c** male significantly different from female, same genotype and diet.

Blood and serum variables in male and female *Igflr^{+/-}* and WT mice on chow and HFD. Concentrations of fasting glucose, insulin and triglycerides were measured by gender, genotype and diet in the serum from 19 month old male and female mice on chow diet at week 0 and at the end of 5 weeks of HFD as described in the materials and methods.

Table 1

Gender	Genotype	Diet	Glucose (Mean ± SE)	Insulin (Mean ± SE)	TGs (Mean ± SE)
Female	WT	Chow	76.8 ± 7.3	0.34 ± 0.38	86.3 ± 24.5
		HFD	72.2 ± 7.3	0.54 ± 0.38	74.1 ± 24.5
	<i>Igflr^{+/-}</i>	Chow	78.0 ± 6.1	0.52 ± 0.38	88.6 ± 20.7
		HFD	99.4 ± 6.1 ^{ab}	1.42 ± 0.35	82.4 ± 22.4
Male	WT	Chow	71.6 ± 4.9	1.15 ± 0.26	94.0 ± 16.5
		HFD	104.3 ± 4.9 ^{ac}	2.68 ± 0.29 ^{ac}	175.2 ± 16.5 ^{ac}
	<i>Igflr^{+/-}</i>	Chow	79.2 ± 4.7	0.89 ± 0.25	64.4 ± 15.8
		HFD	119.2 ± 4.7 ^a	2.42 ± 0.26 ^a	178.2 ± 16.5 ^{ac}

The data were obtained from 11–13 male and 5–8 female mice and the mean ± SE is shown.

^a HFD (week 5) significantly different from chow (week 0), same gender and genotype,

^b *Igflr^{+/-}* significantly different from WT, same gender and diet and

^c male significantly different from female, same genotype and diet.

Liver, muscle and adipose gene expression in male and female *Igflr*^{+/-} and WT mice. The mRNA levels of lipid regulatory genes were measured by gender and genotype in the indicated tissues from male (n=6-7) and female (5-8) mice at the end of 5 weeks of HFD.

Table 2

Gender	Genotype	Liver			Muscle			Adipose		
		fas	cpt1	cd36	fas	cpt1	cd36	fas	cpt1	cd36
Female	WT	0.83±0.75 ^a	0.92±0.13 ^a	0.81±0.07 ^a	1.13±0.50 ^a	1.20±0.19	1.09±0.33 ^a	1.12±0.19		
	<i>Igflr</i> ^{+/-}	1.13±0.60 ^a	0.74±0.10 ^a	1.09±0.05 ^{ab}	1.64±0.40	1.14±0.15	1.84±0.26	1.12±0.15		
Male	WT	4.44±0.69	0.24±0.12	0.23±0.06	3.93±0.46	1.32±0.17	2.63±0.30	1.32±0.17		
	<i>Igflr</i> ^{+/-}	3.64±0.69	0.26±0.12	0.18±0.06	2.59±0.46	0.96±0.17	2.48±0.30	1.36±0.17		

Data are mean ± SE.

^a female significantly different from male, same genotype and

^b *Igflr*^{+/-} significantly different from WT, same gender.