

Review Article

Breast Milk Hormones and Their Protective Effect on Obesity

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Data accumulated over recent years have significantly advanced our understanding of growth factors, cytokines, and hormones in breast milk. Here we deal with leptin, adiponectin, IGF-I, ghrelin, and the more recently discovered hormones, obestatin, and resistin, which are present in breast milk and involved in food intake regulation and energy balance. Little is known about these compounds in infant milk formulas. Nutrition in infancy has been implicated in the long-term tendency to obesity, and a longer duration of breastfeeding appears to protect against its development. Diet-related differences in serum leptin and ghrelin values in infancy might explain anthropometric differences and differences in dietary habits between breast-fed and formula-fed infants also later in life. However, there are still gaps in our understanding of how hormones present in breast milk affect children. Here we examine the data related to hormones contained in mother's milk and their potential protective effect on subsequent obesity.

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1. Introduction

Studies on the physiology of breastfeeding revealed the presence of the two adipokines, leptin [1] and adiponectin [2], hormones, such as IGF-I [3], ghrelin [4], and more recently obestatin [5] and resistin [6] in mother's milk (Table 1). Human milk is a complex biological fluid: leptin and ghrelin are synthesized and secreted into breast milk by the mammary gland and pass from serum into milk. The origin of adiponectin, obestatin, and resistin remains to be established. Leptin and ghrelin have a positive effect on the early control of satiety in infants and could influence the programming of energy balance regulation in childhood and adulthood thereby protecting against later obesity [7]. It is noteworthy that childhood obesity is associated with an increased risk of adult metabolic syndrome [8].

Here, we review data related to hormones contained in mother's milk and their potential protective effect on subsequent obesity.

1.1. Leptin. Leptin is an adipocyte-derived hormone discovered in 1994 [9]. It reduces appetite and increases energy expenditure by acting on the arcuate nucleus in the hypothalamus through its receptor (Ob-R) [10]. Circulating leptin levels correlate with fat mass in adults and children [11].

Leptin is detectable in cord blood from the second trimester of intrauterine life and correlates with adiposity at birth [12]. Interestingly, serum leptin concentration correlates with body mass index (BMI) in infants [13].

In obese subjects, endogenous leptin, even at high circulating levels, fails to exert its normal effects, and administration of exogenous leptin does not significantly reduce adiposity. This condition, known as "leptin resistance", could be due to reduced transport of leptin into the brain and reduced expression of leptin receptor in the arcuate nucleus or an increased concentration of SOCS3, which suppresses leptin signaling by inhibiting leptin-induced STAT activation [14].

Leptin has been implicated in the neonatal development of the hypothalamic pathways involved in the central regulation of energy balance and appetite [15]. Studies conducted in mice have shown that by acting on the brain during a critical neonatal period that coincides with a naturally occurring leptin surge, leptin promotes the formation of neural circuits that control food intake and adiposity later in life [16].

In humans, cord blood leptin concentration has been observed to be inversely related to rates of intrauterine growth, suggesting a possible role of leptin in promoting fetus growth: small-for-gestational age (SGA) neonates have

TABLE 1: Breast milk hormones.

Hormone	Year of discovery	Receptor	Detection of receptor in intestine	Main functions	Year of discovery in breast milk	Method of detection in breast milk	Detection in umbilical cord blood
Leptin	1994	Ob-receptor	In humans [17]	Anorexigenic effect	1997	RIA [1, 18], ELISA [16]	[12, 19, 20]
Adiponectin	1995	Adipo-R1 Adipo-R2	In humans [21]	Improvement of insulin sensitivity, increase in fatty acid metabolism, anti-inflammatory and anti-atherogenic properties	2006	RIA [2], ELISA [22]	[20]
Ghrelin	1999	Growth hormone secretagogue receptor -1a	In humans [23]	Orexigenic action; stimulation of GH secretion; stimulation of acid gastric secretion and motility	2006	RIA [4, 24]	[25]
IGF-I	1950	IR IGF-IR IGF-IIR Insulin receptor-related receptor IR-IGF-IR hybrid receptor	In humans [26]	Primary mediator of growth hormone effects; role in the regulation of postnatal human growth from late infancy onward	1984	RIA [3]	Ibáñez L et al., 2008; Lagiou P et al., 2009
Resistin	2001	Unknown	Unknown	Regulation of insulin sensitivity	2008	ELISA [6]	[27]
Obestatin	2005	GPR39	In mice [28]	Anorexigenic effect?	2008	RIA [5]	Unknown?

lower leptin levels at birth than appropriate-for-gestational age (AGA) infants, and large-for-gestational age (LGA) neonates have higher leptin levels than other infants [19].

Cord blood leptin seems to be a predictor of weight gain also in later life; in fact lower cord blood leptin levels have been observed to be associated with smaller size at birth but more pronounced weight gain in the first 6 months of life and higher BMI at 3 years of age [20].

Leptin is present in human milk [1]; it is produced and secreted by mammary epithelial cells in milk fat globules [29]. Moreover, secretory epithelial cells may transfer leptin from the blood to milk [30]. Leptin concentration was found to be higher in whole than in skimmed samples of human milk [18], probably because a portion of leptin could be associated with the milk fat droplet or fat-associated proteins. Leptin concentration was also higher in colostrum than in transitional milk (4-5 days postpartum milk) [31]. Leptin receptors have been identified in gastric epithelial cells and in the absorptive cells of mouse and human small intestine [17], which suggests that leptin could pass from milk to infant blood and might play a role in the short-term regulation of feeding. This could occur during early lactation. In fact, when neonatal rats were orally supplied with leptin, the hormone was directly taken up by the stomach thereby resulting in an increase in leptin levels in

the stomach and serum [32]. When these rats were fed a chow or a high-fat diet from weaning, those that received physiological doses of oral leptin during the suckling period had a lower body weight and less adiposity in adulthood; they also had greater insulin sensitivity and showed a lower preference for fat-rich food than their controls [33]. Consequently, breast milk leptin could play a role in the short-term control of food intake in neonates by acting as a satiety signal and could also exert a long-term effect on energy balance and body weight regulation [34, 35]. Leptin concentrations in breast milk were found to correlate positively with maternal circulating leptin levels, maternal BMI, and the mother's adiposity [36]. A positive correlation has also been reported between breast milk leptin levels and infant plasma leptin [37]. We observed higher serum leptin concentrations in breast-fed infants than in formula-fed babies in the first months of life [38] and a positive correlation between serum leptin concentration in breast-fed infants and maternal BMI [39]. The presence of leptin in the breast milk of nonobese mothers at 1 month of lactation was found to be negatively correlated with infant BMI at 18 and 24 months of age [40]. Further studies are required to better understand if leptin in human milk could play a role in differences in adiposity later in life according to the type of early feeding; in the first months of life, the relation between

leptin and infant body composition may be present but still remains an undefined link [12].

Using radioimmunoassay, Lage et al. reported variable leptin concentrations in commercial bovine milk and in infant formulas [41]. However, according to O'Connor et al., radioimmunoassay is not appropriate for the detection of leptin in infant formulas because supplemented iron, emulsifiers and other additives contained in formulas could confound the assay [42]. Therefore, further research is required to determine whether leptin is present in milk formula.

1.2. Adiponectin. Adiponectin is the most abundant adipose-specific protein, and its multiple functions have only recently started to emerge [43]. It was discovered in breast milk in 2006 by Martin et al. [2] and Bronsky et al [22]. Martin et al. recently reported that adiponectin levels in human milk decreased with the duration of lactation [2]. Adiponectin circulates in very high concentrations in human serum and its levels are inversely related to the degree of adiposity and positively associated with insulin sensitivity. In fact, plasma adiponectin concentrations are decreased in individuals with obesity and type 2 diabetes [44].

Cord blood adiponectin levels have been observed to be directly associated with birth weight for gestational age, inversely associated with weight gain in the first 6 months of life, and to predict an increase in adiposity in 3 years old-children [20].

Circulating adiponectin levels correlate negatively with the degree of adiposity also in children aged between 5 and 10 years [45]. In contrast, in full-term infants during the first few days of life, serum and plasma adiponectin levels correlate positively with birth weight and length, neonatal adiposity, and circulating levels of leptin [46]. In preterm infants, serum adiponectin levels are lower than in full-term infants, correlate positively with body weight, and increase with postnatal age, which suggests a metabolic adaptation to premature extrauterine life [47]. Given the biological properties of adiponectin, its presence in breast milk, and the expression of adiponectin receptor 1 in the small intestine of neonatal mice [48] and of adiponectin receptor 1 and 2 in human colon epithelium [21], not only adiponectin produced by adipose tissue but also milk adiponectin may affect infant growth and development. Weyermann et al. found that higher levels of adiponectin in breast milk were associated with overweight at two years of age in infants who were breast-fed for at least 6 months [49]. Further research is needed to evaluate whether exposure to adipokine in infancy determines later weight status [50].

Bronsky et al. recently detected in human breast milk also fatty acid binding proteins, which are produced by adipose tissue and are related to lipid metabolism [22].

1.3. Resistin. Resistin was discovered in 2001 as a cytokine secreted by adipocytes [51]. It was recently identified in human milk by Icol et al. [6]. They found that resistin levels decreased during lactation. Moreover, resistin concentrations in both milk and serum of breastfeeding mothers correlated positively with hormone status (estradiol, progesterone,

prolactin, thyroxine, triiodothyronine, cortisol, and leptin levels) and with concentrations of the inflammatory parameter C-reactive protein. Lastly, they found that resistin concentrations were higher in the serum of breast-fed infants than in either breast milk or their mother's serum [3]. Resistin was associated with insulin resistance in obese mice; however homology between mouse and human resistin is only 64%. Resistin has not been associated with insulin resistance or obesity in humans, and the determination of resistin as a marker of insulin resistance in children is not recommended [52]. In the perinatal period, it seems that resistin is not directly involved in the regulation of insulin sensitivity or adipogenesis [53]. Circulating resistin levels were found to be elevated in both genetic (ob/ob and db/db) and diet-induced mouse obesity and insulin-resistance models [8]. The role of resistin in fetal and infantile growth remains to be established. However, in this context, it is known that umbilical serum resistin levels correlate positively with maternal serum resistin levels and negatively with neonatal birth weight [27]. This finding suggests that resistin could have a role in controlling fetal growth and, like the other breast milk hormones, could be involved in appetite regulation and in the metabolic development of infants.

1.4. Ghrelin. Ghrelin is a 28-amino-acid peptide produced primarily in the stomach and so called for its property of stimulating GH secretion in humans [54]. Significant ghrelin concentrations are present in human cord blood [25] and ghrelin is a component of breast milk; it comes from plasma [4] but also it is produced and secreted by the breast, considering that ghrelin levels in breast milk are higher than those found in plasma itself [24].

A portion of serum ghrelin possesses a fatty acid modification, an *n*-octanoylation, at the Ser 3 residue. This acylated form, also known as "active ghrelin," exerts the same biological effects as the hormone. Acylated ghrelin has also been reported in breast milk; its concentrations increase during lactation and are significantly related with serum ghrelin concentrations in breast-fed infants [55].

We identified a direct correlation between the circulating level of ghrelin and age, weight, and length in infants in the first months of life and a negative correlation between circulating ghrelin levels and weight gain only in infants who have been breast-fed for at least four months, but not in them who have been formula fed [56]. We also observed higher ghrelin values in formula-fed infants [57] and, more recently, a positive correlation between circulating ghrelin levels and fasting time in the first 6 months of life in infants fed exclusively with formula [58].

Ghrelin stimulates food intake in rats and humans [59] by acting primarily on the arcuate nucleus of the hypothalamus. Ghrelin also exerts adipogenic activity, and is involved in the long-term regulation of body weight [60]. Administration of ghrelin induced body weight gain and adiposity in rodents by stimulating food intake and reducing fat utilization and energy expenditure [61]. Considering that ghrelin is involved both in short-term regulation of food intake, by stimulating appetite, and in long-term

body-weight regulation, by inducing adiposity, the presence of this hormone in breast milk could be one of the factors through which breast-feeding may influence infant feeding behavior and body composition later in life.

1.5. Obestatin. Obestatin, a 23-amino-acid peptide derived from the ghrelin peptide precursor preproghrelin and produced by the human stomach, small intestine [62], and salivary glands [63], was identified in breast milk by Aydin and colleagues in 2008 [4]. They evaluated obestatin levels in serum and milk from 31 lactating women on days 2 (colostrum) and 25 (mature milk) after delivery and found higher hormone levels in milk than in blood: obestatin levels in colostrum and mature milk were more than twice the corresponding blood levels. It is not clear if obestatin comes from the blood or breast but it may drain through the mammary glands into the milk. The effect of this hormone is not well known. Some authors report that it reduces food intake, body weight gain, and gastric emptying and suppresses intestinal motility [4]. Obestatin is involved in inhibiting thirst and anxiety, improving memory, regulating sleep, inducing cell proliferation, and increasing exocrine pancreatic secretion [64, 65]. Plasma obestatin levels are increased in subjects with anorexia nervosa, in whom obestatin seemed to be a marker of acute and chronic changes in nutritional state [66]. The relationship between obestatin and infant metabolic development merits further study.

1.6. Insulin-Like Growth Factor-I. IGF-I, a 70-amino acid single chain polypeptide, is a member of a superfamily of related insulin-like hormones, and it acts as the primary mediator of growth hormone (GH) effects. The 75% of circulating IGF-I is produced by the liver, and postnatal hepatic production is regulated by pituitary GH as well as nutritional factors; it plays a role in the regulation of postnatal human growth from late infancy onward [67].

IGF-I acts through different receptors, that are the insulin receptor (IR), IGF-IR, IGF-IIR, and several atypical receptors, including the insulin receptor-related receptor and the IR-IGF-IR hybrid receptor (composed of an IR hemireceptor linked to an IGF-IR hemi-receptor) [68]. A family of six high-affinity IGF-binding proteins (IGFBP-1 through IGFBP-6) coordinate and regulate the biological activity of IGF.

IGF-I levels decrease with sustained fasting and poor nutritional status but are unaffected by recent food intake.

IGF-I plays a key role in both embryonic and postnatal growth. Evidences from literature show a correlation between IGF-I levels in cord blood and birth weight [69]; in particular, it has been demonstrated that children with intrauterine growth retardation showed lower concentrations than normal children [70].

Further, IGF-I levels in humans correlate with body size; Klagsburn was the first to show that human milk contained growth factors that stimulated the growth of cells in culture [71]. Baxter et al. demonstrated the presence of IGF-I in human milk [3]; its levels are several-fold higher in colostrum than in mature milk and they decrease in the first few days of lactation.

More recently, IGF-binding proteins (IGFBPs) have been identified in human milk of term and preterm infants [72].

Infants fed with formula milk during the first months of life showed higher IGF-I levels than BF ones [57]. A recent study showed a positive correlation between IGF-I values and Z score for weight, BMI, tricipital skin-fold thickness, and age in healthy infants in the first 5 months of life, sustaining a possible programming of IGF-I axis during infancy [73].

2. Breastfeeding and Obesity

Obesity is a relevant public health problem in both industrialized and developing countries [74], especially because of obesity-related chronic diseases. The rise in obesity has been particularly steep in children. Overweight and obesity result primarily from excess energy intake versus energy expenditure [75]. The interaction between genetic factors that determine susceptibility to weight gain and lifestyle [76] (increased consumption of energy-dense foods and reduced physical activity) is a key factor in the development of obesity. However, recent research suggests that long-term health could be determined during fetal and early postnatal life. The relationship between low birth weight, catch-up growth during the first years of life, and the later occurrence of obesity, insulin resistance, cardiovascular diseases, hyperlipidemia, and type 2 diabetes has been amply documented [77, 78]. Experimental models and epidemiological studies suggest that early nutrition is a key factor for the development of obesity later in life, thereby supporting the concept of “nutritional programming” [79]. In particular, breastfeeding could play a key role in the programming process during early life, but it is still difficult to draw definitive conclusions about the causal relationship between breastfeeding and such long-term health benefits as prevention of obesity. A case-control study by Kramer was one of the first studies to suggest that breastfeeding exerts a protective effect on later obesity [80]. Because it is not ethical to perform randomized experimental studies involving breastfeeding, the data available come from observational studies, and confounding variables remain an issue. Observational studies have confirmed an association between breastfeeding and reduced risk of subsequent obesity, as shown in recent systematic reviews [81, 82]. In particular, Harder et al. reported that prolonged breastfeeding had a beneficial effect on the risk of overweight in later life [83]. Armstrong et al. studied a large cohort study of Scottish children and found that breastfeeding was associated with a reduction in childhood obesity risk [84]. But, how does breastfeeding exert these beneficial effects? The potential benefits of breastfeeding on long-term obesity and cardiovascular disease may be due to slower growth in breast-fed infants compared to formula-fed infants [85]. The potential mechanisms by which breastfeeding protects against rapid weight gain and consequently against later obesity are the same as those that influence nutritional behavior and those related to human milk composition. From a behavioral viewpoint, because breast-fed babies can self-control the amount of milk they consume, they may learn to self-regulate their energy intake better than formula-fed infants [86], although it is not clear if this could influence

nutritional behavior later in life. Moreover, parents who choose to breast feed their babies generally have a healthier lifestyle, and this tends to influence the lifestyle (including diet and exercise) of offspring. Differences in energy and protein content between human milk and infant formula might play a role in programming obesity risk: most infant formulas have a slightly higher energy density and a higher protein content than human milk [87]. A high protein intake in infancy has been suggested to enhance the secretion of insulin and IGF-I with a consequent stimulation of cell proliferation, which promotes an accelerated growth and an increased adipose tissue [88]. Epidemiologic studies shown that high protein intake in early childhood was predictive of an early occurrence of adiposity rebound [89]. In a recent randomized clinical trial an association between a higher protein content of infant formula and higher weight in the first two years of life has been reported [90].

Regarding the issue of human milk composition compared to formula milk, breast milk contains bioactive nutrients that are not present in formula milk [91].

It is known that human milk contains numerous growth modulators, such as epidermal growth factor (EGF) [92], insulin [93], and IGFs, which can stimulate gastrointestinal mucosal proliferation and facilitate maturation and closure of the neonatal gastrointestinal tract [94]. Receptors for these growth factors have been found throughout the gastrointestinal tract and these factors are relatively resistant to proteolysis and remain stable in the gastrointestinal tract [95]. Thus, many factors acting in concert affect gut maturation, leading gastrointestinal tract to change from an organ of relatively high intestinal permeability to one of selective permeability.

The recent identification in breast milk of adipokines and other hormones involved in energy balance regulation suggests that breast milk may uniquely modulate neuroendocrine pathways involved in the regulation of body weight. For leptin [17], adiponectin [48], IGF-I [26], obestatin [28], and ghrelin [23] gastrointestinal receptors have been found, even though it is still not well defined if these hormones are resistant to proteolysis and if these receptors can mediate their absorption and action.

The presence of growth factors, enzymes, hormones, and cytokines gives to breast milk unique properties useful for the maturing neonatal gut and for the metabolic development of infants.

3. Concluding Remarks

It is likely that the next few years will see the emergence of the mechanisms by which early-life programming determines the set-point of energy balance. One mechanism by which breast-feeding may protect against the development of childhood obesity is through the activity of components of breast milk such as hormones involved in appetite and energy balance that we describe in this review. Differences in growth pattern and body composition between breast-fed and formula-fed infants might be due to a different endocrine response to feeding or to bioactive substances present in breast milk that could influence the infant's

response to energy intake and metabolism [96]. However, we are still far short of understanding the effects on children of hormones present in breast milk. Longitudinal investigations will shed light on the new hormones discovered in mother's milk and their potential protective effect on subsequent obesity and metabolic-related disorders.

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