Plasma insulin rise precedes rise in ob mRNA expression and plasma leptin in gold thioglucose-obese mice

JANET M. BRYSON, JENNY L. PHUYAL, DEBORAH R. PROCTOR, STEPHEN C. BLAIR, IAN D. CATERSON, AND GREGORY J. COONEY
Department of Endocrinology, Royal Prince Alfred Hospital, Department of Medicine and Human Nutrition Unit, Department of Biochemistry, University of Sydney, and Garvan Institute of Medical Research, St. Vincent’s Hospital, Sydney, New South Wales 2006, Australia

Bryson, J anet M., Jenny L. Phuyal, Deborah R. Proctor, Stephen C. Blair, Ian D. Caterson, and Gregory J. Cooney. Plasma insulin rise precedes rise in ob mRNA expression and plasma leptin in gold thioglucose-obese mice. Am. J. Physiol. 276 (Endocrinol. Metab. 39): E358–E364, 1999.—Circulating leptin levels are strongly related to the degree of adiposity, with hyperleptinemia being associated with hyperinsulinemia. In the gold thioglucose-injected mouse (GTG), hyperleptinemia is an early abnormality in the development of insulin resistance and obesity. In this study, hyperleptinemia occurred 1 wk post-GTG [GTG, 199 ± 43; age-matched controls (CON), 53 ± 5 µU/ml; P < 0.001], with leptin levels not rising until 2 wk post-GTG (CON, 3.2 ± 0.3; GTG, 9.9 ± 1.7 ng/ml; P < 0.001) in parallel with increases in the size of different fat pads and increased expression of ob mRNA. The ratio of serum leptin to fat pad weight was significantly higher in GTG mice 12 wk postinjection. Starvation-induced reductions in serum leptin (50%), glucose (50%), and insulin (74%) were greater than decreases in fat pad weight (18%). Adrenalectomy decreased both adiposity and serum leptin within 1 wk in both CON and GTG and altered the serum leptin level-to-fat pad weight ratio in CON. Thus hyperleptinemia preceded increased ob expression and hyperleptinemia, which occurred in parallel with increasing adiposity, consistent with the role of leptin as an indicator of energy supplies. Changes in hormonal and nutritional status may modify this relationship.

ob gene; adiposity; adrenalectomy; fasting

IT IS NOW WELL ESTABLISHED in both humans and rodent models of obesity, except the leptin-deficient ob/ob mouse, that both the level of expression of ob mRNA and the circulating levels of leptin correlate highly with the degree of adiposity (18). Leptin is produced mainly by adipocytes, with different adipose sites exhibiting differences in the expression of ob mRNA (10). Less is known of the secretion rates of different adipose sites and whether there is variability in their contribution to circulating leptin levels. The hormonal and metabolic control of secretion rates is also not fully understood. Hyperleptinemia is associated with hyperinsulinemia in both humans and rodents, suggesting a role for insulin in the regulation of leptin production and secretion. However, whereas both acute and prolonged exposure to insulin results in increased ob mRNA expression and leptin secretion (2, 7, 24), prolonged hyperinsulinemia is required for an effect on circulating leptin in both humans and rodents (11, 14, 20).

The gold thioglucose-injected (GTG) mouse is a chemically induced model of obesity in which an infarction of the hypothalamus results in hyperphagia and weight gain (3, 15). This lesion causes a reduction in the number of leptin receptors in the hypothalamus (8), and so it is postulated that the rise in circulating leptin levels is due to leptin resistance caused by the reduction in receptor number. We have previously demonstrated that hyperinsulinemia occurs early in the development of insulin resistance and obesity in this model (3). Conversely, improvements in glucose tolerance, a decrease in fat deposition, and loss of body weight are found after adrenalectomy, implicating glucocorticoids, which upregulate both expression and secretion of leptin in vitro (25) in the development of obesity in this model.

The aims of this study were to compare the timing of the development of hyperleptinemia with that of hyperinsulinemia in the GTG-obese mouse, to observe the relationships between circulating leptin levels and the size of different fat depots during the development of obesity in both the fed and fasted states, and to determine the effect of adrenalectomy and therefore a decrease in glucocorticoids on circulating leptin levels.

METHODS

Animals. Male CBA/T6 mice were obtained at 6 wk of age from the Blackburn Animal House, University of Sydney. Obesity was induced by a single intraperitoneal injection (0.5 g/kg) of gold thioglucose (Sigma, St Louis, MO). Mice were kept on a 12:12-h light-dark cycle (light cycle between 0600 and 1800) and were allowed free access to food and water. Groups of GTG-injected mice and age-matched controls (CON) were weighed and then killed by an overdose of Nembutal at different times after the induction of obesity ranging from 1 day to 12 wk. Half of each group (except during the 1st wk) was starved overnight before being killed, whereas the other half had normal access to food until being killed. The epididymal (epi) fat pad, subcutaneous (sc) fat pad from the femoral region, and retroperitoneal (rp) fat pad were removed, blotted, weighed, and immediately frozen. Fat pads were always removed by the same operator. Blood was collected from the chest cavity and spun, and serum was frozen for subsequent leptin, insulin, and glucose assays. In a subsequent experiment, groups of mice were killed at 3, 7, and 14 days post-GTG, and epididymal fat pads were removed for determination of ob mRNA expression. A further group of GTG mice 4 wk postinjection and their age-matched controls were used to test the effects of adrenalectomy. Half of each group were bilaterally adrenalectomized (ADX), and the remaining animals were subjected to sham-ADX. ADX mice were given...
access to 0.9% (wt/vol) saline ad libitum in place of their normal drinking water. Sham-ADX mice continued to have access to tap water. All animals were killed 1 wk later, and tissues and serum were collected as for the first group. The number of animals in each group was 8–12.

Oral glucose tolerance test. After an overnight fast, groups of 5-wk post-GTG-injected obese mice and age-matched lean mice were given an oral gavage of 200 µl of 50% glucose (~3 g/kg). Tail vein blood samples (10 µl) were collected at 15- to 30-min intervals for 120 min, diluted into heparinized saline, and microfuged, and serum was assayed for glucose and leptin as detailed in Serum analyses.

Serum analyses. Serum leptin was measured by RIA (Linco Research, St. Louis, MO). Serum glucose was measured by a glucose oxidase-peroxidase method with 4-amino-antipyrine as the dye, and serum insulin was measured by a double-antibody RIA with rat insulin standards and anti-rat insulin first antibody (Linco Research).

Measurement of ob mRNA expression. ob mRNA expression was determined in epididymal fat tissue with semiquantitative RT-PCR techniques. Total mRNA was extracted from 100 mg of fat tissue with Tri Reagent (Sigma Biosciences) and was quantitated with the use of Sybr Green II RNA gel stain (Molecular Probes, Eugene, OR) with 50- to 800-ng RNA molecular mass markers (Boehringer Mannheim, Germany) to construct the standard curve. cDNA was synthesized from the RNA with the Superscript preamplification system for first-strand cDNA synthesis (Life Technologies) with random hexamers. PCR of cDNA was performed with Amplitaq Gold (Perkin Elmer, Forster City, CA). Primers for PCR were designed with the aid of the sequence analysis software Macvector (Eastman Kodak Company, Rochester, NY). The forward primer for measuring ob expression was ATG ACC TGG AGA ACC TGC GAG ACC, and the reverse primer was GTC CTG CAG AGA GCC CTG CAG CCT GCT. β-Actin expression was also measured as a control with AAT CCT GTG GCA TCC ATG AAA C as the forward primer and CGC AGC TCA GTA ACA GTC CG as the reverse primer. Cycle parameters were 94°C for 45 s, 55°C for 45 s, and 72°C for 1 min, with 27 cycles used for ob amplification and 25 cycles for β-actin. No genomic contamination was confirmed with control RNA samples that had not undergone RT. Products were analyzed after agarose gel electrophoresis and staining with ethidium bromide. The image was captured with the software package Molecular analyst (Bio-Rad Laboratories, Hercules, CA) and imported into NIH image (National Institutes of Health), and the densities of the PCR products were quantified. Results are expressed as arbitrary intensity units.

Statistics. All results are given as means ± SE. Comparisons between CON and GTG were performed with ANOVA followed by Bonferroni-Dunn post hoc tests with repeated measures where appropriate. Relationships between variables were determined by simple regression with the Statview IV statistical package.

RESULTS

Changes in body weight and the size of individual fat pads during the development of obesity. Twelve weeks after GTG injection, GTG mice were 20% heavier than control mice (CON, 36.2 ± 0.9 g; GTG, 43.0 ± 1.1 g; P < 0.0001). The differences in body weight between fed GTG mice and their age-matched controls became significant during the first 3 wk post-GTG as shown in Fig. 1A. GTG-injected mice initially lose weight in response to the GTG injection but regain this weight within 1 wk and are significantly heavier than controls by 2 wk.

![Fig. 1](http://alipendofphysiology.org) Changes in body weight (A) and in weights of epididymal (B), subcutaneous (C), and retroperitoneal (D) individual fat pads after injection of gold-thioglucose (GTG; ○) and in age-matched controls (CON, ●). Each point is means ± SE for 8–12 mice. **P < 0.01, ***P < 0.001 for differences between GTG and CON groups.
The changes in body weight in the GTG mice were paralleled by similar changes in all three fat pads (Fig. 1, B–D), with significant increases in the size of all fat pads at 2 wk. Strong correlations were seen in the GTG mice between body weight and the weights of all three fat pads during these first 3 wk (epi, $r = 0.949$; sc, $r = 0.905$; rp, $r = 0.880$; $P < 0.0001$). Significant correlations were also seen in CON (epi, $r = 0.771$; sc, $r = 0.541$; rp, $r = 0.608$, $P < 0.0001$).

Changes in serum glucose, insulin, and leptin during the development of obesity. Serum glucose was reduced in the first few days post-GTG, reflecting the fall in food intake after injection. Serum glucose was then normalized, and the GTG-injected mice did not become significantly hyperglycemic until 4 wk postinjection (CON, $17.1 \pm 2.6$; GTG, $25.0 \pm 2.0$ mM; $P = 0.028$). Fed serum levels of insulin and leptin during the first 3 wk after GTG injection when differences between the groups became significant are shown in Fig. 2. Serum insulin in GTG was unchanged during the first few days despite the loss of body weight that occurs after injection, but it was significantly elevated in GTG at 7 days ($P = 0.0008$), preceding the changes in body and fat pad weight. Serum leptin also showed no fall in the early stages with signs of an increase at 7 days and with levels threefold higher than controls by 14 days ($P = \ldots$)

Table 1. Differences in body and epididymal fat pad weights and serum insulin and leptin levels between gold thioglucose-injected mice 3, 7, and 14 days postinjection and age-matched controls used for estimation of obesity expression

<table>
<thead>
<tr>
<th>Days</th>
<th>Body Wt, g</th>
<th>Epi Wt, g</th>
<th>Insulin, µU/ml</th>
<th>Leptin, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>23.4 ± 0.3</td>
<td>0.33 ± 0.02</td>
<td>73.2 ± 5.8</td>
<td>1.98 ± 0.23</td>
</tr>
<tr>
<td>7</td>
<td>24.2 ± 0.5</td>
<td>0.38 ± 0.02</td>
<td>83.7 ± 9.3</td>
<td>2.60 ± 0.23</td>
</tr>
<tr>
<td>14</td>
<td>26.1 ± 1.0</td>
<td>0.47 ± 0.05</td>
<td>77.5 ± 15.3</td>
<td>3.26 ± 0.81</td>
</tr>
<tr>
<td>GTG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21.5 ± 0.6*</td>
<td>0.27 ± 0.03</td>
<td>45.5 ± 4.4†</td>
<td>1.23 ± 0.29</td>
</tr>
<tr>
<td>7</td>
<td>22.8 ± 0.5</td>
<td>0.28 ± 0.03*</td>
<td>203 ± 51*</td>
<td>3.48 ± 0.42</td>
</tr>
<tr>
<td>14</td>
<td>29.1 ± 0.6*</td>
<td>0.87 ± 0.06†</td>
<td>188 ± 37*</td>
<td>14.8 ± 1.25†</td>
</tr>
</tbody>
</table>

Values are means ± SE for 6–12 mice. Epi, epididymal fat pad; GTG, gold thioglucose-injected mice; CON, age-matched controls. *P < 0.05, †P < 0.01 for differences between CON and GTG mice at each time point.
injected mice preceding the rise in serum leptin experiment, with the rise in serum insulin in GTG-were similar to those found in the longer time course in the mice used for determination of epididymal weight, and serum insulin and leptin levels.

Changes in ob expression in epididymal adipose tissue during the development of obesity. Body weight, epididymal weight, and serum insulin and leptin levels in the mice used for determination of ob expression were similar to those found in the longer time course experiment, with the rise in serum insulin in GTG-injected mice preceding the rise in serum leptin (Table 1). There was no difference in the expression of β-actin between CON and GTG (CON, 52.0 ± 2.6; GTG, 56.2 ± 2.8 U) and no effect of time. Changes in ob expression in epididymal fat pads in GTG-injected mice 3, 7, and 14 days postinjection and in age-matched controls are shown in Fig. 4. ob mRNA expression was significantly reduced at 3 days (P = 0.0168) and significantly increased by 14 days post-GTG (P = 0.0268). There was no change in ob expression in the control mice. Strong correlations were found between circulating leptin levels and ob expression at 7 days (r = 0.764, P = 0.0002) and 14 days (r = 0.837, P = 0.0096), with a weaker association at 3 days (r = 0.562, P = 0.069). An association between ob expression and epididymal weight was only seen in GTG mice at 7 days (r = 0.897, P = 0.0002).

Effects of overnight starvation on body and fat pad weights and on serum glucose, insulin, and leptin levels. Significant and consistent starvation-induced reductions in body weight, individual fat pad weights, and serum glucose, insulin, and leptin levels were seen at all time points. Results for 12-wk mice that were typical of all time points are shown in Table 2. The average percent changes in leptin (50%), glucose (50%), and insulin (74%) were similar in both CON and GTG and were much greater than the changes in body weight (12%) and epididymal weight (18%).

Effects of an oral glucose tolerance test on serum leptin in controls and GTG-treated mice. Serum glucose and leptin levels during the oral glucose tolerance test are shown in Fig. 5. Serum glucose rose in both groups, peaking about 30 min postgavage, with a higher peak response being seen in the GTG mice. Although not measured in this study because of the difficulty of obtaining sufficient blood from tail-vein bleeds, we have previously shown parallel changes in serum insulin during an oral glucose tolerance test, with an insulin peak three times the basal level in CON and fourfold higher in GTG (5). Fasting leptin levels before the glucose gavage were 2.06 ± 0.20 ng/ml in CON and 10.60 ± 1.62 ng/ml in the GTG-injected mice. There was no change in leptin levels in either group throughout the 2-h period.

Effects of ADX on body and fat pad weights and on serum glucose, insulin, and leptin levels. Body weight, epididymal weight, and serum glucose, insulin, and leptin levels in the ADX and sham ADX mice 1 wk after

Table 2. Differences in body and epididymal fat pad weights and serum glucose, insulin, and leptin levels between fed and overnight-starved CON and 12 wk GTG-obese mice

<table>
<thead>
<tr>
<th></th>
<th>Body Wt, g</th>
<th>Epi Wt, g</th>
<th>Glucose, mM</th>
<th>Insulin, µU/ml</th>
<th>Leptin, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>36.2 ± 0.9</td>
<td>1.07 ± 0.06</td>
<td>16.6 ± 0.5</td>
<td>182 ± 27</td>
<td>8.3 ± 1.0</td>
</tr>
<tr>
<td>S</td>
<td>31.5 ± 1.1*</td>
<td>0.95 ± 0.07</td>
<td>5.9 ± 0.2†</td>
<td>58 ± 5†</td>
<td>4.4 ± 0.6†</td>
</tr>
<tr>
<td>GTG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>43.0 ± 1.1</td>
<td>1.42 ± 0.08</td>
<td>27.5 ± 1.8</td>
<td>732 ± 125</td>
<td>21.1 ± 2.4</td>
</tr>
<tr>
<td>S</td>
<td>39.7 ± 0.7*</td>
<td>1.27 ± 0.06</td>
<td>12.4 ± 0.5†</td>
<td>101 ± 16†</td>
<td>8.3 ± 2.0†</td>
</tr>
</tbody>
</table>

Values are means ± SE for 8–12 mice. Similar changes were seen at all time points from 7 days post-GTG to 12 wk post-GTG. *P < 0.05, †P < 0.01 for differences between fed (F) and overnight-starved (S) animals.
have shown in this model that the rise in insulin
stages of the development of insulin resistance, we
sulinemia. By more frequent testing during the early
were made before and after the development of hyperin-
26) or elevated
ment of hyperinsulinemia and hyperleptinemia (1, 21,
parallel development of hyperinsulinemia. Parallel develop-
parallel with increased fat deposition and after the
development of hyperleptinemia develop in the GTG obese mouse in

ADX are summarized in Table 3. ADX resulted in
significant reductions in body and epididymal weight in
both CON and GTG mice. No change occurred in serum
glucose in CON, but a reduction did occur in the
hyperglycemia of the GTG mice. Insulin levels were
halved in both CON and GTG mice, whereas leptin
levels were reduced by 57% in CON and 24% in GTG
mice. Once again, the changes in leptin more closely
resembled the changes in insulin than the changes in
fat pad weight. In this experiment, the ratio of leptin to
epididymal weight was significantly higher in GTG
mice (CON, 8.45 ± 0.65; GTG, 13.34 ± 0.61; \( P < 0.0001 \)). Whereas ADX decreased this ratio in CON
(CON + ADX, 5.35 ± 0.43, \( P < 0.0001 \)), it had no effect
in GTG (GTG + ADX, 12.30 ± 0.41, \( P = 0.209 \)).

DISCUSSION

This study shows that elevated ob expression and
hyperleptinemia develop in the GTG obese mouse in
parallel with increased fat deposition and after the
development of hyperinsulinemia. Parallel develop-
ment of hyperinsulinemia and hyperleptinemia (1, 21,
26) or elevated ob expression (7, 12, 19, 21) has been
demonstrated in other studies where measurements
were made before and after the development of hyperin-
sulinemia. By more frequent testing during the early
stages of the development of insulin resistance, we
have shown in this model that the rise in insulin
precedes the rise in ob expression and leptin. Hyperin-
sulinemia in the GTG mouse is accompanied by a
period of increased insulin sensitivity, resulting in
enhanced lipogenesis (3). Thus it is impossible to say
from this study whether the hyperleptinemia is directly
due to the hyperinsulinemia or indirectly due to the
increasing fat content of the adipocytes.

Many studies have shown that exogenous insulin
given either acutely or chronically is able to increase ob
expression in rodents in vivo (7, 24) and both ob
expression and leptin secretion in vitro (2, 22). How-
ever, it appears that whereas insulin has a rapid effect
on expression levels, it requires prolonged exposure to
produce any change in circulating leptin levels (11, 20),
as shown by the lack of change of leptin levels during
the oral glucose tolerance test in this study. Studies in
humans suggest that prolonged hyperinsulinemia is
necessary for the elevation of plasma leptin (14),
whereas in the short term, hyperinsulinemia may
prevent the postabsorptive decline in leptin levels (23).
A recent study looking at ob expression and protein
production rates in suckling Zucker rats was able to
show an increase in leptin secretion earlier than any
change in expression rates (21), suggesting that in-
creased secretion is not due to elevated production
leading to an efflux of leptin, but rather a separate
mechanism is controlling release into the circulation.

The strong relationship seen between circulating
leptin and the size of the different fat pads gives further
support to the theory that the primary role of leptin is
to indicate fatness. The same association also occurred
in the lean mice and has been shown in lean humans
and other models although not in lean Psammomys
obesus (6). The constant ratio of leptin to fat pad weight
over the 12 wk of this study does not suggest an effect of
age independent of increasing adiposity as has been
reported in other studies (1, 16). The ratio tended to be
higher in the GTG mice, and this difference is probably
a reflection of the resistance induced by decreased
receptor numbers in the hypothalamus. Despite the
degree of adiposity being the strongest determinant of
leptin levels in both rodents and humans, other factors
have been shown to influence the rate of production or
secretion per unit of fat, including strain differences
(26), dietary composition (1, 9, 26), and gender (9). It is
of interest then that adrenalectomy had an effect on the
ratio of leptin to fat pad weight in the lean mice but not
the obese mice. Rat studies have shown an increased
sensitivity to leptin after ADX (27), and the lower
production rates in the lean mice may be a reaction to

ADX, adrenalectomy or adrenalectomized. * \( P < 0.05 \), † \( P < 0.01 \) for effect of ADX within a treatment group; ‡ \( P < 0.05 \) for differences
between lean (CON) and obese (GTG).

Table 3. Effect of ADX on body and epididymal fat pad weight and serum glucose, insulin,
and leptin levels in CON and 5-wk GTG mice 1 wk postsurgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Wt, g</th>
<th>Epi Wt, g</th>
<th>Glucose, mM</th>
<th>Insulin, ( \mu g/ml )</th>
<th>Leptin, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON-sham</td>
<td>29.7 ± 0.4</td>
<td>0.56 ± 0.04</td>
<td>12.5 ± 0.5</td>
<td>57.7 ± 6.9</td>
<td>4.77 ± 0.53</td>
</tr>
<tr>
<td>CON-ADX</td>
<td>25.6 ± 0.8†</td>
<td>0.41 ± 0.04*</td>
<td>12.9 ± 0.7</td>
<td>26.9 ± 2.8†</td>
<td>2.05 ± 0.16†</td>
</tr>
<tr>
<td>GTG-sham</td>
<td>40.2 ± 0.7‡</td>
<td>1.87 ± 0.08‡</td>
<td>20.4 ± 1.1‡</td>
<td>279.6 ± 53.2‡</td>
<td>24.6 ± 1.0‡</td>
</tr>
<tr>
<td>GTG-ADX</td>
<td>36.2 ± 0.8‡</td>
<td>1.52 ± 0.04‡</td>
<td>16.6 ± 0.6*</td>
<td>135.5 ± 11.3‡</td>
<td>18.7 ± 0.9‡</td>
</tr>
</tbody>
</table>
this increased sensitivity. In the GTG mice, ADX is not able to increase sensitivity as the leptin receptors are destroyed, and, therefore, higher production rates are maintained. Glucocorticoids stimulate both leptin expression and secretion (25) in vitro, and, therefore, the fall in leptin in both ADX groups may reflect the removal of a direct effect of glucocorticoids on the adipocytes. Once again the relationship between adiposity and circulating leptin is maintained.

Although insulin may not acutely increase circulating leptin levels, starvation-induced decreases in insulin and circulating leptin is maintained.

Insulin stimulates both leptin secretion and expression in all models tested except the Zucker rat (1, 7, 10–12, 17, 19, 24). The starvation-induced changes in leptin in this study more closely paralleled the fall in serum glucose and insulin levels than the changes in body weight or the weight of individual fat pads. Whether the trigger is the fall in insulin or a decrease in total calories or a particular nutrient requires further study. Human studies suggest a change in carbohydrate intake is involved (13), and attenuation of the response in high-fat fed mice (1) is consistent with this hypothesis. In vitro studies suggest a role for free fatty acids in inhibiting leptin production (22), and this is also consistent with the increased lipolysis seen in starvation. The primary role of leptin is to indicate the sufficiency of the energy stores of the body; the administration of exogenous leptin to lean mice induces increased sensitivity as the leptin receptors are increased (13). In intact mice, leptin receptors are expressed in both adipose tissue and hypothalamus (25). The suppression of hypothalamic expression in anorectic states is consistent with this hypothesis. In vitro studies of rat adipocytes indicate that glucocorticoids stimulate both leptin expression and secretion (25) in vitro, and, therefore, the fall in leptin in both ADX groups may reflect the removal of a direct effect of glucocorticoids on the adipocytes. Once again the relationship between adiposity and circulating leptin is maintained.

In summary, in the GTG-injected obese mouse, hyperinsulinemia precedes increased ob expression and hyperleptinemia, which is strongly associated with adiposity. The ratio of circulating leptin to fat pad weight is unaffected by age, reduced by fasting and by the absence of glucocorticoids, and slightly raised in the absence of hypothalamic leptin receptors. Therefore, whereas leptin remains a strong indicator of body fatness, changes in hormonal and nutritional status may modify this relationship.

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Address for reprint requests: J. Bryson, Human Nutrition Unit, Dept of Biochemistry, Univ of Sydney, Sydney, NSW, 2006, Australia.

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