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Milk Intake and Feeding Behavior in the First Week of Life and Its Relationship to Cord Blood Ghrelin, Leptin, and Insulin Concentrations

RACHEL J. A. JAMES, ANDREW JAMES, ROBERT F. DREWETT, AND TIM D. CHEETHAM

Department of Psychology [R.J.A.J., R.F.D.], University of Durham, Durham, DH1 3LE, UK; Department of Endocrinology [A.J.], Sir James Spence Institute [T.D.C.], The School of Clinical Medical Sciences (Child Health), Newcastle University, Newcastle-upon-Tyne NE1 4LP, UK

ABSTRACT: Our aim was to study the feeding behavior of healthy term infants in the first week of life and determine whether this was related to cord blood leptin, ghrelin, and insulin. A total of 100 healthy bottle-fed infants were studied by weighing bottles of milk before and after feeds. Leptin, total ghrelin, and insulin concentrations were measured in cord blood. Mean (SD) birth weight was 3.46 (0.43) kg. Mean milk intake increased from 196.7 (83.0) g on d 1 to 585.0 (128.4) g on d 7. Milk intake over the first 6 d was significantly associated with weight gain to d 7. There was no relationship between cord ghrelin or leptin and milk intake or feed frequency. Cord blood insulin was inversely related to the mean daily number of feeds over the first 6 d ($r = -0.21$, $p < 0.05$). Birth weight and milk intake are the major determinants of weight gain in the first week of life in healthy bottle-fed infants. Total cord ghrelin and leptin are not directly related to milk intake or feed frequency in the first week of life. Circulating insulin concentrations may have a role in the initiation of feeding behavior. **(*Pediatr Res* 62: 695–699, 2007)**

Locally produced, circulating and central nervous system (CNS) hormones and neurotransmitters regulate appetite in adults.

Ghrelin is a 28-amino-acid peptide secreted primarily by the stomach (1) and by other tissues including the pancreas in fetal life. Ghrelin is the first natural ligand for the growth hormone secretagogue receptor (GHS-R). In addition to stimulating growth hormone (GH) release, ghrelin has a potent orexigenic effect (2,3) and is involved in feeding initiation and termination. At least some of these actions appear to be mediated *via* the vagus nerve (4). Ghrelin secretion is pulsatile, with increased secretion during fasting and lower levels after food intake (5,6).

Leptin is expressed and secreted by adipocytes in white adipose tissue. Leptin circulates in plasma at concentrations that are proportional to fat mass and provides the CNS with feedback regarding overall nutritional status. Leptin deficient patients are hyperphagic and develop morbid obesity, while leptin has anorectic effects in humans (7). The relationship between obesity and insulin resistance is widely recognized (8), and humoral signals from compounds like ghrelin, leptin, and insulin act on a hypothalamic neuronal network involved in the central regulation of appetite. One network of neurons is associated with appetite inhibition (including pro-opiomelanocortin or POMC) and one with appetite stimulation (neuropeptide-Y or NPY) (9,10).

Whether the hormonal regulators of feeding behavior in adults function in a similar manner in infancy is less well known, although there is evidence to suggest that this is the case. The fact that infants will consume more of a low-energy than a high-energy feed (11,12) suggests that a homeostatic mechanism regulates feeding behavior. Growth in infancy is related to nutritional intake and therefore potentially to the circulating levels of compounds like ghrelin, insulin, and leptin. Ghrelin secretion has been found to be relatively refractory to the effects of feeding in the neonatal period, and the authors have suggested that increased levels in the first days of life may act as an "anabolic drive" to promote food intake (13). The fall in insulin and leptin levels may have a similar effect (14). A negative relationship between ghrelin levels in the first hours of life and birth weight has been described in term infants in some (15) but not all studies (16), and a negative relationship between cord blood ghrelin and ponderal index in term infants has also been reported (17). Recently ghrelin levels were found to be related to nutritional status on the second day of life in preterm infants, although they were receiving oral and intravenous feeding and hence were not regulating their energy intake (18). The fact that low cord ghrelin concentrations are associated with slow weight gain in the first 3 mo of life (19) and cord leptin levels to weight gain at 2 y of age in small-for-gestational age (SGA) children (20) may indicate that these hormones regulate feeding behavior in early life. The negative relationship described between total ghrelin levels and weight gain during the first year of life may also indicate that ghrelin reflects rather than promotes changes in weight beyond the neonatal period (21).

Although linear growth in infancy is maintained during the first week of life (22), weight often decreases (23). In breast-

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Correspondence: Tim D. Cheetham, M.D., Sir James Spence Institute, The School of Clinical Medical Sciences, Newcastle University, Royal Victoria Infirmary, Queen Victoria Road, Newcastle-upon-Tyne NE1 4LP, UK. E-mail: tim.cheetham@nuth.nhs.uk

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Abbreviations: CNS, central nervous system; **GH,** growth hormone; **GHS-R,** growth hormone secretagogue receptor;; **POMC,** pro-opiomelanocortin; **SGA,** small for gestational age

fed infants, more frequent feeding is associated with higher milk intake and reduced weight loss (24). Therefore, there is good reason to believe that poor weight gain in the first week postpartum may be related to nutritional intake, as it is later in infancy.

We have therefore studied milk intake and feeding behavior in the first week of life using milk of known composition and have examined its relationship to (a) cord blood leptin, ghrelin, and insulin concentrations and (b) change in weight over the same period.

METHODS

Subjects. The local ethical committee approved this study, and parents of each infant provided written informed consent. Women with singleton term pregnancies (between 37 and 42 wk of gestation) were recruited on the delivery suite at the Royal Victoria Infirmary, Newcastle-upon-Tyne. They were approached if they had no known medical conditions and if they intended to feed their infant with formula milk. We used formula feeding as the availability of formula milk to the infant does not depend on the mother's lactogenesis, and its nutritional composition does not vary. Women were not recruited if they had diabetes mellitus (gestational or insulin dependent), hypertension (familial, essential or pregnancy induced), or any other serious medical condition requiring drug treatment before or during pregnancy.

One hundred infants (50 males and 50 females) with no known physical, metabolic, or congenital abnormalities and with an Apgar score of 8 or above at 5 min and a birth weight of 2500 g or more were recruited. Infants with a birth weight less than 2500 g were excluded as their spontaneous feeding behavior was overruled by a strict feeding regimen that included regular waking and nasogastric feeding if they did not consume a set amount of milk. The mothers were between 17 and 43 y of age; 55% smoked during the pregnancy. Their mean height (±1 SD) was 161.9 (6.3) cm (range, 149.5–179.4 cm). Forty-four percent were primiparous and 56% were multiparous.

Auxology. The infants were weighed on electronic weighing scales (Seca, Model 727). The scales used on the delivery suite in the hospital were set to 5-g resolution and were accurate to 0.05% from 0 to 10 kg. They were calibrated at 1-kg intervals from 1 to 5 kg using M3 calibration weights on four separate occasions during the study. The length of the infant was measured in centimeters (accurate to 0.1 cm) using a Kiddimetre (Raven Equipment Limited, Essex, UK). The head circumference of the infant was measured in cm (accurate to 0.1 cm) using a pediatric tape measure (Perspectives Enterprises). Placental weight was measured by the midwife to the nearest 10 g on the Salter balance on the delivery suite.

Cord blood sampling. The sample of cord blood was taken following delivery of the baby and before delivery of the placenta. The cord was double clamped with forceps and cut. Ten milliliters of cord blood was taken by either the attending midwife or the researcher from the clamped portion of the cord at the placental end and placed in the prepared blood bottles.

Feed preparation and milk intake. The infants were fed using numbered 100-mL bottles of ready-made formula milk for the first 7 d of life. The bottles of milk were weighed on a portable Ohaus strain gauge electronic balance (Model CT1200-S, accurate to 0.1 g). Mothers had a choice of two milk preparations (SMA Gold and Cow & Gate Premium) provided in ready-to-feed weighed and labeled bottles. The two types of feed had an identical energy content and a similar carbohydrate, fat, and protein content. SMA gold contains 280 kJ (67 kcal), 1.5 g protein, 7.2 g carbohydrate, 3.6 g fat, and 16 mg sodium per 100-mL bottle, while Cow & Gate Premium contains 280 kJ (67 kcal), 1.4 g protein, 7.5 g carbohydrate, 3.5 g fat, and 19 mg sodium per 100-mL bottle. The weights were recorded on a data collection sheet. In the delivery suite, the researcher explained the procedure that the mother needed to follow for the subsequent 7 d. Although no specific instructions were given to the mothers about how much to feed their infants, the midwives suggested that they give the infants as much as they demanded. The mothers were asked to feed the infants with the milk, starting with the bottle labeled number 1 for the first feed and following the numbers in order until d 7. On completion of the feed, the mother was asked to record on the feed chart provided the number and time of the feed, the amount taken, and whether the baby was sick or if any of the milk was accidentally spilled. She was then asked to replace the lid on the bottle with the remainder of the milk that was left in it and place it in the container provided. A feed was defined as milk consumed at one sitting. If mothers undertook tasks other than nursing the infant between episodes of milk consumption, then this was defined as two feeds rather than one. A date and time was arranged for the 7-d visit and documented on the instruction sheet for the mother. The time of the 7-d visit was scheduled as near to the time of birth as possible (usually within 2 h). The contact telephone number of the researcher was provided in case further advice was required in the interim. On d 7, all the bottles that had been used were reweighed and the difference between the prefeed and postfeed weight of the bottles was used to calculate the milk consumed.

Biochemical assays. The leptin assays were carried out using a commercial leptin RIA (Linco, St. Charles, MO). Intra- and interassay coefficients were 8.3% and 6.2% at 4.9 ng/mL and 3.9% and 4.7% at 10.4 ng/mL, respectively. Insulin assays were performed using the DAKO insulin assay (DAKO, Glostrup, Denmark). This assay is an enzyme-linked immunosorbent assay based on two monoclonal antibodies that measures biologically active insulin with a high degree of specificity. The limit of sensitivity was 0.5 μIU/mL; the intra-assay coefficient was $<5\%$ and the interassay coefficient was $<5.3\%$. Total plasma immunoreactive ghrelin levels were measured with a commercial radioimmunoassay kit (Phoenix Pharmaceuticals, Belmont, CA) at the Diagnostic Systems Laboratories, UK Ltd. The limit of sensitivity was 0.14 ng/mL, intra-assay coefficient was 3.4% at 1.14 ng/mL, and the interassay coefficient was $<14\%$. The assays were all carried out at the end of the study, and so all other measurements were recorded blind to hormone data.

Data analysis. Missing data due to a bottle being discarded by accident on two occasions were dealt with by interpolating from adjacent days in the same infant. A small number of mothers did not complete the study. Complete data were available for 100 infants to d 3, 99 to d 5, 97 to d 6, and 89 to d 7. The data were initially summarized by calculating a total milk intake for each day for each infant with each 24-h period commencing at the time that the infant was born and compared using analysis of variance (ANOVA). Means of these totals over the first 6 d were also used. Pearson correlations were used to relate continuous variables to one another, with multiple regression used to analyze more complex relationships. Comparisons between the sexes used independent-sample *t* tests or *U* tests as appropriate. Birth weight data were compared with UK National Growth Standards (25).

RESULTS

Birth data. The infants in the study had a gestational age from 37 wk 4 d to 42 wk 1 d. They were born following a first stage of labor that lasted a median of 455 min (interquartile range, 295 min) and a second stage that lasted a median of 48 min (interquartile range, 97 min). The mean birth weight was 3.458 kg with an SD of 0.43 and ranged from 2.51 to 4.61 kg. The mean birth weight SD score was 0.05, which is not significantly different from the median of the UK National Growth Standards. The mean birth length was 49.8 cm (SD = 1.8) and ranged from 45.0 cm to 54.0 cm.

Milk intake and infant feeding behavior. Infant milk intake is illustrated in Figure 1. In an analysis using repeated-measures ANOVA, restricted to infants with data on all 7 d

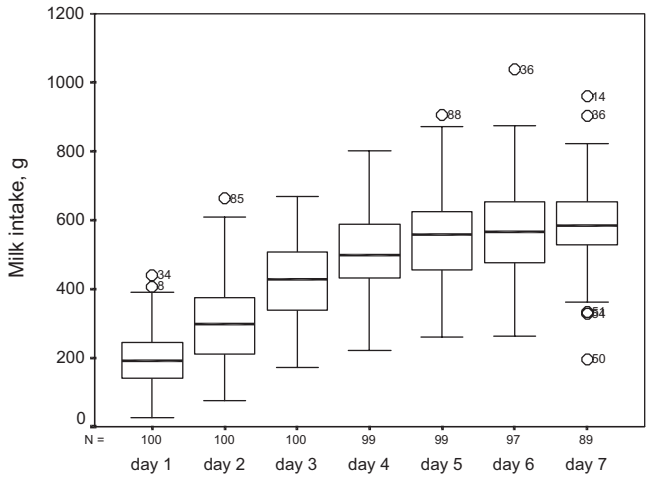

Figure 1. Daily total milk intake (g/24 h) over the first 7 d of life. The box plots show the median and quartiles with outliers.

Table 1. *Descriptive statistics of number of feeds per day from d 1 to d 7*

Day	No.	Minimum	Maximum	Mean	SD
1	100	3	12	6.7	1.7
2	100	3	12	7.3	1.8
3	100	4	14	7.8	1.7
4	99	5	17	8.0	1.8
5	99	5	15	7.7	1.7
6	97	5	14	7.7	1.7
7	89	5	12	7.6	1.4

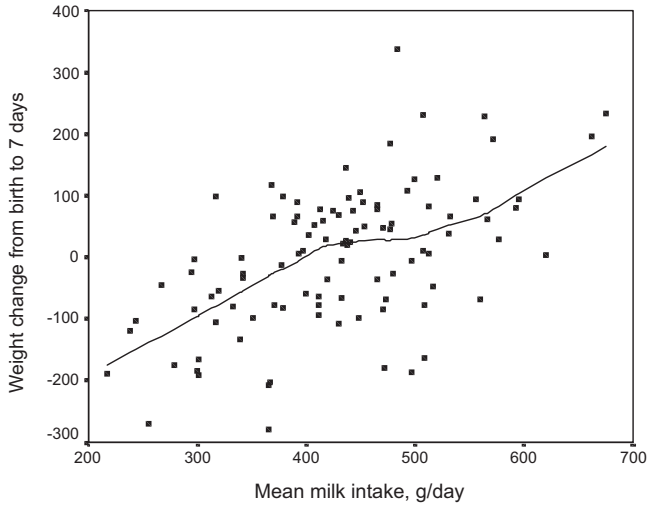

Figure 2. Scatter plot showing the relationship between mean milk intake (g/d) and change in weight (g) from birth to 7 d. The weight changes measure is the residual from the regression of 7-d weight on birth weight and so is adjusted for birth weight. The line is a nonparametric (lowess) regression line.

($n = 89$), milk intake rose significantly from d 1 to d 7 ($F_{6,83} = 168.8$, $p < 0.001$). Both the linear and quadratic trends, but no higher order trend, were statistically significant. The number of feeds varied from three to 12 per day (Table 1). Again, there was a highly significant trend over time ($F_{6,83} = 6.153$, $p < 0.001$) with significant linear and quadratic components. The number of feeds rose over the first 3 d, remaining the same thereafter. There was a significant relationship between the number of feeds recorded and total milk intake for each separate 24-h period from birth to 7 d of age. There was no difference in milk intake between the male and female infants from d 1 to d 7 ($F_{1,98} = 1.97$; $p = 0.164$, not significant). There was no relationship between length of labor, analgesia, anesthesia, or Apgar score and milk intake in the first 24 h or the first 7 d. By 7 d of age, 38% of infants had lost weight (when compared with birth weight), 5% had a weight that was the same as birth weight, and 57% had gained weight.

The milk data for d 7 were excluded from subsequent analyses because of the missing data for this day in 11 infants (Table 1). Mean total daily intakes were based on data from the first 6 d.

Birth weight was significantly associated with mean daily milk consumption over the first 6 d ($r = 0.35$. $p < 0.0001$). In a multiple regression, weight on d 7 was significantly associated with birth weight ($t = 38.35$, $p < 0.001$) and with mean milk intake over the first 6 d ($t = 5.99$, $p < 0.001$). Figure 2 shows the relationship between mean milk intake and the change in weight.

Birth variables, milk intake, feeding frequency, and cord hormone levels. Mean (SD) cord blood leptin concentrations were 10.1 ng/mL (6.7) (range, 1.6–36.7 ng/mL); mean total ghrelin concentrations were 760.9 pg/mL (282.8) (range, 210.0–1670.0 pg/mL); mean cord blood insulin concentrations were 4.5 mU/L (3.0) (range, 0.9–15.8 pmol/L).

Table 2 shows that cord blood leptin was significantly related to birth weight and birth length and to placental weight. Female infants had higher leptin levels than male infants (the means were 12.2 with SD = 7.2 and 8.0 with SD = 5.4, respectively). By the Mann-Whitney U test, $Z = 3.4$ ($p < 0.01$). Cord blood total ghrelin levels were not significantly related to any of the growth measurements made at birth. There was no relationship between cord blood leptin, ghrelin, and maternal smoking status.

Relationships with feeding variables are shown in Table 3. There was no relationship between cord blood leptin and ghrelin and any of the feeding variables, but cord blood insulin was inversely related to the mean number of feeds during the first 6 d of life, *i.e.* the infants with lower insulin levels at birth took more feeds over that time period.

DISCUSSION

Milk intake is the sole provider of both water and food to the infant. Healthy infants gain weight at different rates, suggesting that there are inherent differences in hunger. Milk intake will be affected by the complex interaction between mother and child, but the discovery of gastrointestinal and CNS hormones involved in the regulation of feeding behavior and energy homeostasis in adults has provided a mechanism to explain differences in feeding behavior and hence growth earlier in life. A relationship between leptin and ghrelin in cord blood and subsequent growth parameters has been described, and we wanted to establish whether feeding behavior in the first week of life was related to levels of these hormones in cord blood.

Table 2. *Relationships between cord blood leptin, ghrelin, and insulin levels and infant and placental size at birth*

	Leptin		Ghrelin		Insulin	
	r	*p*	*r*	*p*	*r*	*p*
Birth weight	0.45	0.000	−0.13	0.20	0.33	0.001
Birth length	0.21	0.04	−0.04	0.71	0.08	0.42
Placental weight	0.32	0.001	−0.09	0.34	0.15	0.12
Ponderal index	0.36	0.000	−0.19	0.06	0.34	0.001

Table 3. *Relationship between cord blood leptin, ghrelin, insulin levels, and milk intake during the first 6 d of life*

	Leptin		Ghrelin		Insulin	
Feeding variable	*r*	*p*	*r*	*p*	*r*	*p*
Milk intake (d 1)	−0.06	0.56	−0.06	0.54	0.07	0.487
Mean milk intake (d 1–6)	0.06	0.55	−0.02	0.87	0.11	0.250
Mean no. of feeds (d 1–6)	−0.05	0.66	0.09	0.39	−0.21	0.038

Our data on infant feeding in the first week of life were collected from term infants of normal birth weight. Cord hormone levels were correlated with milk intake and feed frequency. We elected to study bottle-fed infants because of the practical difficulties associated with determining milk intake and milk energy content in breast-fed babies (26,27), and this is one of the most detailed studies of infant feeding in bottle-fed infants in the first week of life conducted to date.

We found that birth weight and milk intake during the first 6 d of life were each significantly associated with weight at 7 d of age. We did not, however, find a relationship between milk intake and feeding behavior in the first week of life and cord blood total ghrelin and leptin concentrations. The extent to which the placenta contributes to cord venous blood ghrelin levels is unclear, with similar values documented in the umbilical vein and artery in some studies (28) but not others (29). However, it is of note that cord values are closely related to levels in the first week of life (13). In contrast to some earlier studies, we did not identify a relationship between ghrelin and birth weight, although we were careful to exclude potential confounders that appear to affect ghrelin such as being born SGA or preterm (16,30).

There are a number of potential explanations for the fact that total cord ghrelin was not directly related to feeding behavior. Serum osmolality and thirst may have a more significant role in determining feeding behavior at this stage of life. However, the immature kidney generates relatively dilute urine, and there is no direct evidence that osmotic thirst affects milk intake in the early days of life, and some direct evidence that it does not (31). Studies in rodents have suggested that there may be relative immaturity of the CNS connections in early life (32) with development of a fasting-associated increase in ghrelin at the end of the first postnatal week (33). Circulating ghrelin and leptin may therefore become more important regulators of infant feeding beyond 7 d of age. Feeding does not appear to have the same inhibitory effect on ghrelin levels in the first days of life in humans either, although this does not necessarily preclude a role in the regulation of feeding behavior (13). Recent studies in rodents have also indicated that the impact of ghrelin on body composition may be more complex than the impact on food intake alone; food intake is not different in ghrelin knockout animals and wild-type controls, but the ghrelin knockout animal is resistant to diet-induced obesity and consumes less food and preferentially uses fat as an energy substrate (34,35).

A potential criticism of our study is that the ghrelin assay measured total (acylated and deacylated) ghrelin rather than the bioactive nonacylated portion alone that amounts to less than 20% of total values. Although the concentrations of total ghrelin reflect those of the acylated fraction in cord blood (36), further studies may also need to take into account the extent to which the different forms of ghrelin are bound to larger molecules (37,38).

Unlike ghrelin and leptin, insulin concentrations fluctuate according to whether an infant is fed or fasted, and we identified an inverse relationship between feed frequency and cord insulin levels. Insulin receptors reside in neural tissues involved in energy regulation and intracerebroventricular administration of insulin to rodents reduces food intake, while the administration of insulin antibodies into the CNS has the opposite effect (39,40). Insulin levels will be reduced in the fasting state and, as in cord blood, will tend to be lower in lighter infants. Low or falling insulin levels or intrinsic insulin "tone" may therefore be an important stimulus to feed in infancy.

In summary, milk intake is a major determinant of weight gain in the first week of life in healthy bottle-fed infants. Cord ghrelin and leptin levels are not directly related to feed volume or feed frequency, but a relationship between insulin in cord blood and feed frequency suggests that insulin concentrations may be involved in the regulation of neonatal feeding behavior.

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