LONG-TERM EFFECTS OF PRE- AND POSTNATAL EXPOSURE TO LOW AND HIGH DIETARY PROTEIN LEVELS

Evidence From Epidemiological Studies And Controlled Animal Experiments

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Abstract: The purpose of this short review is to summarize the available evidence from observational studies and rodent models for an association between maternal protein intake, birth weight, pre- and post-weaning body mass gain and adult body fatness in the offspring.

Key words: observational studies; birth weight; body weight; obesity; maternal low protein model, maternal high protein model; rats.

1. INTRODUCTION

In many populations worldwide epidemiological evidence relates low birth weight to increased risk for syndrome X, coronary heart disease, and high blood pressure in adult age. On the basis of these observations it was suggested that low birth weight is causally related to fetal under- or malnutrition and subsequent fetal growth retardation which permanently affects adult health (Godfrey and Barker, 2000). Evidence is emerging that nutritional programming during fetal development might be involved in the development of obesity.

2. OBSERVATIONAL STUDIES IN HUMANS

Human studies on the relationship of maternal diet, birth weight and adult disease have generated inconclusive results. In one study low birth weight was related to either high carbohydrate intake during early

pregnancy, or to low dairy and meat protein intake during late pregnancy (Godfrey et al., 1996), while in another it was related to reduction of carbohydrate intake between early and late pregnancy (Shiell et al., 2001). No relation between macronutrient intake and birth weight was reported by Mathews et al., 1999. In two other studies an inverse relation between high maternal protein intake and birth weight was found (Langley-Evans et al., 2003; Campbell et al., 1996). Campbell et al., 1996, reported increased blood pressure in adult offspring with maternal animal protein intake below 50 g daily plus a higher carbohydrate intake, and with daily maternal animal protein intake above 50 g, and lower carbohydrate intake. Shiell et al., 2001, found a greater consumption of meat and fish in the second half of pregnancy to be related to higher systolic blood pressure in adult offspring.

An assessment of protein supplementation during pregnancy on protein intakes, gestational weight gain, and the outcome of pregnancy came to the conclusion that high-protein or balanced protein supplementation is not beneficial and may be harmful to the infant (Kramer, 1993; Kramer & Kakuma, 2003). Thus from these studies it appears that there is a tendency for association between high maternal protein intake and low birth weight.

In all studies mean maternal protein intake was 1.2-1.5 g/kg BW and thus above current recommendations. Thus it is likely that the individuals with 'lower' protein intakes are mostly in the recommended range, whereas those with 'higher' protein intakes were largely in excess of recommendations. It is impossible to derive from these studies an optimal range of protein intake in terms of birth weight or whether reported associations between low weight at birth and disease in later life are attributable to the effects of maternal nutrition at all. A further issue in these studies is the timing of acquisition of the maternal nutritional information. Because fetal growth trajectory is established very early in pregnancy it is not clear how relevant estimations of maternal diet in mid gestation are.

Although there is some evidence that birth weight and body fatness of children and young adults are inversely related (Metges, 2001; Jaquet et al., 2000), a meta-analysis of the relationship between birth weight and adult body fatness showed that the association between low birth weight

and high adult BMI is contradictory (Martorell et al., 2001). This is somewhat surprising because excess adipose tissue leads to reduced insulin sensitivity, which is frequently associated with a set of cardiovascular risk factors, including hyperinsulinemia, hypertension, and glucose intolerance. Possibly, obesity is either a less sensitive outcome of fetal growth retardation than other metabolic disorders, or postnatal factors such as overnutrition or sedentary life style mask possible prenatal effects.

3. CONTROLLED STUDIES WITH ANIMAL MODELS

Although the association between birth weight and adult disease has been recently challenged (Huxley et al., 2002), work with animal models suggests that nutritional programming during fetal life does affect adult health. A widely established model to study fetal programming is the maternal low protein (MLP) model in rodents. Usually an isocaloric casein-based semi-synthetic diet of about 40-50 % protein restriction during pregnancy is compared with an adequate maternal diet of 18-20% protein. However, there are subtle but possibly meaningful variations in experimental design. For example, casein-based diets are supplemented by methionine. In some studies the supplemental methionine: protein ratio is balanced (e.g. Bennis-Taleb et al., 1999), but in others methionine is supplemented independently of the dietary protein content (Rees et al., 1999; Gardner et al., 1997). Further, in some reports offspring was exposed to low protein diet in utero and during lactation (Desai et al., 1997), whereas in others the use of foster mothers on control diet throughout pregnancy and lactation allowed separation of dietary protein effects between prenatal and early postnatal phase (Bennis-Taleb et al., 1999). We found recently, that body mass gain pre-weaning differs between offspring exposed to low or high protein diet in utero and lactation, or in utero only (Daenzer, Petzke, Metges, Klaus, unpublished). This indicates that there are independent effects of milk quality during early lactation.

In numerous studies it was shown that a **low protein intake throughout pregnancy** in rats and mice results in low birth weight, altered hepatic glucose output, age-related loss of glucose tolerance and insulin resistance, and hypertension (e.g. Hales and Ozanne, 2003; Gardner et al., 1997). Also increased catch-up growth during lactation and post-weaning and higher body weight at age 10 wk was reported (Ozanne et al., 2004). Data on body fat were not reported. Also isocaloric maternal **high protein diet during pregnancy** was followed by a reduction of body weight at day of life 2 but a higher body weight than controls up to wk 6 in the offspring (Daenzer et al., 2002).

Exposure to high protein diets during pregnancy and lactation resulted in a decreased body weight of pups until weaning (Gambardella et al., 1987; Daenzer et al., 2002). Furthermore, the offspring from maternal high protein feeding had a higher body fatness and a reduced total energy expenditure at wk 9. In contrast, postnatal protein overnutrition only did not lead to an obese phenotype (Daenzer et al., 2002). This suggests that upon prenatal high protein exposure offspring overcompensated in terms of catch-up growth which was followed by increased body fat in young adults, which provides first evidence that in utero high protein exposure can predispose offspring to adult obesity.

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