Appetite Control Hormones in Human Milk – What is Their Role

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Demand the Best

All parents seek optimal nutrition for their children and whilst we believe most know that human milk (HM) meets all the needs of the infant (1), not everyone understands the form of delivery, that is breastfeeding on demand, is also desirable. Breastfeeding mothers meet on average seven deadlines per day in the first months of baby’s life (2) and these deadlines may happen anywhere and anytime. Modern society is still not keen on breastfeeding in public, and any mother daring to address the demand may be frowned upon, yet it is not the actions of a spoiled child we are observing, but the amazing biochemistry behind the appetite control in action.

Human Milk Appetite Hormones

Breastfed infants eat less but more frequently than formula-fed infants and are leaner as a result of lower energy intake (3). They also display a variety of feeding patterns and frequency (2) which can, in part, be explained by HM composition.

HM is a complex mixture consisting not only of nutrients but also bioactive molecules including hormones, growth factors, neuropeptides, immunomodulating and anti-inflammatory agents (4). An increasing number of appetite hormones have been recently identified in HM and a number of studies aimed to elucidate their effect on the infant. These HM appetite hormones are mainly derived from the maternal circulation, with a small contribution by the breast (5,6). As mediators between the adipose tissue, gastrointestinal tract and infant brain, the potential functions of appetite hormones include regulation of satiety, development of appetite control pathways, and modulation of infant growth and development (7). This review discusses the effect of the appetite hormones on infant gastric emptying (GE) and body composition (BC), as both have important roles in regulating appetite, food intake and energy balance.

Leptin

Leptin is a polypeptide hormone synthesised by the white adipose tissue and is the most widely studied of all appetite hormones. It is involved in the regulation of adipose tissue, food intake and body weight. Leptin causes weight loss by suppressing appetite via signalling satiety and increasing metabolic rate. Leptin in HM is derived mainly from maternal serum, following secretion from white adipocytes and gastric chief cells into the bloodstream, with a small contribution from the mammary gland epithelium (5,8).

In infants, HM is believed to be a major source of leptin early in life, due to immature endogenous leptin-synthesising mechanisms (9). Indeed, breastfed infants exhibit higher serum leptin levels compared to formula-fed infants, which is likely due to leptin being rendered inactive during the processing of bovine milk for formula (10). Leptin in HM has been hypothesised to be involved both in the short-term control of appetite and in developmental programming of appetite and energy signalling pathways, promoting efficient energy control and storage throughout life (8,11). In support of this, leptin administered during the first 14 days of life acts as a neurotrophic agent, promoting neural growth from the arcuate nucleus of the hypothalamus to multiple appetite control centres located in the central nervous system (12). However the influence of leptin on GE, a key regulator of appetite, has not been well studied. Animal models show that central administration of leptin delays GE (13) and reduces food intake (14). In contrast, we have measured infants’ stomachs (Fig. 1) sequentially to assess the effect of an array of HM components on GE for a single breastfeed and we found that HM leptin does not appear to impact GE in term infants (15,16), nor has it been linked to either the frequency of feeding or time between the feeds (15-17). This suggests the action of HM leptin on short-term appetite control may be mediated by upregulation of circulating melanocortins, potent anorexigenic agents that promote satiety (18). Thus actions other than regulation of GE or downstream effects of HM leptin not yet measured are likely responsible for the beneficial effects of HM in protecting against obesity later in life.

Fig. 1. Ultrasound technique for measuring infant’s stomach. The longitudinal and transverse planes for measurement of stomach volume are indicated.

With respect to regulation of BC, higher HM leptin levels are associated with lower infant weight gain in the first six months, lower infant BMI at two years of age (18),...
lower infant weight and adiposity (18,19) and greater lean body mass (total body water) in breastfed infants (20,21), suggesting a pivotal role for leptin in regulating infant growth and BC. Research in our laboratory confirms these results and also shows that both higher HM leptin concentration and 24-hour intake of leptin are associated with lower infant weight, lean body mass and fat mass (measured with bioimpedance spectroscopy, Fig. 2) during first 12 months of lactation (Gridneva and Geddes, unpublished data). Given that many of the benefits of breastfeeding are associated with the growth rate of the infant, these findings suggest that HM is indeed bioactive. Further studies should incorporate exploration of the regulation of leptin levels in HM, which have been shown to be influenced by maternal adiposity, but also display a circadian rhythm (17).

**Adiponectin**

Adiponectin is the appetite hormone present in the highest concentrations in HM and its concentration is more than 40 times higher than that of ghrelin and leptin (22,23). Adiponectin is secreted by adipose tissue and also synthesised by the breast (5). Adiponectin circulates as oligomers of different sizes, from low-molecular-weight trimers to high-molecular-weight octodecamers, the latter being the most common in HM (24), in contrast to the middle-molecular-weight form of bovine adiponectin (25). It is present in a biologically active form and is resistant to digestion (26). Interestingly, HM adiponectin levels are only moderately related to both maternal circulating levels and adiposity, indicating adiponectin is regulated within the mammary gland (27). Amongst its various functions, it has anti-inflammatory properties, breaks down fatty acids and heightens sensitivity to insulin. Strong correlations between adiponectin levels in HM and infant serum (26) along with the presence of adiponectin receptors in the infant’s intestinal tract (26) emphasise its importance for the infant. Indeed, higher levels of circulating plasma adiponectin are related to lower BMI and healthier metabolism.

In animal models, adiponectin inhibits tension sensitive gastric vagal afferent mechanosensitivity, modulating satiety signals in both lean and obese animals, while simultaneously increasing the mechanosensitivity of mucosal gastric vagal afferent in an obesity-induced model (28). In humans, elevated serum levels of adiponectin are associated with more rapid GE in diabetic patients (29). We are the first to have studied HM adiponectin in fully breastfed term infants and have found that increased levels and doses are associated with longer time between feeds in this population (16). This indicates adiponectin’s potential action on the gastric vagal nerve via decreased sensitivity of tension receptors, potentially resulting in delayed satiety signalling, leading to higher food intake.

The modulating effects of GE in infants and potentially on appetite and nutrient intake may partially explain the growth-regulating effect of adiponectin in infants in earlier months of life, as we and other researchers have shown (30). The relationship between changes in HM adiponectin and body composition and growth over the first two years of life has been studied. High levels of adiponectin are associated with lower weight, lean body mass and adiposity (30) (Gridneva and Geddes, unpublished data) in the first months of life, whereas in the second year of life, infants display more rapid growth and accretion of lean body mass and in a sense, ‘catch up’ to infants that received lower levels of adiponectin (31). Slower growth appears to be in part regulated by HM adiponectin and thus constitutes a potential mechanism for the lower risk of obesity in later life.

**Ghrelin**

Ghrelin is a less studied orexigenic peptide produced primarily in the stomach, but also in the lactating breast, resulting in HM having a higher ghrelin concentration than maternal serum (32). Ghrelin is an antagonist to leptin and stimulates appetite, gastric motility, acid secretion and food intake and is involved in long-term regulation of growth, weight and energy metabolism; thus heightened concentrations in HM could be vital for the infant drive to feed.

Ghrelin stimulates appetite and food intake and increases GE in rats (33) and humans (34) via the vagal nerve and afferent activity. High infant serum ghrelin levels are associated with increased age, length and weight in both formula-fed and breastfed infants (35,36), with formula-fed infants having higher ghrelin levels than breastfed infants (due to higher levels in formula) (10,35). Further, longer fasting times are associated with higher serum levels of ghrelin in formula-fed infants in the first six months of life (37). The inverse correlation between ghrelin and leptin in infant serum (10) indicates that HM leptin may play a role in lowering ghrelin levels. Since ghrelin and leptin actions are mediated by neuropeptide Y (NPY), reduced leptin levels allow ghrelin NPY stimulation and increase in food intake (10). Indeed, more comprehensive studies are required to clarify potential interactions between these appetite hormones.

HM ghrelin levels increase progressively in first months of lactation (38) and therefore, may influence infant feeding patterns and BC. Higher serum ghrelin levels in breastfed infants are associated with lower weight gain (36) and in formula-fed infants, with lower BMI (10), indicating a role for ghrelin in the regulation of body weight in healthy
infants. Higher ghrelin levels in HM are associated with higher infant weight gain (39,40) but lower weight (39). These somewhat contradictory results may be due to the combined effects of other HM hormones that were not measured in previous studies. Also it is not clear if ghrelin levels precede changes in appetite (37) and body weight (36,41) or follow them.

Ghrelin influences novelty seeking behaviour in rodents and humans (42), which may translate into an advantage in terms of locating new sources of food. Levels of ghrelin are blamed for impulsive shopping behaviour, as images of food become more desirable (43). These behaviour modulations mean that raised ghrelin levels in the infant will translate into hunger cues to gain the attention of the mother.

Other Key Appetite Hormones

Insulin is a major hormone involved in glucose metabolism and is produced by the pancreas. Studies in rats show that dietary insulin is not degraded in the stomach and plays an important role in the maturation and development of the small intestine (44); thus HM insulin could play a similar role in the development of human intestinal epithelium. Insulin is actively transported into HM in concentrations similar to maternal circulating levels (45) and is significantly higher (almost four times) than in bovine milk and infant formula, where it is barely detectable (46). While one study showed no differences in serum insulin concentration, fasting time and anthropometrics of breastfed and formula-fed infants (47), another study found that higher levels of milk insulin were related to lower weight and fat-free mass but not the fat mass in one month-old breastfed infants (19), reflecting insulin’s role as a regulator of energy balance, food intake and adiposity. Recently HM insulin has been associated with microbial diversity in the infant gut, with both insulin and leptin associated with beneficial microbial metabolic pathways that are able to reduce inflammation (48), further highlighting the diverse effects of these hormones.

Obestatin is an appetite-suppressing derivative of the ghrelin peptide precursor, which further emphasises the complexity of the appetite hormone system. Obestatin is produced by the cells lining the stomach and small intestine and salivary glands (49). Early studies reported that obestatin opposes ghrelin’s effects on body weight, food intake and GE (50). However, obestatin was later implicated in the inhibition of thirst and anxiety, regulation of sleep, memory improvement, induction of cell proliferation and increasing the secretion of the pancreatic juice enzymes (49). HM obestatin has been identified (51) with a concentration more than twice that of corresponding circulating maternal levels. Surprisingly however, the source of obestatin has still not been established. The relationship between obestatin and infant development and BC clearly requires further investigation.

A myriad of hormones have already been identified in HM and there are likely still many more to be discovered. Hormones such as apelin, resistin, insulin-like growth factor-I and motilin also play significant roles in the metabolic development of infants and could be of interest in further research.

Conclusion

HM appetite hormones influence GE and BC in breastfed infants and are associated with early infant growth and development and subsequently health later in life. So the next time you see an infant being breastfed, think of all the delicate, complex mechanisms and pathways signalling to ensure programming of appetite regulation, leading to a reduced risk of obesity and chronic disease in our next generation.

References

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