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Perinatal programming effects on feeding behavior

Efectos de la programación perinatal sobre el comportamiento alimentario

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Abstract

To address the growing prevalence of obesity and its associated metabolic consequences, it is essential to understand the evolutionary origins of health and disease. Current evidence attributes the rise in obesity to environmental factors, such as the Western diet and unhealthy lifestyles. However, this review argues that adverse conditions during early developmental stages significantly influence adult health outcomes. It has been proposed that an adverse perinatal environment triggers adaptive physiological changes that ensure fetal survival but simultaneously increase the long-term risk of chronic diseases. In addition to structural and functional alterations in the organism, changes in feeding behavior have been identified and linked to the presence of chronic non-communicable diseases. This narrative review aims to present the last half century's worth of evidence regarding the impact of in-utero environmental changes on eating behavior within the framework of perinatal programming theory.

Keywords: feeding behavior, perinatal programming, hyperphagia, diet, obesity

Resumen

Para hacer frente a la creciente prevalencia de la obesidad y sus consecuencias metabólicas es necesario comprender el origen evolutivo de la salud y la enfermedad. La evidencia actual atribuye la prevalencia de obesidad a factores ambientales, como la dieta occidental y estilos de vida poco saludables; no obstante, en esta revisión se argumenta que la exposición a condiciones adversas durante etapas tempranas de la vida afecta el estado de salud durante la vida adulta. Se ha propuesto que condiciones adversas durante la gestación llevan a una serie de modificaciones fisiológicas adaptativas que garantizan la supervivencia del feto, pero incrementan el riesgo de presentar enfermedades crónicas durante la adultez. Además de las alteraciones estructurales y funcionales en los organismos, se han evidenciado cambios en la conducta alimentaria, los cuales se han relacionado con la presencia de enfermedades crónico-degenerativas. Esta revisión narrativa tiene como objetivo presentar la evidencia que se ha generado a lo largo del último medio siglo con respecto al efecto de las alteraciones durante la vida intrauterina sobre la conducta alimentaria como parte de la teoría de la programación perinatal.

Palabras clave: comportamiento alimentario, programación perinatal, hiperfagia, dieta, obesidad

Introduction

Studies in human populations identify nutrition during the perinatal period as a critical factor influencing obesity risk on later life (Ravelli et al., 1976). To investigate this phenomenon, various animal models have been developed, employing techniques such as bilateral uterine artery ligation, maternal dietary restriction, glucocorticoid exposure, and variations in macronutrient consumption, including low- or high-protein and high-fat diets. Models have also examined the effects of restricting individual micronutrients like iron, zinc, and calcium (Da Silva Cunha et al., 2015; Desai et al., 2007; Hong, 2022; Langley-Evans et al., 2005; Passos et al., 2001; Portella et al., 2012; Simmons et al., 2001; Tarry-Adkins & Ozanne, 2011).

Although a diverse range of methodologies has been employed, these models consistently produce phenotypes associated with hypertension, glucose intolerance, insulin resistance, renal disorders, and obesity (Dötsch et al., 2016; Jones et al., 2012; Langley-Evans, 2009). In addition to physiological changes, eating behavior alterations have been found and linked to the presence of chronic non communicable diseases (Breier et al., 2001). Hyperphagia and alterations in food selection are among the most reported changes.

This review aims to present evidence generated over the past five decades regarding the impact of intrauterine life changes on eating behavior. The first section addresses the historical and theoretical aspects of perinatal programming. Subsequent sections examine the modifications in food consumption and selection behaviors across different perinatal programming models, alongside the physiological pathways underlying these behavioral changes. Finally, the discussion integrates these findings to provide a comprehensive understanding of the topic.

Perinatal programming

The environment in which an individual develops during the perinatal period plays a crucial role in determining health during adulthood (Remmers et al., 2008). It has been proposed that adverse perinatal environments trigger adaptive physiological changes aimed at ensuring survival. However, these adaptations simultaneously increase the risk of chronic diseases in the long term (Barker, 2004). In recent years, the term "nutritional programming" has been proposed and has been characterized as the process by which variations in the quantity or quality of nutrients consumed during pregnancy exert permanent effects on fetal development (Langley-Evans, 2009; Michonska et al., 2022).

In 1990, Barker identified a link between hypertension risk and birth weight, as well as placental weight. He argued that maternal nutrition is a key determinant in this relationship (Barker, 1990). This marked the beginning of what would later be known as the thrifty phenotype hypothesis, which posits that epidemiological associations between reduced perinatal growth and the development of type 2 diabetes and metabolic syndrome result from suboptimal nutrition during development. This hypothesis attributes the development of these diseases to alterations in glucose metabolism caused by early-life nutritional deficiencies (Hales & Barker, 2001).

The thrifty phenotype hypothesis is also referred to as perinatal or intrauterine programming, developmental origins of health and disease (DOHaD), or Barker's theory. This is named after epidemiologist David Barker, who first studied the association between intrauterine conditions and the prevalence of diseases in adulthood (de Boo & Harding, 2006; De Moura & Passos, 2005; Silveira et al., 2007).

Through studies of perinatal programming, several foundational principles have been established (Nathanielsz, 2006): 1) critical periods of vulnerability to suboptimal conditions exist, varying by tissue and developmental stage (Colombo et al., 2019; Fowden, 2006); 2) programming effects persist into adulthood and influence disease susceptibility (Aguayo-Guerrero et al., 2023; Godfrey & Barker, 2001); 3) programming involves structural alterations in developing organs (Desai & Hales, 1997); 4) the placenta plays a pivotal role in the programming process (Fowden et al., 2008); 5) fetuses respond differently to suboptimal conditions compared to newborns or adults (Galjaard et al., 2013; Widdowson & McCance, 1963); 6) programming effects can span multiple generations (Drake et al., 2005) and 7) programming exerts differential effects based on sex (Grigore et al., 2008; Zambrano et al., 2014).

Several models have been proposed to represent intrauterine alterations and their links to several factors. One of the earliest models, proposed by Hales and Barker, connected maternal malnutrition with metabolic syndrome and explained this relationship through alterations in pancreatic beta cells, as well as a reduction in their number and function (Hales & Barker, 2001). Building on this, Cripps et al. (2005) proposed a model called "obesity programming" which attributes obesity to maternal malnutrition and abnormalities in maternal and placental function that result in malnutrition during pregnancy and low birth weight. This model also included postnatal overnutrition as a contributing factor, suggesting that appetite, growth, energy expenditure, and hormonal milieu programming play a role in obesity development (Cripps et al., 2005).

Similarly, Fowden et al. (2008) proposed the "causes and consequences of intrauterine programming" model, which considered environmental factors, hormone levels, maternal diseases, diet, nutrient availability, and oxygen levels as causal factors in intrauterine programming of various organs and tissues. These factors were shown to increase the risk of cardiovascular diseases and metabolic syndrome. While Cripps et al. (2005) accounted for postnatal overnutrition, other models did not fully integrate postnatal factors that might alter health outcomes, highlighting the need for a more comprehensive explanation of perinatal programming phenomena.

Changes in food consumption and selection behavior

A widely reported effect of perinatal programming on eating behavior is hyperphagia, reporting an increase in food consumption among subjects exposed to nutritional alterations during pregnancy. Evidence indicates that a 70% food restriction combined with exposure to a high-fat diet induces hyperphagia, which is exacerbated by the presence of a high-calorie diet. This phenomenon has been linked to the development of adulthood pathophysiologies, including hypertension and obesity (Vickers et al., 2000). These findings suggest that postnatal environmental factors are significant in the etiology of diseases during adulthood.

Similar results were reported by Warren and Bedi, who found that rats subjected to dietary restrictions during gestation and continuing into adulthood consumed significantly higher amounts of food under free-access conditions (Warren & Bedi, 1985).

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However, changes in eating behavior are not only related to prenatal nutritional conditions. Evidence suggests that food restriction during the early postnatal stage can also cause hyperphagia. For example, Sefcikova and Mozes reported that rats with a history of food restriction during lactation consumed significantly more food after being subjected to a 23-hour food restriction program (Sefcikova & Mozes, 2002). Similarly, Smart and Dobbing observed increases in food and water consumption per unit of body weight in rats subjected to protein restriction during gestation (Smart & Dobbing, 1977).

Several studies have documented hyperphagia as a result of perinatal programming, and this has been identified by recording consumptions over a 24-hour period. However, few studies have examined the microstructure of feeding behavior, including meal length, feeding rate, amount of food consumed, and latency intervals. Orozco-Solis et al. (2009) reported that offspring with a history of protein restriction during pregnancy and lactation exhibited hyperphagia during the first 60 days of life. These offspring consumed more food both during the day and nighttime period, and increased their food intake primarily by enlarging meal sizes rather than meal frequency, reduced resting times, delayed transitions from eating to resting, and showed a shorter latency to initiate meals. In relation to the microstructure of food consumption, Dalle Molle et al. (2015) obtained similar results in males, although females did not increase the size of meals but the number. These consumption patterns led to males having a higher intake of calories and females showing a lower consumption.

The effects of perinatal programming on feeding behavior are not limited to ad libitum conditions but are also evident following food deprivation. Lesage et al. (2004) conducted a study using a pregnancy stress model induced by immobilization. Consumption baseline did not differ between the group exposed to stress during pregnancy and the control group. They found that offspring of stressed mothers ate significantly more food during the first three hours following a 24-hour food deprivation compared to control offspring, who increased food intake only during the first hour. The authors explain the increase in food consumption as an alteration in eating behavior in stressful situations.

Despite the prevalence of hyperphagia, not all perinatal programming methods result in this behavior. The occurrence of hyperphagia largely depends on the type, timing, and duration of maternal dietary alterations. For instance, Bellinger et al. (2006) found that short periods of protein restriction during early, middle, or late gestation produced sex- and timing-specific effects on food consumption. Males and females exposed to mid-gestation malnutrition increased their food intake, whereas females exposed to late-gestation or entire-gestation malnutrition showed significantly lower consumption. Under a similar model of perinatal programming, pups were exposed to 12 weeks high fat diet or standard food. High-fat diet intake resulted in a decrease in food consumption because offspring adjusted their consumption to offset the increase in the food energy density (Erhuma et al., 2007).

Hyperphagia is hypothesized to be driven by increased growth and tissue differentiation needs, suggesting that it is a transient effect. It has been reported that although hyperphagia occurs within the first 60 days of life, food intake normalizes around eight months of age, even under high-fat diet exposure (Orozco-Solis et al., 2009). Similarly, Ong and Muhlhausler (2014) reported that offspring exposed to maternal junk food diets during pregnancy did not exhibit hyperphagia for palatable diets at six months of age.

Contrary to hyperphagia reported by several authors, there is evidence that offspring dietary restriction during lactation through an increase in the number of pups per litter, significantly reduces food intake (De Oliveira et al., 2012). Evidence indicates that when overnutrition is present during lactation, an increase in food consumption occurs in offspring's adulthood (Oscai & McGarr, 1978; Plageman et al., 1992).

Food selection behavior also changes as a result of perinatal programming and has been linked to obesity development. Exposure to high-protein, carbohydrate, or fat diets at 12 weeks of age results in an increase in high fat food consumption and a decrease in the high carbohydrate diet intake. However, exposure to a standard diet causes hypophagia (Bellinger et al., 2004). Moreover, Bellinger and Langley-Evans (2005) observed that in shorter periods of alterations in the intrauterine environment, only females showed a change in eating behavior, presenting hypophagia. Energy restriction during gestation also induces a significant increase in consumption and a greater preference for palatable diets, especially during nighttime (Dalle Molle et al., 2015).

Consuming a diet high in energy, fat, sugar, and salt (namely junk food) during gestation and lactation exacerbates preferences for salty, sweet, and fatty foods, while reducing protein-rich food intake, contributing to obesity development (Bayol et al., 2007).

These findings raise an important question: does hyperphagia resulting from exposure to palatable diets during early life have permanent effects on eating behavior? To provide a possible answer, Ong and Muhlhausler (2014) conducted a study to determine if the negative effects of "junk" maternal feeding on dietary preferences could be reversed by a change in diet after weaning. After weaning, the subjects were exposed to a low-fat diet and at six months of age a palatable diet was presented. The study showed that the effect of maternal diet remained at six weeks of age, and was registered as hyperphagia upon access to a palatable diet in both males and females; however, this effect decreased in males when subjects were exposed to the palatable diet at six months of age.

Under the idea that hyperphagia has been related to physiological alterations that occur in organisms exposed to changes in the prenatal environment, the following questions arise: what will happen if food consumption is controlled by avoiding hyperphagia and an opportunity to perform physical activity is provided? Will the same physiological changes occur? There is evidence that postnatal environmental factors such as controlled feeding and the opportunity to perform physical activity may modulate the effects of perinatal programming by food restriction during pregnancy. Barbero et al. (2014) conducted a study with a food restriction technique in pigs. The amount of food that was provided was controlled and the offspring had a space 7-12 times wider than the one recommended for them, to provide the opportunity to perform physical activity. The results showed an absence of effects secondary to maternal food restriction. It was concluded that controlled food consumption and the opportunity to exercise can modulate the postnatal pattern of growth and increased adiposity.

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Physiological pathways related to changes in food consumption and selection

Feeding behavior is regulated by a complex network of cellular signals that originate in the gastrointestinal tract or are generated in the brain. Depending on the type of signal, their effect is either orexigenic or anorexigenic. The idea that nutritional levels during the perinatal period influence long-term appetite regulation is reasonable, as this period is critical for the formation of projections from the arcuate nucleus to other hypothalamic nuclei involved in regulating food intake (Cripps et al., 2005). Skowronski, Leibel, and LeDuc (2024) indicated that perinatal undernutrition and overnutrition alter the hormonal and metabolic environment during intrauterine and postnatal periods. These effects are mediated through disruptions in hypothalamic maturation, which result in the perinatal programming of adiposity.

One explanation for hyperphagia observed in subjects exposed to nutritional alterations during development is the modification of anorexigenic hypothalamic signals and reduced anorexigenic physiological responses. Furthermore, it has been reported that rats with intrauterine growth restriction exhibit alterations in the mesolimbic reward pathway, favoring a preference for highly palatable foods. This alteration is evidenced by changes in tyrosine hydroxylase, phosphotyrosine hydroxylase, and D2 receptor levels in the nucleus accumbens (Dalle et al., 2015).

Similarly, López et al. (2005) argued that neuropeptide Y, agouti-related protein (r-agouti), and leptin receptor isoforms play key roles in hypothalamic programming due to perinatal nutrition in rats. López et al. (2005) argued that rats subjected to perinatal overnutrition exhibit hyperleptinemia, reduced hypothalamic mRNA levels of the long leptin receptor isoform, and increased expression of the cocaine- and amphetamine-regulated transcript, neuropeptide Y, and r-agouti in the arcuate nucleus. Conversely, rats exposed to perinatal food restriction exhibit hypoleptinemia, increased hypothalamic mRNA levels of short leptin receptor isoforms, and elevated expression of neuropeptide Y and r-agouti. These results suggest that the programming of feeding behavior occurs primarily in the arcuate nucleus.

Another hormone implicated in altered feeding behavior is ghrelin. Camacho-Morales et al. (2022) reported that exposure to high-energy diets during gestation increases ghrelin sensitivity to overfeeding with cafeteria diets in male offspring. This was demonstrated through hyperphagia following ghrelin administration.

Recent studies have shown that prenatal undernutrition programs obesity and metabolic syndrome through DNA methylation changes. These changes result in high concentrations of orexigenic neurons in the hypothalamus, elevated neuropeptide Y levels, and increased expression of the brain-specific homeobox transcription factor (Bsx), which is related with NPY and AGRP expression (Han et al., 2024; Schredelseker et al., 2020).

However, there is also evidence of the absence of hyperphagia in some cases, where alterations are attributed to reduced hypothalamic neuronal activity, increased fat mass, decreased glucose tolerance, reduced insulin sensitivity, elevated plasma leptin levels, and higher plasma thyroid-stimulating hormone levels (Kulhanek et al., 2022).

Discussion

Changes in food consumption and selection behavior are pivotal to understanding the development of obesity in subjects who experienced growth restriction during gestation. It has been established that the postnatal environment also plays a significant role in the emergence of obesity and its comorbidities (Barker, 2004). However, organisms interact with their environment through behavior, particularly regarding the availability and variety of food through eating behavior. Pecorelli (1997) emphasized that the environment encompasses all physical surroundings in which an organism lives, and that an appropriate definition of environment must take into account all the influences that have formed an individual since its conception, since two subjects can live in the same physical environment, but their behavior may be substantially different and consequently obtain different health status. Therefore, the intrauterine environment and external environmental factors must be considered together as they jointly shape an organism's behavior.

On the other hand, although the dietary behavior modifications due to perinatal programming are undeniable, the methodology used is an element that must be considered when interpreting results. Notably, many studies did not incorporate standardized physical activity protocols, restricting rats to limited housing spaces. As Miles et al. (2009) suggested, research on perinatal programming and eating behavior should include standardized protocols for physical activity, as these could significantly alter findings (Miles et al., 2009).

In this review it was evident that nutritional alterations during gestation resulting in intrauterine growth restriction modify food consumption and selection behaviors in adulthood. Specifically, intrauterine growth restriction due to nutritional deficiencies leads to hyperphagia, which is further exacerbated by exposure to hypercaloric diets. Additionally, the lactation stage was identified as a critical period for programming eating behavior. Food restriction during lactation leads to hypophagia, while overnutrition during this period results in hyperphagia.

Regarding food selection, the evidence indicates a preference for high-fat and "junk" foods, further linking perinatal programming to obesity development. These findings underscore the need for a comprehensive understanding of both prenatal and postnatal influences on eating behavior and their implications for long-term health outcomes.

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