Role of Triglyceride/Fatty Acid Cycle in Development of Type 2 Diabetes

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1. Introduction

In United States, the prevalence of obesity has increased from 11.9% to 33.4% in men and from 16.6% to 36.5% in women from 1971 to 2006 (Austin, Spadano-Gasbarro et al. 2011). In general, obesity is caused by energy imbalance where energy intake exceeds energy expenditure for an extended period of time. The excess energy is stored in adipose tissue and results in enlarged fat cells and/or increased number of fat cells. Obesity is of great concern because a subset of the population has co-morbidities that develop as a consequence of obesity. Previous studies have shown that obesity is one of the risk factors linked to metabolic syndrome (Bray 2004). The World Health Organization (WHO) defines metabolic syndrome as a cluster of disorders that require the presence of diabetes, impaired glucose tolerance (IGT), impaired fasting glucose or insulin resistance and any two of the following abnormalities: central obesity, dyslipidemia (high triglycerides or low high-density lipoprotein (HDL) cholesterol concentration), elevated blood pressure, or micro albuminuria (Alberti and Zimmet 1998).

Type 2 diabetes mellitus (T2DM) is well known to be a metabolic disease that is characterized by insulin resistance and impaired insulin secretion. Insulin resistance is a condition in which the peripheral tissues, such as muscle and adipose tissue, lose the ability to uptake plasma glucose efficiently at physiological concentrations of insulin. As a result, the pancreas secretes more insulin to compensate. Therefore, insulin resistance leads to high plasma concentrations of insulin and glucose, and results in T2DM. Moreover, hyperglycemia causes cardiovascular diseases and disease-specific complications such as blindness and kidney failure (Zimmet, Alberti et al. 2001). The increased prevalence of T2DM is strongly associated with obesity (Mokdad, Ford et al. 2003) and is becoming an increasing problem worldwide (King, Abdullaev et al. 1998; Cowie, Rust et al. 2006; Yoon, Lee et al. 2006). In just the United States, 23.6 million people over the age of 20 have diabetes, of which 90% to 95% have T2DM (Cowie, Rust et al. 2006). An overwhelming 25.9% of the US population over 20 years old has early stages of disease by exhibiting impaired fasting glucose levels (Cowie, Rust et al. 2006). Additionally, The International Diabetes Federation predicted that 333 million people will have diabetes by 2025 (King 1998; King, Abdullaev et al. 1998; King, Aubert et al. 1998). Therefore, it is very important to determine the causes of this disease and develop strategies for its prevention.

The correlation between obesity and the prevalence of T2DM has been well established, but how does T2DM develop? In 1963, Randle *et al* proposed that lipids impaired insulin-

stimulated glucose uptake in muscle and was caused by inhibition of glycolysis (Randle 1963). Excess circulating free fatty acids (FFA) in obesity is one of the main factors that contribute to development of T2DM (Randle 1963; Randle 1998). Because FFA are elevated in the blood of obese individuals, the muscle has access to more FFA compared to lean individuals and thus obese individuals have increased fatty acid oxidation in their muscles (Boden 1997). This in turn, results in an increased generation of metabolites from FFA β-oxidation such as, nicotinamide adenine dinucleotide (NADH), acetyl-CoA and adenosine triphosphate (ATP). These metabolites inhibit key regulatory enzymes in the glycolytic pathway such as pyruvate dehydrogenase complex (PDC). The increased concentration of ATP also inhibits phosphofructokinase (PFK-1) and pyruvate kinase muscle isoform (PK-M), thus blocking the rate controlling steps in muscle glycolysis and subsequently leads to an accumulation of glucose-6-phosphate (G6P). Increased concentration of G6P inhibit hexokinase and therefore decreases the rate of glucose phosphorylation by muscle which increases the blood glucose concentration (Randle 1963). Randle *et al* also found that FFA oxidation blocks the recycling of the glucose transporter 4 (GLUT4) to the surface of muscle cells, thus decreasing glucose uptake and contributes to the increased blood glucose levels (Randle 1963). In summary, the elevated FFA have been demonstrated to lead to insulin resistance in peripheral tissues by inhibiting insulin-stimulated glucose uptake in the muscle causing elevated blood glucose (Boden 1997).

2. Triglyceride/fatty acid cycle and glyceroneogenesis

What regulates the flux of FFA between tissues? The triglyceride/fatty acid cycle regulates this flux. In the fed state glucose is metabolized to glycerol-3-phosphate via glycolysis and esterifies with three FFA to generate triglycerides (Figure 1). This occurs in both the liver and white adipose tissues (WAT). FFA are derived both from either the diet or *de novo* lipogenesis in the liver. FFA generate energy via β-oxidation as described above in various tissues (muscle, heart) or can be stored as triglycerides in adipose tissue for energy production at a later time.

During fasting however as much as 65% of FFA are re-esterified back to triglycerides in WAT (Jensen, Chandramouli et al. 2001). Since glucose is at a premium during fasting, the synthesis of glycerol-3-phosphate from glucose is minimal. Additionally, in WAT the glycerol released during lipolysis cannot be phosphorylated and used for triglyceride synthesis because the activity of glycerol kinase in this tissue is negligible. Reshef, Ballard and Hanson demonstrated that gluconeogenic precursors such as pyruvate and lactate are converted into glycerol backbone of triglyceride (Reshef, Hanson et al. 1970; Reshef, Meyuhas et al. 1972). This pathway called "glyceroneogenesis" is an abbreviated version of gluconeogenesis. Glyceroneogenesis is defined as the conversion of precursors other than glucose or glycerol into glycerol 3-phosphate for triglyceride synthesis. The pathway is essential for the regulation of the FFA flux between tissues during fasting (Botion, Kettelhut et al. 1995; Botion, Brito et al. 1998; Festuccia, Kawashita et al. 2003).

Glyceroneogenesis, like gluconeogenesis, is regulated by phosphoenolpyruvate carboxykinase (PEPCK-C/*Pck1*), a key enzyme which catalyzes the conversion of oxaloacetate (OAA) to phosphoenolpyruvate (PEP) in both pathways. During fasting, increasing hepatic *Pck1* expression enhances the rates of gluconeogenesis to maintain glucose homeostasis as well as glyceroneogenesis, thus increasing hepatic glucose output and triglycerides synthesis by re-esterification of circulating FFA (Fig. 1). In adipose tissue, glyceroneogenesis controlled by *Pck1* contributes to the regulation of FFA release to the

blood. Support for *Pck1* regulation of glyceroneogenesis contributing to the development of disease was shown by Franckhauser et al. They over-expressed of *Pck1* in WAT through a transgene specific for adipose tissue and found increased FFA re-esterification in adipose tissue led to obesity *without* insulin resistance (Franckhauser, Antras-Ferry et al. 1995; Franckhauser, Munoz et al. 2002). The increased glyceroneogenesis reduced the availability of FFA to the muscle and thus prevented impaired glucose tolerance. Therefore the regulation of triglyceride/FFA cycle is important in the development of obesity and T2DM. Figure 1. Triglyceride/FFA cycle regulates the flux of lipids between tissues.
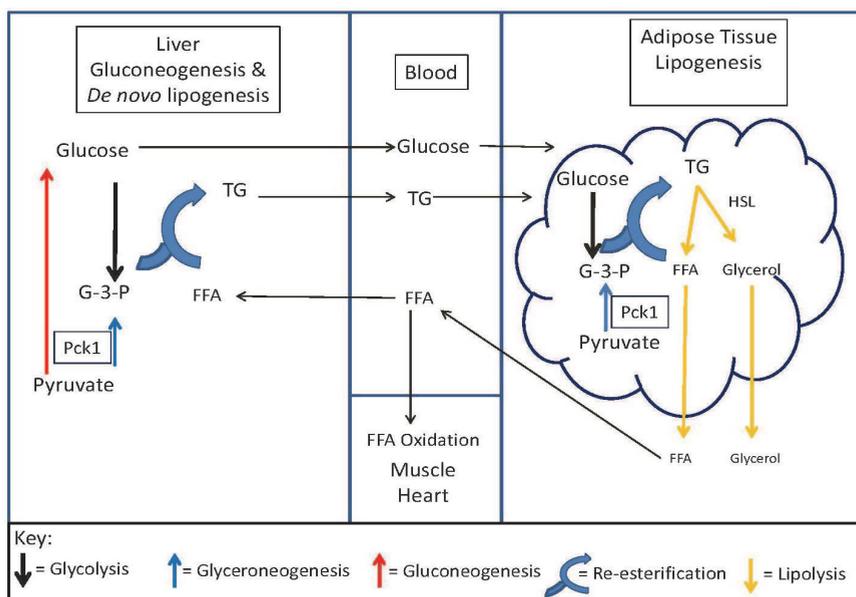

Fig. 1. Triglyceride-fatty acid cycle. During fasting triglycerides are hydrolyzed to glycerol and FFA. However as much as 65% of FFA are re-esterfied back to triglycerides. *Pck1* regulates this process in both adipose tissue and liver.

In order to investigate the disturbance of triglyceride/fatty acid cycle in development of obesity and T2DM, various genetic alterations of the *Pck1* gene have been conducted. Mice with a whole body null mutation of *Pck1* do not survive beyond 3 days after birth (She, Shiota et al. 2000). Therefore, the PPARE^{-/-} mice were generated to circumvent this problem. The binding site for the peroxisome proliferator-activated receptor γ (PPARγ), called the peroxisome proliferator-activated receptor element (PPARE), at -1000 bp of the *Pck1* promoter is essential for adipose tissue expression (Devine, Eubank et al. 1999). The deletion of PPARE region in *Pck1* promoter in mice (PPARE-/-) led to dramatic loss of *Pck1* expression in WAT and mammary gland, and slight reduction in BAT (Hsieh, Millward et al. 2009). Loss of *Pck1* expression in the adipose tissue resulted in reduced adipocyte size and fat content (Olswang, Cohen et al. 2002) due to impaired glyceroneogenesis in adipose tissue. Further research found PPARE^{-/-} mice displayed insulin resistance and altered lipid and glucose homeostasis (Millward, DeSantis et al. 2010). Thus the alteration of the triglyceride/FFA cycle can lead to development of impaired glucose tolerance.

Further evidence for the role of *Pck1* in the regulation of the triglyceride/FFA cycle has been shown in genomic analysis in humans. Beale *et al* have established that two C/T single nucleotide polymorphisms (SNPs) were in complete linkage disequilibrium at position –1097bp and –967bp of the *Pck1* promoter and these SNPs are associated with obesity and T2DM. Patients with T/T polymorphisms have higher HbA1c and higher fasting glucose levels (Beale, Harvey et al. 2007). The region of the identified polymorphisms in these patients is located within the same PPARE site of *Pck1* promoter that has been deleted in PPARE$^{-/-}$ mice (Millward, Desantis et al. 2010). These mice lack *Pck1* expression in WAT and develop insulin resistance with elevated plasma FFA (Millward, DeSantis et al 2010).

In mice that had altered triglyceride/FFA cycle via loss of *Pck1* in mammary gland and WAT, the dams' had 40% reduction of milk triglycerides during lactation. The pups reared by these dams had reduced growth in the perinatal period and developed insulin resistance that persisted into adulthood (Hsieh, Millward et al. 2009). Thus understanding the regulation of lipid metabolism during pregnancy and lactation may provide new insights into the mechanism(s) for development of T2DM.

3. The thrifty hypothesis

How does the alteration of perinatal nutrition program the fetus for T2DM? One theory for the interaction of environment in development of disease is "the thrifty phenotype hypothesis". The thrifty phenotype hypothesis suggested that the metabolic adaption during early life altered "thrifty genes" expression to help people survive when food sources were limited; however, those genes predispose us to diabetes and became detrimental in our modern lifestyle with an abundance of food (Neel 1962). The theory associates poor fetal growth with increased risk for a number of chronic conditions, including diabetes, hypertension, dyslipidemia, coronary artery disease and stroke, in adulthood (Barker 2004; Fernandez-Twinn and Ozanne 2006). Suboptimal nutrition during pregnancy is one of the significant problems that causes infants to suffer from intrauterine growth retardation (IUGR) (Marsal 2002). IUGR has been strongly associated with the development of metabolic disorders, hormone imbalance, organ dysfunction and abnormal development, as well as cardiovascular disorders (Wu, Bazer et al. 2004). Malnutrition and overnutrition during pregnancy as well as alterations in placental function all contribute the development of IUGR and further "program" the fetus to development of a variety of chronic diseases (Wu, Bazer et al. 2004). The "programming" hypothesis suggests that maternal malnutrition can induce permanent changes in the fetal genome through DNA methylation, histone acetylation, or other modifications on transcriptional or translational levels (Meaney and Szyf 2005) and contribute to development of metabolic diseases in the future. Therefore, low birth weight (LBW) is regarded as an independent risk factor for development of T2DM and other adult-onset diseases in adulthood (Hernandez-Valencia and Patti 2006).

4. Animal models for studying programming of the metabolic syndrome during pregnancy/lactation

Several nutritional models have been used to illustrate the mechanism that would explain fetal origins for adult diseases. We summarized some of these models for studying programming of the newborns (Table 1). To investigate the impact of maternal overnutrtion on the fetus, several studies have used the high-fat diet during pregnancy /lactation. They have shown that exposure to the high fat diet during pregnancy results in altered

metabolism in the newborn can also lead to the development of metabolic diseases, including insulin resistance and dysfunction of pancreatic β-cells, in the offspring (Elton, Pennington et al. 2002; Buckley, Keseru et al. 2005; Taylor, McConnell et al. 2005). Thus, maternal nutrition directly impacts the developing β-islet cells and can program the fetus for insulin resistance as adults.

Manipulation	Duration	Consequences	Reference
Undernutrition			
Maternal calorie restriction 50% caloric need	3rd week of pregnancy	•Impaired β-cell development	Garofano, Czernichow et al. 1997
	3rd week pregnancy and lactation	•Reduced β-cell mass and number •Fetus has impaired glucose tolerance	Garofano, Czernichow et al. 1998
Maternal caloric restriction 30% Caloric needs	During pregnancy	Fetus develops hypertension, increased fasting insulin concentration and obesity	Vickers, Breier et al. 2000
Maternal protein is reduced to 8% of caloric needs	During pregnancy	•Low birth weight fetus, reduced β-cell islet size •Reduced β-cell islet insulin concentration, adult animals develop insulin rsistance	Snoeck, Remacle et al. 1990 Dahri, Snoeck et al. 1991 Ozanne, Dorling et al. 2001 Ozanne, Olsen et al. 2003
Tubal ligation	During pregnancy	•Reduced β-cell mass	Wigglesworth 1974; De Prins and Van Assche 1982
Maternal diet of conjugated linoleic acid	During pregnancy and lactation Dam's milk had reduced triglycerides	•Impaired fetal growth •Increased pup mortality	Ringseis, Saal et al. 2004
Loss of *Pck1* in mammary gland and WAT	PPARE-/- dams had reduced milk triglycerides during lactation	•Reduced weight gain during lactation •Develop insulin resistance	Hsieh, Millward et al. 2009
Overnutrition			
Reduction of litter size	Reduced from 14 rat pups to 4	•Pups develop obesity and insulin resistance	Plagemann, Heidrich et al 1992
Maternal High fat diet	During pregnancy	•Dysfunction of β-cell •Fetus develops insulin resistance	Elton, Pennington et al. 2002; Buckley, Keseru et al. 2005; Taylor, McConnell et al. 2005
Artificial feeding of pups high carbohydrate diet	Pups fed via intragastric tube high carbohydrate diet for three weeks after birth	•Develop obesity, insulin resistance •Impaired β-cell development	Aalinkeel, Srinivasan et al. 1999; Aalinkeel, Srinivasan et al. 2001; Patel and Srinivasan 2002

Table 1. Imprinting the fetus for T2DM

To investigate the impact of undernutrition on programming the fetus for adult diseases, two different dietary strategies are commonly used, global nutritional restriction and isocaloric low protein manipulation. In rodents, total maternal restriction of 50% of caloric needs in the last week of pregnancy results in impairment of β-cell development (Garofano, Czernichow et al. 1997). If calorie restriction continues during suckling, permanent reduction in β-cell mass and β-cell number occurs resulting in impaired glucose tolerance (Garofano, Czernichow et al. 1998). If rodent dams are more severely restricted to 30% of total caloric intake, the fetus develops systolic hypertension, increased fasting insulin concentrations, increased food intake and obesity (Vickers, Breier et al. 2000). Limiting a single macronutrient in the dams also imprints the fetus. When maternal protein intake during pregnancy is reduced to 8%, the offspring have low birth weight (LBW), reduced β-cell islet size (Snoeck, Remacle et al. 1990) and reduced β- islets insulin content and secretion (Dahri, Snoeck et al. 1991). Peripheral tissues are also affected in the pups from dams fed low protein diet. When the pups were adults (15 months old), insulin stimulated glucose

uptake in skeletal and adipose tissues is reduced (Ozanne, Dorling et al. 2001; Ozanne, Olsen et al. 2003). Small birth weight can also be due to impaired nutrient perfusion through the placenta (Haggarty, Allstaff et al. 2002). To mimic placental insufficiency in rodents, unilateral and bilateral uterine artery ligations have been used. These studies established that the fetus develop reduced β-cell mass which persists into adulthood (Wigglesworth 1974; De Prins and Van Assche 1982).

5. Alterations in fetal nutrition

LBW in newborns is a reduction in both lean body mass and fat mass. After birth, these infants have accelerated postnatal growth or catch-up growth (CUG) (Eriksson, Forsen et al. 1999; Bhargava, Sachdev et al. 2004). Several studies have suggested that the fat mass accrues preferentially during CUG and the fat accumulation during childhood is a significant risk factor for T2DM as adults (Crescenzo, Samec et al. 2003; Rasmussen, Malis et al. 2005; Ibanez, Ong et al. 2006; Leunissen, Oosterbeek et al. 2008). Several strategies have been employed to test the consequences of overnutrition on programming the fetus for adult disease. These include reduction of litter size during lactation, high fat diet during pregnancy. Reduction of litter size from 14 to 4 rat pups per litter results in hyperinsulinemia, increased body growth and obesity as adults (Plagemann, Heidrich et al. 1992). Rats fed a high fat diet (20% kcal fat) during pregnancy and lactation had significantly higher milk lipid, protein and lactose concentration compared to the low fat diet group (5%kcal fat). The weights of the pups from the high fat mothers is similar at birth but increases after 6 days and persists into adulthood (Del Prado, Delgado et al. 1997).

During the suckling period, milk lipids provide the major source of both calories and essential fatty acids for the rodent newborn. The neonate uses fatty acids and ketone bodies as their primary energy substrate during lactation and must switch to carbohydrate after weaning (Grigor, Allan et al. 1986; Rolls, Gurr et al. 1986; Del Prado, Delgado et al. 1997; Del Prado, Villalpando et al. 1999).). Patel et al have extensively studied the patterning effect of overnutrtion in the perinatal period by high-carbohydrate feeding during the suckling period (Aalinkeel, Srinivasan et al. 1999; Aalinkeel, Srinivasan et al. 2001; Patel and Srinivasan 2002). They used an artificial rearing technique where newborn rats were raised in styrofoam cups floating in a temperature-controlled water bath called "pup-in-a-cup". At day 4 postpartum, the rats were fed through intragastric cannulas a high carbohydrate formula where 56% of the total calories is carbohydrate compared to 8% normally found in rodent milk. The pups develop hyperinsulinemia within 24 hours which persists into adulthood. Patel et al have investigated both cellular and molecular adaptations in response to the patterning of high carbohydrate diet and insulin secretion. The pancreas has profound changes. The pancreas from the high carbohydrate fed animals has increased number of smaller sized β-islets with an increase of immunopositive staining area for insulin. The islets also has reduced apoptosis (Petrik, Srinivasan et al. 2001). The molecular changes include increases in expression of transcription factors regulating the expression of the preproinsulin mRNA.

Undernutrition during lactation can also impact the fetus. A study using female rats showed that exposure to dietary conjugated linoleic acids resulted in decreased triglyceride concentration in the milk via reduced *de novo* fatty acid synthesis in the mammary gland and an impaired uptake of fatty acids from lipoprotein into mammary gland (Ringseis, Saal et al. 2004). The lower triglyceride concentration of milk led to impaired fetal growth and

increased mortality of the suckling pups. As we discussed earlier, alterations in the triglyceride/FFA cycle also reduce triglyceride concentration of milk and lead to programming the fetus to develop insulin resistance (Hsieh, Millward et al 2009). Thus understanding the regulation of lipid metabolism during pregnancy and lactation may provide new insights into the mechanism(s) for development of insulin resistance.

6. Transgenerational programming of fetus

The data described above suggests epigenetic patterning of the fetus for disease due to either genetic or environmental conditions. However there is little evidence for transgenerational effects of the environment in mammals. Most examples of transgenerational environmental effects described in the literature are maternal effects. In Table 2 we have summarized these studies. Aalinkeel et al analyzed pups that were fed a high carbohydrate diet instead of the normal high lipid diet during the first three weeks of life. These pups develop insulin resistance and become obese (Aalinkeel, Srinivasan et al 1999). The F1 generation from these mice also develop obesity and insulin resistance even though the F1 generation had no dietary alterations (Aalinkeel, Srinivasan et al 2001; Patel, Srinivasan 2002). In another study C57BL/6J dams (F0) were fed high fat diet during pregnancy. The pups develop obesity and metabolic syndrome that is transmitted through to the F3 generation (Dunn, Bail et al 2011). Another study showed that caloric restriction of the dam during pregnancy (F0) results in reduced birth weight, impaired glucose tolerance and obesity (Jimenez-Chillaron, Isganaitis et al 2009). The environmental imprinting caused by F0 dam also imprints not only the F1 generation but also the F2 generation (Jimenez-Chillaron, Isganaitis et al 2009). Thus, the original environmental insult to the grandmother or mother imprints not only the fetus but future generations as well.

Recent evidence indicates that it is not just the mother that can imprint the fetus for development of disease. Several studies showed that environmental insults to the grandfather or father imprint the fetus for several generations as well (Table 2). In congenic strains derived from an obesity susceptible strain, C57BL/6J and a resistant strain, A/J, identified a region that protects the fetus from diet-induced obesity on high fat diet. This small region of the A/J chromosome, $Obrq2a^{A/J}$, in an otherwise C57BL/6J background shows that the paternal or grandpaternal allele is sufficient to inhibit diet-induced obesity and reduce food intake in the normally obesity-susceptible C57BL/6J strain (Yazbek, Spiezio et al 2010). In another study when the male C57BL/6J mouse (M) was fed a low-protein diet and then mated to C57BL/6J female mouse (F), the progeny has increased hepatic gene expression for genes in the lipogenic pathway (Carone, Fauquier et al 2010). Finally, when obese male Sprague-Dawley rats were mated to females fed a low-fat diet the F1 generation developed altered β-cell function (Ng, Lin et al 2010). Therefore, environmental insults to the grandfather and father can also imprint the fetus for development of obesity and insulin resistance.

7. Conclusion

The development of obesity and insulin resistance is a complex disease since it is mutlifactorial and both genetics as well as the environment contribute to the development of T2DM. Environmental stresses to either parent can result in imprinting of the fetus for

T2DM. Future studies will define the mechanism(s) responsible for imprinting the fetus for disease and offer new therapeutic strategies for prevention of T2DM.

8. Acknowledgement

9. References

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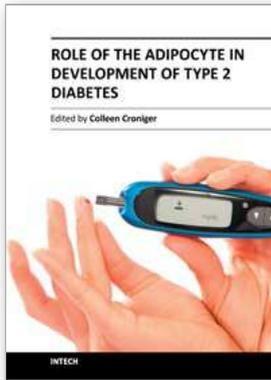
Role of the Adipocyte in Development of Type 2 Diabetes

Edited by Dr. Colleen Croniger

Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

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