Early Human Development (2005) **81**, 981–988

ELSEVIER

Early Human Development

www.elsevier.com/locate/earlhumdev

Programming of appetite and type 2 diabetes

Malgorzata S. Martin-Gronert [1], Susan E. Ozanne *

Department of Clinical Biochemistry, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QR, UK

KEYWORDS
Type 2 diabetes;
Obesity;
Appetite;
Fetal programming;
Maternal diet

Abstract In the past decade, epidemiological findings and data from experimental studies in animals have shown that the structure and function of the organism can be programmed during critical periods of development which can lead to detrimental long-term consequences for the health of an individual. Low birth weight has been linked to many adult diseases in humans including type 2 diabetes. The full detrimental effects of early growth restriction are often accompanied by the presence of obesity, which itself might be a manifestation of programmed appetite regulation in fetal and neonatal life. The understanding of interactions between leptin and insulin and their roles in glucose and body weight regulation provides clues towards mechanisms underlying altered appetite regulation and increased risk of type 2 diabetes in low birth weight individuals. Molecular mechanisms involved might include epigenetic alteration of the fetal genome in response to maternal nutrition.

1. Introduction

The term programming has been used for many years to describe the process whereby an insult or stimulus occurring during a critical or sensitive period of development causes long-term or permanent change to structure and function of the organism [1]. Over the last decade, immense interest in programming has been prompted by the results of a large number of epidemiological and animal studies, which have shown that there is a relationship between the early environment in which a child grows and subsequent development of adult degenerative diseases such as type 2 diabetes, ischaemic heart disease, hypertension and some cancers. One factor — obesity — seems to be key to the appearance and development of the full detrimental effect of early growth restriction and obesity itself may be a manifestation of altered nutrition in early life.

It is well established that obesity is a major risk factor for type 2 diabetes. Worldwide, at least 1 billion adults are overweight (i.e. have body mass index BMI greater than 25 kg m^{-2}) and 300 000 are clinically obese (BMI > 30 kg m^{-2}). Even more worrying is an increase in childhood obesity as nearly 17.6 million children under five are classified as overweight. The increased prevalence of obesity

* Corresponding author. Tel.: +44 1223 762636; fax: +44 1223 330598.
E-mail addresses: msm32@cam.ac.uk (M.S. Martin-Gronert), seo10@cam.ac.uk (S.E. Ozanne).
[1] Tel.: +44 1223 336784; fax: +44 1223 330598.

0378-3782/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.earlhumdev.2005.10.006

parallels the increased rates of type 2 diabetes. This trend is clearly noticeable in the pediatric diabetic centres in the U.S. in which prevalence of type 2 diabetes (formerly termed 'adult onset') doubled during the past 10–20 years. Although type 1 diabetes (formerly termed 'juvenile onset') still remains the predominant form of the disease in children worldwide, it is predicted that within 10 years type 2 diabetes will become the main type in many ethnic groups. In light of these predictions and the fact that obesity not only contributes to the development of type 2 diabetes but also to the development of cardiovascular disease and some cancers, the costs associated with the epidemic of obesity in terms of health care expenditure as well as quality of human life, morbidity and mortality are causing concern.

It is clear, however, that as not all obese individuals develop type 2 diabetes, different people must have different susceptibilities to the detrimental effects of obesity. A number of studies have reported that there is a J-shaped or U-shaped relationship between birth weight and adult obesity. Individuals born small for gestational age appear to be one group of people that are at an increased risk of the detrimental consequences of obesity.

2. Epidemiological studies

It has been 70 years since Kermack et al. demonstrated that in Sweden and United Kingdom, death rates from all causes fell between 1751 and 1930 as a result of improved childhood living conditions. Further evidence for the importance of the early environment came when geographical variations in arteriosclerotic heart disease in Norway were studied showing a positive correlation between different geographical regions with past infant mortality rates but not with current infant mortality rates. Subsequently, after studying the mortality rates from cardiovascular diseases in England and Wales, Barker and colleagues proposed that environmental influences, which impair growth and development in fetal life, result in an increased risk of ischemic heart disease. Epidemiological studies that followed extended the initial observations linking pre- and postnatal growth and cardiovascular disease to include associations between early growth and subsequent onset of hypertension, insulin resistance and type 2 diabetes.

The relationship between early growth and the subsequent development of glucose intolerance and type 2 diabetes was first established in 64-year-old men from Hertfordshire, UK. The proportion of men with impaired glucose tolerance steadily increased with decreasing birth weight and the poorest glucose tolerance was observed in the individuals who were small at birth (<2.5 kg) but were currently obese [2]. At the age of 64, men with low birth weight were 6 times more likely to have diabetes compare to those with high birth weight. As human pancreas has half of its adult β-cell mass present by the age of one, these findings suggest that fetal and neonatal life are crucial periods for pancreatic β-cell development and insults causing alterations to pancreatic development during that period are detrimental to future glucose metabolism.

Some of the strongest evidence for the importance of the intrauterine environment has been derived from the study of twins. As monogenetic twins are genetically identical, any differences in birth weight are not caused by genetic variations, sex or gestational age but are related to the fetal environment. A study of middle-aged twins in Denmark revealed that, in both monozygotic and dizygotic twin pairs who were discordant for type 2 diabetes, the diabetic twin was much more frequently the lighter of the pair at birth. Similar observations were made in a study of younger Italian twins.

3. Thrifty phenotype hypothesis

The "thrifty phenotype" hypothesis was proposed by Hales and Barker in 1992 [3]. The hypothesis postulates that the fetal and early environment, especially nutrition, play an important role in determining the susceptibility of an individual to type 2 diabetes and other diseases. Fetal malnutrition occurs when fetal demand for nutrients exceeds the supply, for example as a result of maternal malnutrition or placental dysfunction. As the growing fetus responds and adapts to the poor nutrition, it adopts a number of strategies to enhance its chances of postnatal survival. First, the nutrients are selectively distributed to protect tissues that are important for immediate survival, especially the brain (so-called brain sparing). This occurs at the expense of other organs and tissues such as liver, pancreas and muscle, with organs growing rapidly at the time being the most affected. Second, metabolic programming is proposed to occur, which leads to altered postnatal metabolism, beneficial to survival in conditions of poor postnatal nutrition. If the fetus is born into the conditions of poor postnatal nutrition, there are no detrimental effects to its long-term health. This would explain the low prevalence of diabetes in populations of rural middle Africa known for the