Relationship between Concentration of Serum Leptin and Fetal Growth

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ABSTRACT

The serum leptin concentration reflects the amount of adipose tissue in the body. Although fat deposition in the fetus in the third trimester markedly increases, the role of leptin during pregnancy has not been clarified. In the present study, whether or not the serum leptin concentration correlates with growth in utero was investigated, in addition to how leptin levels change in the first few days after birth.

One hundred sixteen Japanese infants were divided into term (n = 95) and preterm groups (n = 26). Term infants were divided into 3 subgroups: birth weight appropriate for gestational age (AGA) (n = 44), birth weight large for gestational age (LGA) (n = 26), and birth weight small for gestational age (SGA) (n = 20). Longitudinal changes in the concentration of serum leptin after birth were examined in all infants. The serum leptin concentration was determined by RIA.

No significant difference in leptin levels between cord sera and infants' sera obtained within the first 6 h of life (n = 26) was observed. Within the first 6 h of life, the concentration of serum leptin in LGA infants (15.8 ± 19.2 ng/mL) and SGA infants (11.6 ± 1.1 ng/mL) was significantly higher and lower, respectively, than that in the AGA infants (4.4 ± 3.6 ng/mL) (P < 0.01). A significant positive correlation was found between the leptin concentration within 6 h of life and birth body weight (r = 0.59, P < 0.01). After birth, the concentration of leptin in LGA and AGA infants significantly decreased to the level in SGA infants within 48 h of delivery (P < 0.05). After 48 h of life, no significant differences in the concentration of leptin were observed among the three groups, and low levels continued to 7 days of age.

These findings indicate that serum level of leptin correlates with fetal body weight gain. (Clin Endocrinol Metab 88: 3281–3284, 1997.

LEPTIN IS 16 kDa protein encoded by the ob gene and produced by adipocytes (1, 2). The concentration of serum leptin is high in obese adults and low in lean adults (3, 4). These reports have also demonstrated a strong positive correlation between the serum leptin concentration and amount of body fat. Leptin signals the amount of fat stored in the body to the brain and affects food intake, energy expenditure, and thermogenesis to maintain a constant amount of stored body fat (5, 6). However, the physiological role of leptin in growing children has not been clarified. Two reports have demonstrated that leptin levels correlate highly with body mass index in obese children and rise just before the onset of puberty (7, 8).

Fat deposition in the fetus in the third trimester increases markedly (9). The mechanism of adiposity and physiological roles of leptin in the fetus have yet to be elucidated. In the present study, whether or not the concentration of serum leptin correlates with growth in utero was investigated, in addition to how leptin levels change in the first few days after birth.

Subjects and Methods

One hundred sixteen Japanese infants were examined. All subjects were born in our hospital between March and December 1996, and the study was limited to infants for whom informed consent could be obtained. Neonates with dysmorphic features, major congenital malforma-


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Statistical analysis

All data are expressed as mean ± SD. Differences between groups were tested using the Mann-Whitney test for unrelated samples and the Wilcoxon test for paired samples. Linear regression analysis was used
to evaluate correlation. Variance analysis was used to determine significant differences among the groups. The results

A comparison between the concentration of leptin in cord blood and venous blood obtained within 6 h of birth from the same subjects (n = 28) in three groups is shown in Fig. 1. No statistically significant differences in the concentration of leptin was found between these two samples. Thus, for the remainder of this study, the serum concentration of leptin within 6 h of life was assumed to reflect the levels in fetal circulation.

The clinical characteristics of each group of term infants are presented in Table 1. The placental weight and Ponderal Index of the LGA group were significantly higher than those of the AGA group. Although no statistically significant differences were found among the three groups with respect to serum insulin levels, the LGA group had slightly higher insulin levels.

The concentrations of serum leptin within 6 h of birth in the term infants (LGA, AGA, and SGA groups) are presented in Fig. 2. The serum leptin levels in term AGA infants (4.4 ± 3.0 ng/mL) were significantly lower than those of normal adults in our laboratory (16.9 ± 11.9 ng/mL). The serum leptin concentration in LGA (12.8 ± 10.2 ng/mL) and SGA infants (1.6 ± 1.1 ng/mL) was significantly higher and lower, respectively, than that in AGA infants (P < 0.01).

A longitudinal study of the concentration of serum leptin in 48 term infants (LGA: n = 12, AGA: n = 27, and SGA: n = 9) is shown in Fig. 3. The concentration of leptin in LGA and AGA infants was initially higher than that in the SGA infants and drastically decreased within 48 h of delivery. These changes in the LGA and AGA infants were statistically significant (P < 0.05). In contrast, the serum concentration of leptin in SGA infants did not change significantly in the first 7 days after birth. After 48 h of life, no significant difference in the serum leptin concentration was found between the three groups, and low levels continued at least 7 days of age.

Upon analysis of the data of 91 term infants, significant positive correlation was found between the leptin concentration within 6 h of life and birth body weight (r = 0.59, P < 0.01), indicating a progressive increase in the leptin levels with increasing birth weight (Fig. 4, A). In term and preterm AGA infants (n = 69), leptin levels within 6 h of life positively correlated with gestational age (r = 0.30, P = 0.01; Fig. 4, B).

The body length at birth of 80 term infants had been recorded, and thus the Ponderal Index of these infants could be calculated. Significant positive correlation was found between the leptin levels and Ponderal Index (r = 0.37, P < 0.01; data not shown).

In term AGA infants, the concentration of serum leptin within 6 h of birth in males (n = 25) and females (n = 19) was 4.8 ± 2.7 and 5.0 ± 3.3 ng/mL, respectively. Therefore, no statistically significant gender effect was observed.

No statistically significant correlation between the concentration of leptin and insulin was observed (data not shown).

Discussion

In the present study, the concentration of serum leptin within 6 h of birth was significantly lower in SGA infants compared with AGA infants. Within 48 h of delivery, the serum leptin levels decreased dramatically in the LGA and AGA groups, and no significant differences in leptin concentration were found among the three groups. In all infants, increases in the serum leptin concentration correlated with increases in body weight at birth. These findings indicate that serum leptin correlate with the fetal body weight gain.

The total amount of body fat is less in SGA infants and greater in LGA infants compared with AGA infants (10). In addition, although body weight was determined in 80 term infants in the present study, the Ponderal Index, which is considered useful for assessment of the nutritional state of infants (9), was higher in the LGA group. Thus, we believe that the concentration of serum leptin within 6 h of life closely correlates with the amount of adipose tissue in infants. Linear regression analysis demonstrated there was a significant positive correlation between blood leptin levels and body weight at birth. These results are compatible with the recent reports (11-13) in which the leptin levels in cord blood correlated positively with birth weight. In a normal pregnancy, the fetal body components grow proportionally, which suggests the presence of fetal feedback and regulatory systems for fetal growth. However, these systems have yet to be elucidated. The findings of the present study indicate that leptin may be involved in one of these systems. A recent study has indicated that a low serum concentration of leptin leads to a reduction in energy expenditure through the increase in neuropeptide Y concentration in the hypothalamus (5). Conversely, an increase in the levels of leptin increases energy expenditure (6). Because the energy balance in a growing fetus must be positive, a low concentration of serum leptin is physiologically suitable for fetal growth. In Pima Indians, subjects prone to weight gain initially have lower plasma leptin concentrations than weight- and body composition-matched subjects who maintain a stable weight (14). This data indicates that a relatively low plasma leptin concentration may play a role in the development of obesity in Pima Indians and that the mechanism may be similar to weight gain in the fetus. In addition, to maintain the increase in body mass, a positive feedback system may be operating. In some individuals in the LGA infants, the serum level of leptin were low and overlapped with those in the SGA infants. Although the reason for this overlapping is unknown, the same phenomenon is found in obese adults. Leptin concentration heterogeneity is known to exist between individuals with the same body mass index. Some obese patients have extremely high leptin levels, whereas others have levels similar to those seen in lean subjects. One possible explanation for this heterogeneity is that individuals with high plasma levels of leptin are clinically different from individuals with low leptin concentration, resulting in different response to the leptin.

In the present study, within 48 h of delivery, the serum leptin concentration in the LGA and AGA infants dramatically decreased to the low levels observed in the SGA infants regardless of birth body weight. One possible explanation for this phenomenon is that the nutritional state reflects the leptin concentration. After delivery, infants can not take full nutrition for several days. In human adults, serum leptin levels rapidly and drastically decreased during fasting in obese and normal subjects (15), suggesting that leptin release is regulated by factors other than changes in body fat mass. An alternative explanation is that the origin of leptin in total

| TABLE 1. Clinical characteristics of the AGA, LGA, and SGA groups. |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                        | AGA (n = 41)    | LGA (n = 28)    | SGA (n = 28)    |                |                |                |
| Gestational age (weeks)| 39.0 ± 1.0     | 39.6 ± 1.3     | 39.9 ± 1.4     |                |                |                |
| Birth weight (kg)      | 2.9 ± 0.1       | 3.1 ± 0.1       | 3.2 ± 0.2       |                |                |                |
| Birth length (cm)      | 49.0 ± 1.2      | 49.2 ± 1.3      | 49.4 ± 1.5      |                |                |                |
| Head circumference (cm)| 35.6 ± 0.9     | 36.1 ± 1.0     | 36.5 ± 1.1     |                |                |                |
| Placental weight (g)   | 564 ± 123       | 566 ± 116       | 498 ± 110       |                |                |                |
| Ponderal Index (g/cm²) | 2.6 ± 0.3      | 2.8 ± 0.3       | 2.4 ± 0.2       |                |                |                |
| Serum insulin (μU/mL)  | 3.4 ± 1.1       | 9.5 ± 1.9       | 4.7 ± 2.0       |                |                |                |

Data are the mean ± 1 SD.

*P < 0.01 vs. AGA.

Fig. 2. Concentration of serum leptin in the AGA, LGA, and SGA infants 6 h after birth. Mean levels of serum leptin in term AGA, LGA, and SGA infants were 4.4, 12.8, and 1.6 ng/mL, respectively.

Fig. 3. Changes in concentration of serum leptin in term SGA, AGA, and LGA infants. Day 0 means within 6 h of birth.

Fig. 4. A. Comparison of concentration of serum leptin within 6 h after birth with body weight at birth of the 91 infants (44 AGA, 28 LGA, and 19 SGA). B. Comparison of concentration of serum leptin within 6 h after birth with gestational age in the preterm and term AGA infants (n = 69).

Fig. 4. A. Comparison of concentration of serum leptin within 6 h after birth with body weight at birth of the 91 infants (44 AGA, 28 LGA, and 19 SGA). B. Comparison of concentration of serum leptin within 6 h after birth with gestational age in the preterm and term AGA infants (n = 69).
blood may be placental or maternal blood. A recent abstract reported that leptin messenger RNA was expressed in the placenta (16). However, no reports detailing leptin transfer from the mother to the fetus through the placenta have been published.

The effect of gender on leptin concentration has received considerable attention. Although an earlier study did not find a gender effect on leptin levels in human adults (5), such an effect independent of body fat has been detected in another study (17). In the present study, gender had no effect on the concentration of serum leptin in term AGA infants.

References