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Review article

Developmental influences on circuits programming susceptibility to obesity

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ABSTRACT

Suboptimal maternal nutrition exerts lasting impacts on obesity risk in offspring, but the direction of the effect is determined by the timing of exposure. While maternal undernutrition in early pregnancy is associated with increased body mass index, in later pregnancy it can be protective. The importance of the timing of maternal undernutrition is also observed in rodents, however, many of the processes that occur in the last trimester of human gestation are delayed to the postnatal period. Neonatal leptin administration exerts lasting impacts on susceptibility to obesity in rodents. Although leptin can influence the formation of hypothalamic circuits involved in homeostatic control of feeding during the postnatal period, these effects are too late to account for its ability to reverse adverse metabolic programming due to early gestational exposure to maternal undernutrition. This review presents an alternative framework for understanding the effects of neonatal leptin through influences on developing thermoregulatory circuits.

0. Introduction

The rapid increase in the prevalence of childhood obesity and the concomitant rise in type 2 diabetes/obesity-related medical morbidities and costs, lend urgency to the need for new insights into the causes and potential preventive measures for this disease. Because the trajectory of this increase is very steep- as much as 60% between 1988 and 2000 in some populations – it is unlikely that genetic and conventional environmental factors are sufficient to explain these trends (Ogden et al., 2002). There is a growing appreciation that maternal nutritional and metabolic status during gestation can exert lasting effects on susceptibility to obesity in offspring. In their "thrifty phenotype hypothesis", Hales and Barker propose that maternal influences on the developing hypothalamus, pancreatic islets, adipose tissue and liver result in metabolic adaptations in the progeny that promote survival under conditions of limited nutrient availability, but render them vulnerable to nutritional excess later in life (Hales and Barker, 2001).

In rodents, the nutritional environment during lactation (roughly equivalent to the third trimester of human gestation) has lasting impacts on body weight and susceptibility to diet-induced weight gain (Widdowson and McCance, 1963; Stephens, 1980). As the amount of milk consumed during lactation determines the level of voluntary food intake after weaning (Oscai and McGarr, 1978), efforts to elucidate the mechanism of maternal programming of obesity have often focused on hypothalamic feeding circuits (Bouret, 2012). This review will explore the possibility that susceptibility to obesity due to suboptimal nutrition during development is mediated via effects on thermoregulatory circuits.

1. Association between suboptimal fetal growth and susceptibility to obesity in humans

1.1. Gestational undernutrition followed by catch-up growth

Suboptimal nutrition during gestation, due to famine or other factors that reduce birth weight, has been associated with long-term impacts on body mass index (BMI). However, in some situations maternal undernutrition is linked to increased body weight in progeny, while in others it is associated with reduced body weight. The timing of developmental exposure to famine and the abundance of food in the postnatal environment appear to determine whether offspring are at increased or decreased risk of obesity. The 5-month period of extreme food shortage in the Dutch Winter Hunger of 1944–1945 afforded the unique opportunity to parse the consequences of severe maternal undernutrition in early vs. late gestation on offspring outcomes. Whereas maternal exposure to famine in early gestation is associated with increased BMI, exposure late in gestation and early infancy appears to be protective with respect to obesity, but is linked to impaired glucose

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tolerance (Ravelli et al., 1976, 1998; Painter et al., 2005). These observations support the idea that maternal programming of obesity and metabolic dysregulation are mediated via effects on distinct developmental processes. This review will focus on programming of obesity-related endpoints, while the Brüning review in this issue will focus on glucose tolerance.

Another important determinant of the impact of maternal undernutrition on offspring BMI is the abundance of food in the postnatal environment. Maternal programming of increased BMI is typically observed in situations when the period of famine is followed by relative nutritional abundance, as in the Dutch Winter Hunger. On the other hand, long-lasting famines involving exposure to undernutrition in both the gestational and postnatal periods, such as that caused by the Siege of Leningrad from 1941 to 1945 (Stanner and Yudkin, 2001), are not associated with increased BMI in offspring. The lasting impact of gestational undernutrition is not limited to famine conditions, but can also be observed in small for gestational age (SGA) babies that received suboptimal fetal nutrition but ample postnatal nutrition (Hales and Barker, 2001). These observations are consistent with the idea that the undernourished fetus develops in anticipation of limited nutrient availability in later life (Hales and Barker, 2001). While these adaptations promote survival under conditions of food scarcity, they are not well-suited to a nutrient-rich environment and thus increase susceptibility to diet-induced weight gain (Hales and Barker, 2001; Gluckman and Hanson, 2004).

1.2. Rapid weight gain in infancy as a risk factor for obesity

One common feature of SGA babies and those exposed to the Dutch Winter Hunger early in gestation is that readily available food sources in the postnatal environment promote rapid "catch-up growth". Fast growth trajectories in early infancy are associated with increased prevalence of obesity, even in babies with normal birth weights (Stettler et al., 2003; Sachdev et al., 2005; Ong and Loos, 2006; Ekelund et al., 2007; Taveras et al., 2011). It has been proposed that preferential deposition of fat mass in neonates as compared to older infants underlies this observation (Veldhuis et al., 2006; Gillman, 2008). In support of this idea, rapid weight gain during the first three months of life is associated with a higher percentage of body fat and more central adiposity in early adulthood than weight gain that is distributed evenly throughout the entire first year (Leunissen et al., 2009). Thus, constrained postnatal growth in infants born into famine conditions could underlie observations that these individuals have reduced BMI in adulthood (Ravelli et al., 1976; Stanner and Yudkin, 2001). Distinguishing between directs effects of maternal undernutrition on the development of circuits regulating energy balance and indirect effects due to increased risk of rapid growth in infancy could lead to more effective strategies to prevent obesity in at-risk SGA infants.

2. Rodent models of maternal undernutrition

Experimental animal models have been used to gain mechanistic insights into the fetal origins of adult obesity. Obesity-related outcomes in sheep models of maternal nutrient restriction depend on the timing of exposure, similar to observations from studies of the Dutch Winter Hunger (as discussed in Section 1.1 of this paper and reviewed in Ojha et al. (2013)). Suboptimal nutrition during the first two-thirds of sheep gestation leads to increased adiposity that persists to adulthood (Gnanalingham et al., 2005), while restriction in late gestation results in reduced adiposity (Brennan et al., 2005). While the formation of neural circuits that regulate food intake and energy expenditure is largely completed at parturition in precocial newborns, such as sheep and humans, these processes continue into the suckling period in altricial newborns, such as mice and rats (Symonds, 2013). Because distinct developmental events occur in the gestational and postnatal periods in the rodent, they can be used to distinguish which periods, and therefore processes, are developmentally sensitive to maternal influences. At the same time, it is important to keep in mind that situations in which the early and late gestational environments in humans are discordant are the exception, rather than the rule. This review will focus on rodent models of maternal programming, although corresponding periods in precocial species will be discussed in Section 9.

2.1. Gestational undernutrition followed by catch-up growth programs sensitivity to diet-induced obesity

Rodent models of maternal undernutrition recapitulate observations that the timing of developmental exposure and postnatal dietary factors determine whether the offspring exhibit susceptibility or resistance to diet-induced weight gain. Maternal nutrient restriction throughout gestation and lactation has little effect on offspring fed a chow diet, but leads to increased adiposity when challenged with high fat diet (HFD) in adulthood Desai et al., 2005; Yura et al., 2005; Ikenasio-Thorpe et al., 2007. A rapid increase in the postnatal growth trajectory in rodents, whether or not it was preceded by growth retardation, can lead to increased body weight and adiposity on chow and susceptibility to HFD-induced weight gain (Stephens, 1980; Desai et al., 2005; Jimenez-Chillaron et al., 2006; Isganaitis et al., 2009; Cottrell et al., 2011).

2.2. Postnatal undernutrition can be protective against DIO

Models involving maternal dietary restriction during lactation and suckling in a large litter have been used to study the impacts of undernutrition in the suckling period. While postnatal undernutrition is consistently associated with reduced body weight at weaning (Widdowson and McCance, 1963; Plagemann et al., 1999), these effects do not always persist into adulthood (Jimenez-Chillaron et al., 2006; Prior et al., 2008). Protective effects of reduced nutrition during lactation are more pronounced in mice with genetically- or diet-induced obesity (DIO) Johnson et al., 1973; Patterson et al., 2010.

In summary, rodent models recapitulate fundamental observations in precocial species that maternal undernutrition early in gestation programs increased susceptibility to obesity, while late exposure programs resistance to HFD-induced weight gain. Consistent with delayed maturation of circuits regulating energy balance in altricial newborns, impacts associated with exposure in late human gestation are shifted to the suckling period in rodents. In both precocial and altricial species, the long-term impact of maternal undernutrition on obesity is most clearly observed when progeny are challenged with a calorically dense diet in adulthood.

3. Developmental influences on hypothalamic feeding circuits in rodents

Pioneering studies by Widdowson and McCance demonstrated that manipulations of litter size could be used to assess the long-term impact of changes in caloric intake during the suckling period (Widdowson and McCance, 1963). As maternal milk supply is finite, the primary determinant of food intake in species with large litter sizes is the number of suckling pups (Fiorotto et al., 1991). Postnatal undernutrition (UN) by lactation in a large litter leads to persistent reductions in body weight (Widdowson and