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Review on intrauterine programming: Consequences in rodent models of mild diabetes and mild fat overfeeding are not mild

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ABSTRACT

An adverse intrauterine programming occurs in diabetes and obesity as the consequence of an adverse maternal environment that affects the appropriate fetoplacental development and growth. Experimental models of diabetes and fat overfeeding have provided relevant tools to address putative mechanisms of the adverse intrauterine programming. The current knowledge far extends from the original thoughts of the resulting intrauterine programming of metabolic and cardiovascular diseases to a full range of alterations that affect multiple tissues, organs, and systems that will compromise the long-life health of the offspring. This review examines the postnatal effects of rodent models of mild diabetes and fat overfeeding, identifying the multiple organ derangements in the offspring resulting from mild maternal adverse conditions. In addition, the comparison of experimental models of severe diabetes and fat overfeeding and the crucial role of the placenta are discussed, providing an update of the actual scenario of the putative mechanisms and adverse consequences of maternal metabolic derangements.

1. Introduction

The incidence of metabolic diseases is increasing worldwide, and the intrauterine programming is clearly involved in this increase [1,2]. Barker et al. were the first in developing the concept of intrauterine programming, identifying the relationship of adverse fetal growth outcomes and adult diseases [3]. Although the concept of intrauterine programming was initially described in relationship to famine and growth restriction, it was rapidly extended to be linked to macrosomia, the other extreme of the adverse fetal growth, an adverse outcome that is clearly associated with maternal diabetes and fat overfeeding [4–6]. Currently, the concept of intrauterine programming is wide and complex and refers to the ability of an adverse exposure during development to cause changes in the physiology, metabolism, and/or epigenome of an individual, which will lead to an increased risk of disease in their later life [7]. This concept includes changes originating at different developmental windows, and changes resulting from a disturbance at the cellular, tissue, or organ level that can be either adaptive or not in the intrauterine milieu but lead to adverse effects in a postnatal situation [7,8].

In diabetes, the intrauterine programming of metabolic diseases in the offspring's later life is evidenced in type 1, type 2, and gestational diabetic pregnancies, and human studies have identified nongenetic causes for this adverse programming [9–11]. Accordingly, nongenetic causes of intrauterine programming of offspring diseases are clearly evidenced in chemically induced experimental models of diabetes [12,13]. In dietary fat overfeeding, a main cause of overweight and obesity, it is clear that intrauterine programming of offspring diseases can be generated under different genetic backgrounds, despite different periods of the administration of the fat diet [14–16].

Aiming to illustrate the capacity of minor disturbances to affect the offspring's later life, this review addresses intrauterine programming in the offspring of experimental models of mild diabetes and mild fat overfeeding, evaluated mainly in rodents. In addition, a comparison of the adverse outcomes in mild or more severe conditions is addressed. Finally, the role of the placenta as a major player in determining the intrauterine programming is considered.

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2. Intrauterine programming in experimental models of mild diabetes

Traditionally, pathogenic mechanisms underlying hyperglycemia have been evidenced in *in vitro* experiments carried out in the presence of glucose concentrations over 15 mM. Similarly, fasting blood glucose values in most experimental models of diabetes, induced either chemically or genetically, are higher than 15 mM. In reproductive studies, these high blood glucose levels often lead to embryo or fetal loss [12]. Thus, those diabetic animals in which pregnancy is achieved became experimental models useful to analyze the impact of maternal diabetes on the first stages of development, resorption, and malformation rates, and allowed to gain insights into the mechanisms of induction of these alterations [12,17,18]. On the other hand, sustaining pregnancy until term under these levels of hyperglycemia has become a larger challenge, and different approaches, including the induction of diabetes by administration of chemicals in the already pregnant animals and/or partially controlling the hyperglycemia with insulin, have been used to bypass this problem [12].

In these experimental models of severe diabetes, fetal growth retardation and reduced neonatal weight are mostly observed. These adverse outcomes may also be observed in poorly controlled diabetic women and are associated with the intrauterine programming of metabolic and cardiovascular diseases [12,19]. On the other extreme of fetal growth impairments, macrosomia is the most common adverse outcome in human diabetic pregnancies, a hallmark highly associated with altered programming of metabolic and cardiovascular diseases [6,20]. In parallel, macrosomia is the most frequent outcome in mild experimental models of diabetes [19,21,22]. This section examines the evidence of adverse intrauterine programming in mild diabetes experimental models (blood glucose values below 15 mM), as the outcomes and mechanisms involved may be more closely related to that observed in human diabetic pregnancies, and thus may further facilitate translational approaches from basic science to clinical medicine in the field of diabetes and pregnancy. Of note, in many rodent strains, healthy pregnant animals show blood glucose values around 5–6.5 mM, and thus, only values over 6.7 mM are used to diagnose diabetes. Fasting glycemia values in healthy rats can be higher than those in healthy women (in which normal glycemia values are up to 5.1–5.5 mM according to the diagnostic criteria). Thus, mild glycemia values in rats may be higher than those considered mild in humans, and caution should be taken when translating these results to humans.

2.1. Intrauterine programming of alterations in glucose metabolism

Experimental models of mild diabetes, induced either genetically or chemically, have convincingly demonstrated a disturbed metabolism in the offspring. In genetic models, it is important to differentiate those genetic alterations that will lead to diabetes in the offspring and the effects of the intrauterine programming. Embryo transfer experiments in Goto Kakizaki (GK) rats, a genetic model of diabetes with blood glucose values around 7 mM, have shown hyperglycemia and glucose intolerance in the adult offspring when wild-type embryos are transferred to GK female recipients, evidencing the intrauterine programming of the diabetic disease [23].

The chemical models of diabetes allow evaluating intrauterine effects under a wild-type genetic background. The degree of hyperglycemia induced by streptozotocin is dependent on the exquisite regulation of the pancreatic β-cell death/survival pathways; thus, variations in the strain, housing and/or diet are as important as the route of administration and dose [11,12]. This implies that the indicated dose/route of administration of streptozotocin may result in different blood glucose values among different settings. Therefore, rather than the dose administered when comparing different settings, the resulting blood glucose values are the values that will define the mildness or severity of the model.

Studies in mild diabetic rats (diabetes induced by a low dose of streptozotocin administration (30 mg/kg i.v) have identified that the adult offspring on day 1 of gestation; maternal fasting blood glucose values around 10 mM) shows decreased insulin responses and impaired glucose tolerance as well as morphological alterations in the endocrine pancreas [24,25]. The adult macrosomic offspring from diabetic rats (diabetes induced by streptozotocin administration (37 mg/kg i.p.) on day 5 of gestation; maternal fasting blood glucose values around 10 mM) show abnormal glucose tolerance and insulin response curves as well as reduced ^{14}C-glucose conversion to triglycerides in adipocytes [26].

Pregestational mild diabetes induced in rat neonates by streptozotocin administration (90 mg/kg s.c.; fasting blood glucose values around 11 mM) causes increased fasting glycemia and insulinemia in the adult offspring, which is evident from the fifth month of age in both males and females [27]. Indicating a link between gestational diabetes mellitus (GDM) and the future development of type 2 diabetes, gestational diabetes is induced in 3-month-old female offspring from these mild diabetic rats when mated with control males [28].

Altogether, the evidence shows intrauterine programming of diabetes in the offspring of mild diabetic rodents when diabetes is induced either before and during pregnancy, denoting the compromised metabolism due to the adverse development of the fetus exposed to mild maternal hyperglycemia.

2.2. Intrauterine programming of alterations in lipid metabolism

The importance of altered lipid metabolism in the induction of complications of the diabetic disease is now clearly recognized not only in nonpregnant patients but also in diabetic pregnancies and offspring's diseases [5,29]. Alterations in the offspring's lipid metabolism and deposition are observed in both chemically induced and genetic experimental models of mild diabetes. The db/+ mouse is a model of gestational diabetes, as these mice are not diabetic prior to gestation. The genetic defect is a heterozygous loss-of-function mutation in the leptin receptor gene that leads in the pregnant mice to impaired glucose tolerance and insulin responses [30,31]. In this model, comparing wild-type offspring (+/+ born to db/+ females mated with +/+ males) with controls (+/+ born to control dams), it is clear that the altered intrauterine environment leads to impaired glucose tolerance and increases in body weight and adipocyte size, as well as increased leptin and apelin serum concentrations in the adult offspring [32].

In the streptozotocin-induced neonatal model of mild diabetes (90 mg/kg s.c., maternal blood glucose values around 11 mM), not only the mothers have increased circulating lipids during pregnancy, but also the fetuses accumulate lipids in different organs including the liver, the lungs, and the heart [33–35]. Interestingly, the adult male and female offspring of these mild diabetic rats show increased triglycerides circulating levels, suggesting intrauterine programming of lipid metabolic disbalances [27]. Although the mechanisms involved remain unclear, it is interesting that treatments during gestation with olive oil (treatments with antioxidant capacity and ability to activate the peroxisome proliferator activated receptor (PPAR) pathway) prevent the increased triglyceridemia in the adult offspring [27].

Macrosomic male newborn offspring from diabetic rats (diabetes induced by streptozotocin administration on day 5 of