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Ghrelin and feeding behaviour in preterm infants

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ABSTRACT

The importance of early life events in the development of metabolic diseases is well recognized. Early postnatal environment, including nutrition, is key to future health, and this is particularly true for preterm infants. It is important that these infants receive sufficient nutrients to prevent growth restriction and promote neurodevelopment, while minimizing predisposition to metabolic diseases later in life. Feeding habits are the fundamental elements of nutrition and are influenced by many factors, including personal and familial habits, socioeconomic status, and cultural environment. In the last decades, there has been an important scientific interest toward the comprehension of the molecular and neural mechanisms regulating appetite. In these networks, act many peptide hormones produced in brain or gut, among which ghrelin is important because of its action in the short-term regulation of food intake and the long-term regulation of body weight. Ghrelin stimulates appetite and plays a role in regulating feeding behaviour. Ghrelin levels vary from fetal life through to early adulthood, with the highest levels observed in the very early years. Cord ghrelin levels have been evaluated in term and preterm newborns and high ghrelin levels have been observed in small-for-gestational age newborns and in newborns with intrauterine growth restriction. Moreover, ghrelin has been detected in term and preterm human breast milk, suggesting that it may play a role in the development of neuroendocrine pathways regulating appetite and energy homeostasis in early life. However, more research is required to better define ghrelin's role in breast milk and on feeding behaviour.

1. Introduction

Feeding behaviour is a complex interaction of physiological, psychological, social, and genetic factors that influence meal quantity, frequency and timing, and food choices. Studying the biological mechanisms guiding feeding behaviour is important for understanding the pathophysiology of obesity, as food intake is a significant factor impacting the development and treatment of this disorder and its associated comorbidities [1].

Feeding habits are the fundamental elements of nutrition, and are influenced by many factors, including personal and familial habits, socioeconomic status, and cultural environment. Feeding is a primary event in the life of an infant, and early feeding experiences affect both health and psychological well-being, setting the stage for healthy feeding-associated behaviours in childhood and adulthood.

Proper nutrition in early infancy is essential for normal growth and may have a substantial impact on long-term health and optimal neurological and cognitive development [2]. Also the length of gestation and birth weight are strong predictors of an infant's future health and survival. In the last 20 years, significant progress has been made in the quality of care provided to preterm infants, with particular attention being paid to their nutrition in order to achieve proper growth [3].

Growth in infancy is related to nutritional intake and therefore potentially to the circulating levels of hormones such as ghrelin, insulin, and leptin. In particular, ghrelin, a hormone primarily produced by the stomach and pancreas, is involved in the neuroregulation of appetite and feeding behaviour, promoting meal intake and hunger, and contributing to obesity risk by increasing caloric intake. The study of this hormone and its genetic variants can provide new insights into the understanding of the mechanisms of eating behaviour [4].

Behavioural research in infant feeding has focused on breastfeeding showing that it has beneficial effects on infant-feeding style, improving infant's ability to self-regulate appropriate food intake and contributing to healthier eating patterns [5]. The recent identification in breast milk (BM) of adipokines and other hormones, such as ghrelin, involved in energy-balance regulation suggests that BM may modulate neuroendocrine pathways involved in the regulation of appetite and feeding behaviour [6,7]. Diet-related differences during infancy in serum levels of factors involved in energy metabolism might explain anthropometric differences and differences in dietary habits between breast-fed (BF) and formula-fed (FF) infants also later in

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life, and may thus have long-term health consequences, in particular on the development of obesity [8].

2. Importance of feeding in the first periods of life: the preterm infant

The first years of life are particularly important because a child's feeding abilities and needs change with motor, cognitive, and social development. In the first 3 months of life, the infant integrates experiences of hunger and satiety to develop regular feeding patterns. Afterwards, the infant forms an attachment with the primary caregiver and parents' behaviours influence the infant's feeding experience. From the sixth month of life, the infant gradually discovers a sense of autonomy, using motor and language skills to control the environment and establish self-regulation feeding [9]. These stages in the development of feeding behaviour are fundamental for infant growth.

Achieving appropriate growth and nutrient accretion is particularly important and often difficult for preterm infants, because of their special needs, as a result of metabolic and gastrointestinal immaturity, compromised immune function, and other complicating medical conditions. For preterm infants, these problems include immaturity of bowel function, inability to suck and swallow, high risk of necrotizing enterocolitis, illnesses that may interfere with adequate enteral feeding, and medical interventions that preclude feeding. In fact, preterm neonates are subject to physiological and metabolic stress that can affect their nutritional needs, such as respiratory distress or infections. Moreover preterm infants, especially those who have been growth restricted in utero, have fewer nutrient reserves at birth than term infants. Thus, multiple problems regarding premature infants may affect nutritional issues.

Particularly, preterm birth interrupts gut maturation and the development of gastrointestinal (GI) functions and feeding abilities. In fetal life, gut has formed by 10 weeks of gestation. By 16 weeks, the fetus can swallow amniotic fluid: it contains carbohydrates, protein, fat, electrolytes, immunoglobulins, and growth factors, and plays an important role in the development of GI functions. GI motor activity is present before 24 weeks, but organized peristalsis is not established until 29 or 30 weeks, and coordinated sucking and swallowing develops at 32–34 weeks [10]. Preterm birth interrupts all of these processes.

In the last 20 years, significant progress has been made in the quality of care provided to preterm infants. During this period, studies on neonatal nutrition have produced important results looking for the optimal feeding policy to achieve proper growth in these infants. However, a disparity in nutritional practice and feeding strategies in neonatal units has been noticed. Indeed, most investigations of nutrient metabolism over the past two decades have reached conflicting conclusions. Most of the research showed analysis of observational data and was conducted on heterogeneous populations with consequent limitations.

The goal of nutrition in preterm infants is to attempt to optimize growth and neurodevelopmental outcomes, avoiding short-term and long-term adverse outcomes. There is increasing evidence that the nutrition of the appropriate-for-gestational age (AGA) versus intrauterine growth-restricted infants may need to be different, given the differences in growth in intrauterine life and in metabolic homeostasis. The identification of infants that have suffered growth failure in utero has become of primary importance. A single marker for altered metabolism in infants with intrauterine growth restriction (IUGR) has not yet been detected. Recent studies have focused on indices of fetal blood sampling (e.g. acidosis), abnormal fetal blood flow indices, cortisol and leptin levels in cord or neonatal blood, and modified insulin sensitivity testing [11-13].

The American Academy of Pediatrics has proposed some specific nutrient requirements for preterm infants distinct from those for term infants. Nutrient amounts recommended for preterm infants must be sufficient to allow growth similar to that achieved by term infants of comparable postconceptional age. Many preterm infants are also born small-for-gestational age (SGA), so there is an additional need for enough catch-up growth to bring them to the size of a normal fetus of comparable gestational age. Nevertheless, the question emerges of whether a growth rate of 15 g/(kg · d), which has been used as a minimum growth standard, is adequate. Neonatal undernutrition is a risk to physical and mental development. On the other hand, overfeeding could also be harmful.

Furthermore, an important nutritional issue is the need to determine how the composition of formula affects the composition of weight gained, particularly whether there is an optimum energy-to-protein ratio above which an increase in energy intake would result in mainly fat storage.

On the basis of studies of the effects of diet on composition of weight gain, the European Society for Paediatric Gastroenterology and Nutrition recommended that the protein-to-energy ratio for preterm infant formula should be 3.2 to 4.1 g/100 kcal [14]. The goal in estimating the protein nutritional needs of the preterm infant is to provide the quantity and quality of protein needed to achieve fetal rates of tissue growth and to avoid accumulation of potentially harmful protein metabolic products [15].

Besides gestational age, birth weight is also an important biological condition that may influence infant neurodevelopment. A recent study has shown that among preterm infants, low-birth-weight infants who are extremely preterm may be the most at risk for nutritive feeding maturation problems compared with less preterm infants [16]. On the one hand, vigorous feeding in low-birth-weight infants in order to accelerate growth and improve nutritional status could help reduce infant morbidity and mortality. However, recent studies suggest that catch-up growth and rapid postnatal weight gain may be associated with the development of chronic adult diseases, such as obesity, cardiovascular disease, and type 2 diabetes [17]. Strategies to modify accelerated growth will need to evaluate the benefits of improved nutritional status and the potential costs of future chronic disease [18].

3. Ghrelin

Ghrelin is a 28-amino-acid peptide hormone first described in 1999 as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R). Ghrelin is predominantly produced in the oxyntic mucosa of the stomach by enteroendocrine X/A-like cells, and lower amounts are derived from the bowel, pancreas, kidneys, immune system, placenta, testes, pituitary, lung, and hypothalamus [19]. In mammals, ghrelin is derived from a 117-amino-acid polypeptide termed pro-ghrelin, following cleavage after the 28th amino acid residue by prohormone convertase 1 [20]. It circulates in the bloodstream, bound to lipoproteins [21]. A portion of ghrelin has a fatty acid modification, an *n*-octanoylation, attached to the serine at position 3. This form, known as acylated or active ghrelin, accounts for only 5–10% of the total circulating ghrelin, and is thought to be essential for binding to the GHS-R-1a. More than 90% of ghrelin immunoreactivity in human plasma consists of the unacylated portion, also called desacyl-ghrelin, which results from ghrelin deacylation by butyrylcholinesterase and platelet-activating factor acetylhydrolase [22].

Besides the stimulation of growth hormone (GH) release from the pituitary [23], ghrelin has a broad spectrum of biological functions which includes stimulation of appetite and a positive energy balance, control of gastrointestinal motility and gastric acid secretion, modulation of endocrine and exocrine pancreatic secretions, cell proliferation, glucose and lipid metabolism, and action in cardiovascular and immunological processes [24].

3.1. Ghrelin's role in energy homeostasis

The regulation of appetite and food intake represents one of the most important ghrelin actions. Ghrelin administration increases appetite and

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stimulates food intake both in animals and humans [25]. The secretion of ghrelin into circulation increases prior to feeding, and decreases postprandially, suggesting a role of ghrelin in meal initiation [26].

Ghrelin stimulates appetite by acting on the hypothalamic arcuate nucleus, a region known to control food intake (Fig. 1). Ghrelin-induced feeding results from the activation of the orexigenic neurones expressing neuropeptide Y (NPY) and agouti-related protein (AgRP) in the hypothalamic arcuate nucleus [27]. Ghrelin also inhibits anorexigenic neurones expressing pro-opiomelanocortin, preventing the release of α-melanocyte-stimulating hormone and activates neurones expressing orexin in the lateral hypothalamic area [28].

In NPY/AgRP cells in the hypothalamic arcuate nucleus, ghrelin stimulates adenosine monophosphate-activated protein kinase (AMPK) and regulates fatty acid metabolism. In fact, through its binding to the GHS-R, ghrelin increases intracellular calcium, which induces the phosphorylation of AMPK. Phosphorylated AMPK, through the phosphorylation of the acetyl-coenzyme A carboxylase, inhibits the formation of malonyl-coenzyme A and consequently activates carnitine palmitoyltransferase-1. Mitochondrial β-oxidation is increased, reactive oxygen species (ROS) are generated and uncoupling protein-2 is stimulated, which promotes ROS scavenging and stimulates NPY/AgRP transcription [29].

In addition to playing a role in the control of food intake by orexigenic and anorexigenic pathways, ghrelin may stimulate appetite through the vagus nerve by mediating the signal from the gut to the brain [29].

Recent studies have suggested that, besides stimulating appetite by hypothalamic circuits, ghrelin is involved in the regulation of feeding behaviour, acting on two dopaminergic regions of the mesolimbic system, the striatum and ventral tegmental area (VTA). Administration of ghrelin into the VTA increases food intake and stimulates dopamine release from the VTA [30]. Ghrelin also stimulates brain activity in the amygdala, orbitofrontal cortex, anterior insula, and striatum, which are involved in the control of appetitive behaviour [31].

The role of ghrelin in energy-balance regulation consists not only in the short-term orexigenic action, but also in the long-term regulation of body weight [32]. Ghrelin induces body weight gain and adiposity by stimulating food intake, with a preference for fat ingestion, promoting fat storage, reducing energy expenditure and fat utilization, and increasing carbohydrate utilization [33]. Plasma ghrelin levels are negatively correlated with body mass index. Indeed, patients with obesity and anorexia have, respectively, lower and higher plasma ghrelin levels than healthy subjects with normal body weight [34]. Ghrelin level variates in a compensatory manner to body-weight variations: ghrelin secretion is increased in response to weight loss induced by food restriction and long-term exercise, while it decreases under positive energy-balance conditions, such as weight gain resulting from overfeeding, pregnancy, and high-fat diet [35].

Ghrelin has been also reported to play a role in glucose homeostasis. In humans, peripheral injection of ghrelin is followed by an increase in glycaemia, that is then followed by a transient decrease in circulating insulin levels, probably through a direct GH-independent glycogenolytic effect [36]. Also, ghrelin secretion seems to be suppressed, at least in part, by increased plasma glucose level as well as by insulin [37].

3.2. Ghrelin in fetus, term and preterm neonates

Ghrelin levels vary from fetal life through to early adulthood ranging from 200 to 800 pg/ml, with the highest levels observed in the first years of life [38]. Ghrelin has been detected in human cord blood as early as 22 weeks of gestation, suggesting a possible role of ghrelin during intrauterine life [39]. The source of ghrelin in fetal life is not well defined as it seems to be produced by fetal tissues [40], even though it may also originate from the maternal compartment or may be secreted by the placenta [41]. Immunoreactive

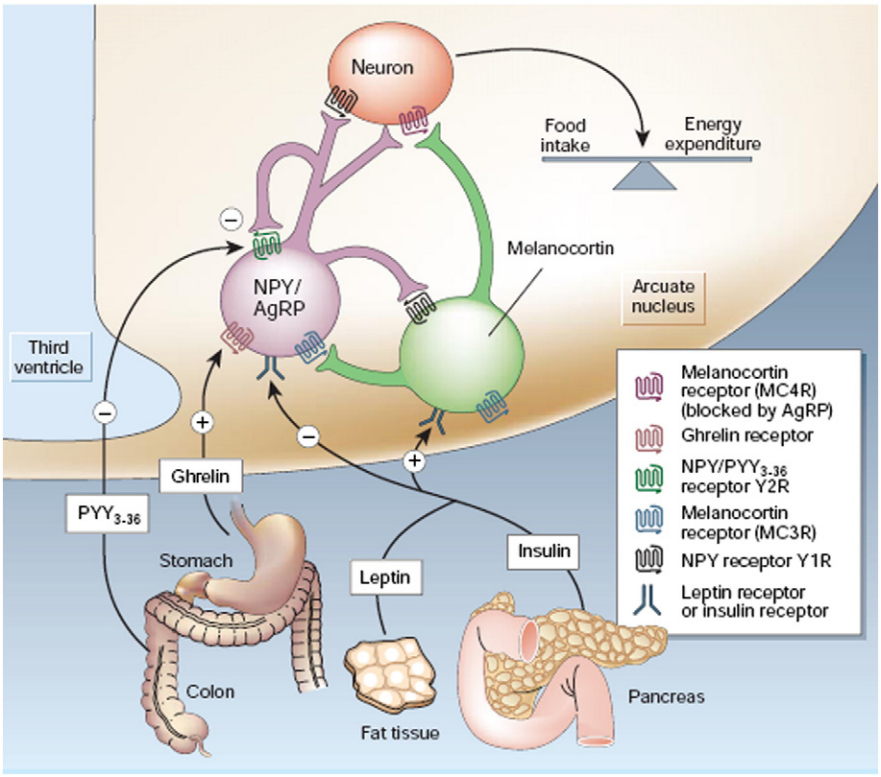

Fig. 1. Hormones that control eating: ghrelin stimulates appetite by activating the NPY/AgRP-expressing neurones. [Modified by Schwartz MW and Morton GJ. Nature 2002.]NPY, neuropeptide Y; AgRP, agouti-related protein.

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ghrelin cells have been observed in fetal stomach, duodenum, pancreas, and lung from the 10th week of gestation [42].

Some studies have shown that circulating ghrelin levels remain relatively constant throughout the gestation and at birth, with no differences in cord ghrelin levels between term and preterm newborns [43,44]. However, another study reported that cord ghrelin levels are higher in term than in preterm neonates (median [25th–75th percentile] 399.0 [229.0–438.0] pg/ml versus 208.0 [144.5–278.9] pg/ml, respectively) [45]. The same discrepancy regards the correlation between ghrelin levels and neonatal anthropometric parameters, as in term infants, plasma ghrelin was inversely associated with birth weight and length [46], while another study reported that ghrelin levels did not correlate significantly with anthropometric parameters in newborns [47].

Moreover, it is not well defined how ghrelin acts in energy homeostasis and metabolism during fetal and neonatal life. In a study conducted on premature infants with a gestational age ranging from 25 to 35 weeks, cord blood acylated and total ghrelin did not correlate with GH concentration, suggesting that ghrelin probably is not responsible for the high GH concentrations observed during gestation [48]. In the same study, cord blood ghrelin correlated positively with maternal ghrelin and negatively with neonatal glucose levels. Total ghrelin concentration in cord blood of SGA infants was significantly higher than in AGA infants [49]. Higher cord blood ghrelin levels have been also detected in preterm SGA newborns than in AGA ones [39] and in newborns with IUGR [50]. It has been suggested that, in these infants, higher ghrelin levels could play a role in fetal adaptation to intrauterine malnutrition, stimulate appetite, and result in higher nutritional intake by the neonate, contributing to catch-up growth [51]. The same observation emerges from another study in which it has been reported that, in the first days of life, ghrelin secretion is refractory to the effect of feeding, and increased ghrelin levels may act as an anabolic drive to promote food intake [52]. Moreover, low cord ghrelin concentrations have been associated with slow weight gain in the first 3 months of life [53], supporting that this hormone may regulate feeding behaviour in early life and promote growth. In a study evaluating serum ghrelin levels of preterm infants in the early neonatal period, it has been observed that hormone levels are influenced by the beginning of the enteral feeding, supporting the hypothesis that the functional profile of the ghrelin system in early life is orientated to anabolic purposes [54] .

Higher ghrelin levels during the neonatal period could also influence hormone levels later in life. In fact, it has been observed that increased ghrelin levels in preterm born children in the early neonatal period are sustained up to prepubertal ages.

Two possible explanations may be proposed to explain the reason why ghrelin is significantly higher in preterm than in full-term neonates: the first one is that its synthesis or secretion could be increased; and the second one is a possible reduction in the ghrelin clearance rate. Evidence exists that the kidney is the primary site of ghrelin clearance, while the liver plays a minor part. It is possible that the elevated ghrelin level in the peripheral blood of preterm infants may result from the decrease in the clearance rate because the two main clearance sites of ghrelin are not fully mature in preterm infants.

3.3. Ghrelin in infants

Studies on serum ghrelin levels in infants are scanty. Ghrelin levels increase after birth, peaking during the first 2 years of life [38]. We have conducted a study on infants in the first 4 months of life, showing that the kind of early feeding could influence ghrelin levels: in fact, FF infants seem to have higher serum ghrelin levels compared with BF infants [55]. In a cohort of infants aged up to 18 months, serum ghrelin correlated positively with fasting time and a negative influence of insulin on ghrelin levels was observed [56]. A positive correlation between circulating ghrelin levels and fasting time was also observed in exclusively FF infants in the first 6 months of life, suggesting that ghrelin could be involved in appetite regulation from the first months of life [57]. The negative relationship described between total ghrelin levels and weight gain during the first year of life may also indicate that ghrelin reflects changes in weight beyond the neonatal period [58].

A different feeding behaviour has been described in BF and FF infants [59], and this could be related to differences in ghrelin levels between the two groups of infants. Recently, it has been observed that the proportion of infants completely emptying their bottle or cup of milk during the second half-year of infancy differs according to feeding mode during the first months of life, with the highest percentage observed in infants only bottle fed (68% versus 27% of infants only fed at the breast and 54% of infants fed both at the breast and by bottle) [60]. Considering that ghrelin plays an important role in food intake regulation, different hormone levels in early life could influence feeding behaviour both in the short- and long-term.

3.4. Ghrelin in breast milk

Ghrelin has been detected in both term and preterm human BM with similar concentrations and higher than those typically found in plasma; moreover it has been observed that its levels are higher in whole milk than in skimmed milk [61]. Ghrelin concentration has been evaluated in colostrum (70.3 ± 18 pg/ml), transitional milk (83.8 ± 18 pg/ml) and mature milk (97.3 ± 13 pg/ml), showing lower levels than those typically found in plasma [62]. Also, acylated ghrelin has been reported in BM, showing that its concentrations increase during lactation and are significantly related to serum ghrelin concentrations in BF infants; active and total ghrelin concentrations in BM were lowest at 0–3 days, whereas they increased progressively during 180 days of the lactation period [63].

4. Concluding remarks

Early nutrition could influence the programming of metabolic development and growth, exerting both short- and long-term effects, and particularly, this could be a time when dietary practices are established and will continue throughout childhood. Food preferences are shaped by a combination of genetic and environmental factors, a better understanding of which is critical to the development of effective dietary interventions.

Providing appropriate nutrition is a cornerstone of the care of preterm infants and it represents a challenge for paediatricians. Pathways involved in appetite regulation and feeding behaviour mature early in postnatal life. Among the biological factors involved in the development of these mechanisms, ghrelin plays a key role. The presence of ghrelin in cord blood as early as 23 weeks of gestation suggests a role for this peptide in the developing fetus, possibly as a promoting factor for fetal growth. During the later stages of gestation, ghrelin may acquire its metabolic role inducing adiposity, stimulating appetite, and regulating glucose homeostasis. Preterm infants may have an immaturity in energy-balance regulation that also involves neuronal pathways that mediate the effects of ghrelin. Moreover, ghrelin could represent a marker for altered metabolism in infants' IUGR. In fact, higher cord blood ghrelin levels in term and preterm SGA newborns and in newborns with IUGR suggest that ghrelin could play a role in fetal adaptation to intrauterine malnutrition and contribute to catch-up growth in these neonates. Considering that early life nutrition and growth could programme the set-point of energy homeostasis later in life, investigation of the possible actions of ghrelin in fetal and neonatal life can contribute to the understanding of its role in feeding behaviour in infancy.

Conflict of interest statement

All the authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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