

Editorial

Ghrelin, Energy Balance, and Weight in Infants: The Chicken or the Egg?

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Ghrelin, a novel peptide consisting of 28 amino acids was first characterized in 1999 (1), is produced predominantly in the stomach, and is now also known to be present in the hypothalamus, the anterior pituitary gland, testis and ovarian tissue and in a variety of tumors (2-4). Ghrelin has been shown to stimulate appetite, gastric motility and acidity in adults and via these mechanisms may also act to regulate energy balance. The effects of ghrelin on appetite appear to be due to its modulation of hypothalamic neuropeptide Y (5). However, ghrelin also likely plays a major role in the modulation of somatic growth via the secretion of pituitary growth hormone (GH).

It is now well understood that ghrelin functions in this latter respect by attaching to the growth hormone secretagogue receptor (GHS-R) (1,6), thereby stimulating GH secretion. Further studies (7) have now also shown that in addition to acting upon secretion of stored hormone, ghrelin also stimulates GH gene expression directly, also via the GHS-R. The literature on the effects and biochemistry of ghrelin has grown steadily since its discovery and, to date, a literature search using PubMed (8) produced a total of 1,315 references in which the term "ghrelin" appeared. Because of the link between ghrelin

and growth modulating factors, such as GH, Insulin-Like Growth Factor-I (IGF-I) and leptin, a number of investigators have concentrated on the potential for ghrelin to serve as a modulator during the period of rapid growth associated with early infancy (9-12).

In this issue of the *Journal of Pediatric Gastroenterology and Nutrition*, Savino et al. (13) have presented data from their work in a cross sectional study at the University of Turin, Italy, that when data from the study population were pooled, serum concentrations of ghrelin from babies in their first year of life rise with advancing age, with no gender differences noted. Thus, in this cross sectional study, the larger the infant at the time of sampling, the higher the ghrelin concentration. It is not clear whether this finding is based predominantly on the effects of advancing age in general on ghrelin concentration, as this correlation has been documented previously by others (11,12), or whether maturation of the ghrelin-GH axis is an additional independent variable.

In term babies, birth weight seems generally not to correlate with ghrelin concentration unless there has been significant growth restriction in utero, in which case cord blood levels have been found to be markedly above those of babies normally grown (9,14). By one year of age, however, these differences are no longer apparent, (15) perhaps due to catch up growth.

However, Savino, et al have also shown that although ghrelin concentrations can be directly correlated with postnatal weight and length at time of collection in both breast fed (BF) and formula fed (FF) babies, weight gain from birth correlates negatively with serum ghrelin levels in the BF group but not at all in the FF group. This constitutes an extension of a previous study from birth through 4 months of age, in which these authors (16) also found that FF babies had higher serum ghrelin levels during this period, but that these differences did not persist. The negative correlation between total weight gain in the first year of life and ghrelin level in only the BF group is intriguing, particularly since ghrelin is thought

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to modulate somatic growth by increasing appetite, thereby increasing caloric intake. In animal and human experiments, endogenous ghrelin levels are elevated in fasting and fall with refeeding (2,6) in adults but data regarding any cause and effect relationship between ghrelin levels and weight gain in infancy and childhood is very limited (12,15,17).

How does one interpret these disparate findings? It is generally accepted that GH plays only a small role in modulation of growth in the fetus, predominantly because of the relative paucity of GH receptors (18). Therefore, plasma ghrelin concentrations in the fetus may not have any predictive value re perinatal growth rate, despite the role that ghrelin might play in gastric or other organ physiology.

Do postnatal changes in ghrelin levels precede changes in appetite or follow them? Do the postnatal data presented in the studies by Savino, et al. and others suggest that breast fed babies are either underfed or overfed relative to their bottle fed cohorts?? The data are difficult to interpret in part because of the large variation in ghrelin concentration in infants with similar weight gain. Statistically speaking, breast fed infants do exhibit a lower growth velocity in the first year (19) than bottle fed cohorts, although this was not apparent in the present study. The data do suggest that examination of circulating blood ghrelin concentrations may offer an insight into the fine-tuning of the coordination between dietary intake (both quality and quantity), energy balance, and growth factor modulation of somatic growth in the first years of life.

There are also some technical problems yet to be overcome in interpretation of data regarding ghrelin measurements. For example, in various published studies, ghrelin levels in the cord blood of healthy babies have been reported by various investigators, using different, or in some cases, the same assays, as being between 0.3 and 3.2 ng/ml, a difference of 10-fold (11,20). Thus, an assay that uses standard methodology and accepted ghrelin standards seems in order. In addition, it has recently been shown that to be activated, the ghrelin peptide must be esterified with octanoic acid (from dietary sources) on its third serine (21–23). The deacylated form is much more abundant but inactive. The majority of the assays currently used to estimate circulating levels of ghrelin measure only *total* ghrelin peptide and, thus, viewed in this light, our ability to interpret the above findings is limited.

In summary, further studies examining ghrelin measurements in blood may allow for a better insight into the variety of mechanisms—neural and otherwise—that control growth via modulation of appetite and energy balance in infancy. The recent studies presented in this issue of *JPGN* confirm the observations of a general rising of serum ghrelin levels in the first year of life and suggest that one mechanism for the previously observed finding of less weight gain in BF infants at one year may be the change in ghrelin level. However, technical difficulties in interpretation of past data using current assay techniques, requires caution. Lastly, the question of

whether ghrelin synthesis and systemic and local action are reflected by peripheral blood concentrations in the neonate and infant remains open to debate and further research.

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